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Efficacy of extracts from eight economically important forestry species against grapevine downy mildew (*Plasmopara viticola*) and identification of active constituents

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ABSTRACT

Downy mildew caused by the oomycete *Plasmopara viticola* is the most devastating pathogen of grapevine. In this study, extracts of the bark of eight important northern forestry species were screened to find extracts showing activity against this pathogen and to identify the active compounds. Extracts from all eight species showed activity against *P. viticola*, the most promising, dichloromethane extracts of three *Larix* species, almost completely protecting grapevine from downy mildew under semi-controlled conditions. Five promising lead compounds were isolated: larixol, larixyl acetate, lariciresinol and lariciresinol acetate from *Larix* species and 7α,15-dihydroxydehydroabietic acid from *Pinus sylvestris*. These compounds showed 90%–100% efficacy. Larixol and larixyl acetate or 7α,15-dihydroxydehydroabietic acid are present in significant amounts in *Larix* or *P. sylvestris* bark extracts, respectively.

The identified active compounds are gained from a renewable resource potentially available in large quantities at relatively low prices, making them interesting candidates for the development of a plant-derived fungicide active against a key pathogen in agriculture, providing an opportunity to the forest industry to transform low value by-products into high value-added, bioactive extracts.

1. Introduction

Plant protection products are essential in agriculture to control pests and diseases to ensure yields. Yet, there is growing concern related to the impacts of plant protection products on human health and the environment (Bolognesi, 2003; Eijsackers et al., 2005; Gilliom, 2007; Mullin et al., 2010; Schwarzenbach et al., 2010; Weisenburger, 1993). Because of this, the European Union has obliged all member states to adopt national action plans on pesticides (Article 4 of EUR-Lex Directive, 2009/128/EC, 2009). These action plans should reduce risks and impacts of pesticide use on human health and the environment, and encourage the development and introduction of integrated pest management and of alternative approaches or techniques in order to reduce dependency on the use of pesticides. Copper-based fungicides are one example for plant protection products which should be replaced by more environmentally friendly alternatives. Copper-based fungicides are used to control many devastating plant diseases of important crops, including potato, grapevine, apple trees and many vegetables and ornamentals (Finckh et al., 2015). They are widely used in conventional as well as in organic production systems. Even though copper usually does not represent a toxicological problem for terrestrial mammals and vertebrates (Massaro, 2002), long-term application of copper leads to accumulation in the soil, thus potentially negatively affecting soil organisms and soil fertility (Bünemann et al., 2006; Merrington et al., 2002; Wang et al., 2009). In European agriculture, copper-based fungicides are used most intensively in grapevine, apple and potato production (Speiser

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et al., 2015). In this context, we have been searching for substances which might replace copper-based fungicides for the control of plant diseases, particularly downy mildew of grapevine and apple scab.

Plant-derived plant protection products have long been used for the control of insect pests (e.g. pyrethrum, rotenone, neem, nicotine) (Isman, 2014). By contrast, their potential for the control of plant pathogens has been explored much less (Isman, 2006; Seiber et al., 2014). Even though several plant extracts have been shown to be effective against different plant pathogens (as reviewed by Yoon et al., 2011), only very few have been developed for commercial use (Tamm et al., 2011; Yoon et al., 2011). Commercially available plant-based products include fennel oil (against powdery mildews and rust on grapevines, some berries, vegetables and ornamentals), lecithine (against powdery mildews on some vegetables and ornamentals), coconut potassium soap (against rainspot disease of pome fruit) and laminarine (a stimulator of natural defence mechanisms in plants derived from brown algae, to be used on pome fruit, grapevines, strawberries, some vegetables and cereals) (http://www.psm.admin.ch/psm/produkte/index.html?lang=de). None of these substances can replace copper fungicides on the grapevines, apples and potatoes, the crops where they are used in greatest quantities (Speiser et al., 2015).

Tree bark is known to contain a broad range of secondary metabolites with many potential uses (Turley et al., 2006). It has been shown that bark extracts and pure compounds isolated thereof can have antifungal properties. For example, Mori et al. (1997) have screened extracts from 51 deciduous and 21 coniferous Japanese trees *in vitro* against several soil borne plant pathogens and wood decay fungi (Mori et al., 1995, 1997). Alfredsen et al. (2008) showed an *in vitro* antifungal effect of *Larix decidua, Picea abies* and *Pinus sylvestris* bark extracts against brown and white rot fungi, canker and blue stain fungi (Alfredsen et al., 2008), and Kokalisburelle and Rodriguezkabana (1994) reported activity of *Pinus tadea* and *Pinus elliotti* bark extracts against soil borne pathogens including *Rhizoctonia solani, Phytophthora parasitica, Alternaria solani* and *Fusarium oxysporum*. Bark as a forestry by-product is a naturally occurring, rapidly renewable, readily available, large-volume, low-price raw material. The European forestry industry produces annually about 50 M m^3 of bark, which is currently mainly used as an energy source (Mantau, 2016).

The potential use of bark and other wood residues especially from economically important species of the genera *Betula*, *Pinus*, *Picea*, *Larix*, *Abies* and *Populus* species (San-Miguel-Ayanz et al., 2016) coming from the wood processing industry as a raw material to produce environmentally benign industrial chemicals and polymers as well as bioactive compounds for the use in medicine, cosmetics and plant protection (herbicide, insecticide, fungicide) was evaluated in the EU-funded project ForestSpecs (http://cordis.europa.eu/project/rcn/91266_en.html). One of the main aims of this project was to create options for total usage of processed wood residues, so that the operations suggested were economically feasible. Here we show results of part of this project aiming at (i) the identification of bark extracts with activity against grapevine downy mildew caused by *Plasmopara viticola*, the most devastating disease of grapevine in humid parts of the world and (ii) the identification of active compounds in these extracts.

2. Materials and methods

2.1. Plant material

Bark from *Pinus sylvestris* L., *Larix gmelinii* (Rupr.) Kuzen., *Larix sibirica* Ledeb., *Larix decidua* Mill., *Populus tremula* L., *Picea jezoensis* (Siebold & Zucc.) Carrière, *Picea abies* (L.) H.Karst and *Abies nephrolepis* (Trautv. Ex Maxim) Maxim. was collected from sites in Finland and northern and far eastern Russia during 2009 & 2010. Details of geographical locations of collection sites are given in the Supplementary Material (S1). Voucher specimens were retained and plant material was sent to the University of Surrey for processing. Dried material was milled with a Glen Creston cross-beater mill (mesh size 4 mm).

2.2. Extraction of plant material

Plant material was extracted successively with three different solvents, dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and methanol (MeOH) using a CEM MarsXpress Microwave extractor. For each plant, 10.0 g of plant material was packed into each of 40 Teflon vessels together with a magnetic stirrer (to assure equal mixing) and solvent (25 mL). The vessels were then capped, placed in a turntable and the appropriate method was loaded (*voltage*: 1600 W, power: 100%, time: 10 min hold: 20 min, temp. 50 °C for CH_2Cl_2, 50 °C for EtOAc and 110 °C for MeOH). After extraction, the solution was filtered into *a pre*-weighed 1000 cm^3 round bottom flask and the solvent was reduced *in vacuo*. In each case this procedure was repeated so each plant sample was extracted twice with each solvent.

2.3. Isolation and identification of compounds present

Column chromatography over silica gel (Merck 9385) or Sephadex LH 20 (Sigma Aldrich) was used to separate and purify the extracts. Detailed methods of separations for the different extracts are provided in the Supporting Information (S2). Structures were determined using NMR spectroscopy, mass spectrometry, infrared and optical rotation methods. NMR analysis was performed on a Bruker 500 MHz NMR spectrophotometer and spectra were recorded in $CDCl_3$ or CD_3OD with tetramethylsilane as the internal standard. ESIMS were recorded on a Finnigan MAT 95 XP High Resolution Double Focussing MS at the University of Surrey. Compounds isolated had all been reported previously and identification was confirmed by comparing experimental data against literature values as shown, along with their structures, in the Supporting Information (S3 & S4).

Nine compounds present in the most active CH_2Cl_2 extracts were selected for further screening: 8(17),14-labdadien-6α,(13*S*)-diol (larixol) (**1**), 6α-acetoxy-8(17),14-labdadien-(13*S*)-ol (larixyl acetate) (**2**) and (+)-4,4′,9′-trihydroxy-3,3′-dimethoxy-7′,9-epoxylignan (lariciresinol) (**3**) from *L. decidua*, (+)-4,4′-dihydroxy-3,3′-dimethoxy-7′,9-epoxylignan-9-*O*-acetyl (lariciresinol acetate) (**4**) and again lariciresinol (**3**) from *L. sibirica*, 15-hydroxydehydroabietic acid (**5**) (also isolated from *L. gmelinii*), 7-oxo-15-hydroxydehydroabietic acid (**6**), 7α,15-dihydroxydehydroabietic acid (**7**) from *P. sylvestris* and rhaponticin (**8**), piceatannol-5-*O*-glucopyranoside (**9**) from *P. abies*.

2.4. Bioassays: plant material and pathogens

Grapevine – *Plasmopara viticola* bioassays were performed as described before (Thuerig et al., 2016). Small grapevine (*Vitis vinifera* L. cv. 'Chasselas') seedlings were transplanted into individual pots (0.275 L) containing a standard substrate ('Einheitserde Typ 0', Gebr. Patzer GmbH & Co. KG, Sinntal-Jossa, Germany) previously amended with 3 g L^{-1} of a mineral fertilizer (Tardit 3M, Hauert Günther Düngerwerke GmbH, Erlangen, Germany). Plants were grown in the greenhouse at a temperature of 18–28 °C under natural light. In wintertime, the photoperiod was extended with mercury lamps to 16 h. Plants were used for bioassays when they had 3-4 fully developed leaves (2–3 weeks after transplanting).

Plasmopara viticola (Berk. & M.A. Curtis) Berl. & De Toni was maintained on grapevine (*Vitis vinifera* L.) seedlings cv. 'Chasselas' by weekly re-inoculation (described below). Sporangia suspensions of *P. viticola* were prepared by washing fresh, sporulating grapevine leaves with demineralized water. Suspensions were filtered over a cheese cloth, the concentration was assessed using a Thoma cell counting chamber, and adjusted to desired concentrations (5×10^4 sporangia mL^{-1}).

2.5. Test products

Extracts from L. *decidua* and *L. sibirica* were dissolved in ethanol (EtOH) or isopropanol at 5–10 mg mL^{-1}, all other plant extracts were dissolved in DMSO at 20–25 mg mL^{-1}. Pure compounds were dissolved in EtOH at concentrations of 5–10 mg mL^{-1}. Stock solutions were diluted in water containing 2 g L^{-1} of a sticker and wetting agent (Trifolio S-Forte) (*L. decidua* and *L. sibirica* extracts) or in water (all other extracts) to the appropriate concentrations. Extracts and pure compounds were tested in concentrations between 0.1 and 2 mg mL^{-1}. None of the solvents significantly inhibited *Plasmopara viticola* on grapevine seedlings at the used concentrations (Table 1). A standard treatment (copper hydroxide, Kocide® Opti™, DuPont de Nemours, Wilmington, DE, USA) at two concentrations (300 μg mL^{-1} and 30 μg mL^{-1} of Cu^{2+}) was included in each experimental set.

2.6. Experimental design

Plant-pathogen bioassays were carried out under semi-controlled conditions in experimental facilities (greenhouse and growth chambers). Each experimental set included a non-treated non-inoculated control, a water-treated inoculated control, a standard copper treatment at two concentrations, and at least 12 test treatments. All experiments included six replicate plants per treatment. Plants were sprayed with the test products using an automatic spray cabinet (plant extracts) or an air-assisted hand sprayer (DeVilbiss® Compact MINI HVLP Touch-Up Spray Gun) (pure compounds) until leaves (adaxial and abaxial side) were completely covered with a dense layer of small droplets. Plants were subsequently left to dry at room temperature before inoculation with fresh sporangial suspensions of *Plasmopara viticola* (Berk. & M.A. Curtis) Berl. & De Toni. Plants were spray-inoculated using an air-assisted hand sprayer on the abaxial leaf side. Inoculated plants were subsequently incubated at 20–21 °C and 80–99% of relative humidity (RH) in the light for 24 h. Then, plants were maintained at 20 °C, 60–80% RH, and a 16/8-h day/night light regime. 5–6 d after inoculation, plants were incubated overnight in the dark at 20 °C and 80–99% RH to promote sporulation.

Disease incidence (percentage of leaves with disease symptoms) and disease severity (percentage of leaf area covered by lesions) were assessed 6–7 d after inoculation. All disease assessments were made using continuous values of percentage based on the European and Mediterranean Plant Protection Organisation (EPPO) standard scale (EPPO, 2001).

2.7. Calculations and statistics

Efficacies were calculated according to Abbott (1925) as (1- (A x B^1)) x 100, with A = disease severity on an individual plant and B = mean disease severity of non-treated control plants. For statistical analysis, all data were arcsin-transformed: 360 x $2\pi^{-1}$ x arcsin (squareroot (A × 100^{-1})), with A = disease severity in %. Treatments were compared to the non-treated control using Dunnett's test. Efficacies of different extracts were compared by an ANOVA followed by Tukey's HSD pairwise-comparisons.

3. Results

Efficacies of MeOH, EtOAc and CH_2Cl_2 extracts from eight economically important European forestry species were evaluated for activity against grapevine downy mildew caused by *Plasmopara viticola* on grapevine seedlings under semi-controlled conditions. While none of the MeOH extracts significantly reduced downy mildew disease severity compared to the non-treated control (Fig. 1A), the less polar extracts (EtOAc and CH_2Cl_2) from all eight species significantly protected grapevine plants against downy mildew ($p < 0.001$, Dunnett's test), but to different degrees (Fig. 1B and C).

CH_2Cl_2 extracts from all three *Larix* species showed very high efficacies between 88% and 98% at 1 mg mL^{-1} (Fig. 1C), and were comparable to a reference copper treatment. Results were confirmed in a second experiment for CH_2Cl_2 extracts of *L. decidua* and *L. sibirica* (Fig. 2). High efficacies between 80% and 90% were observed for EtOAc and CH_2Cl_2 extracts from *A. nephrolepis* and *P. abies* at 1 mg mL^{-1} (Fig. 1B and C). *P. abies* extracts were also significantly active at the lower tested concentration (40–50% efficacy at 0.25 mg mL^{-1}) (Fig. 1B and C). Results could be confirmed for *P. abies*, but not for *A. nephrolepis* extracts in a second experiment (Fig. 2).

P. sylvestris EtOAc and CH_2Cl_2 extracts showed intermediate efficacies between 50% and 80% against downy mildew at 1 mg mL^{-1} (Fig. 1B and C, 2). *P. sylvestris* extracts were also significantly active

Table 1
Efficacy of three solvents at different concentrations against *Plasmopara viticola* on grapevine seedlings. Solvents were tested at concentrations used in experiments with plant extracts and active ingredients.

Solvent	Concentration in spray broth	n[b]	Efficacy (%)[a]	
			mean	95% confidence interval[c]
DMSO	0.5%	4	1%	−38%/40%
	1%	4	−8%	−38%/22%
	2%	8	9%	−11%/29%
Isopropanol	2%	3	−16%	−41%/6%
	5%	1	−5%	
	10%	1	−3%	
Isopropanol + T-S-Forte[d]	20%/0.2%	2	12%	9%/15%
EtOH	2.5%	2	1%	−18%/20%
EtOH + T-S-Forte	20%/0.2%	3	21%	11%/31%

[a] Percentage reduction of infected leaf area.
[b] Number of independent experiments.
[c] Calculated as mean ± 1.96*SD*square root(n)$^{-1}$.
[d] T-S-Forte (Trifolio-S-Forte) is a sticker and wetting agent.

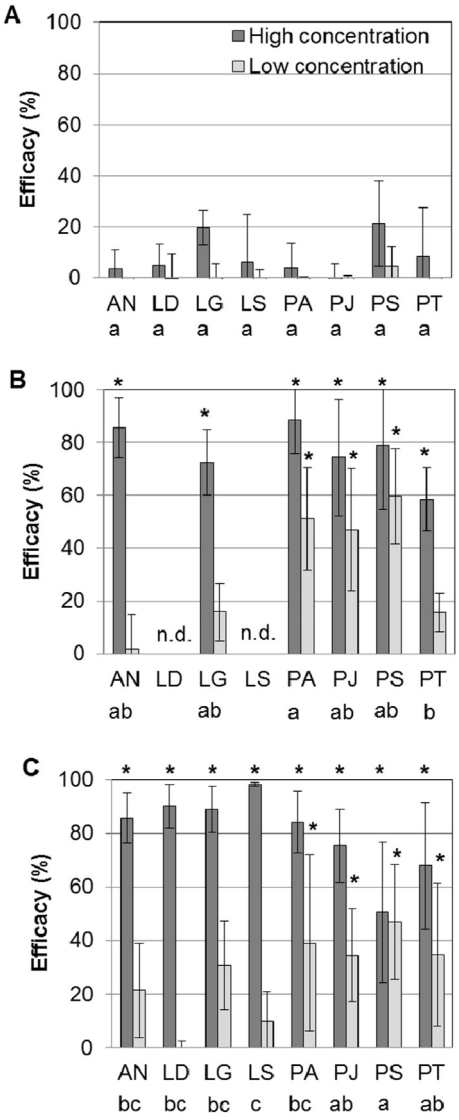

Fig. 1. Efficacy of methanol (A), ethyl acetate (B) and dichloromethane (C) extracts from the bark of eight different tree species against *Plasmopara viticola* on grapevine seedlings under semi-controlled conditions. The extracts were tested at two concentrations: high (0.9–1 mg mL^{-1}) and low (0.1 mg mL^{-1} (LD, LS) or 0.21–0.26 mg mL^{-1} (all other species)). The figures show means ± SD (n = 6). Disease severity of the non-treated control in the three experiments was 84% ± 1% (mean ± SD), efficacy of the copper control was 97% ± 2% (0.03 mg mL^{-1} Cu^{2+}) and 83% ± 13% (0.003 mg mL^{-1} Cu^{2+}). AN *Abies nephrolepis*, LD *Larix decidua*, LG *Larix gmellini*, LS *Larix sibirica*, PA *Picea abies*, PJ *Picea jezoensis*, PS *Pinus sylvestris*, PT *Populus tremula*. n.d.: not determined. Asterisks indicate significant differences to the non-treated control (Dunnett's test, $p < 0.05$), distinct lower case letters indicate significant differences between treatments at 1 mg mL^{-1} (Tukey's HSD, $p < 0.05$).

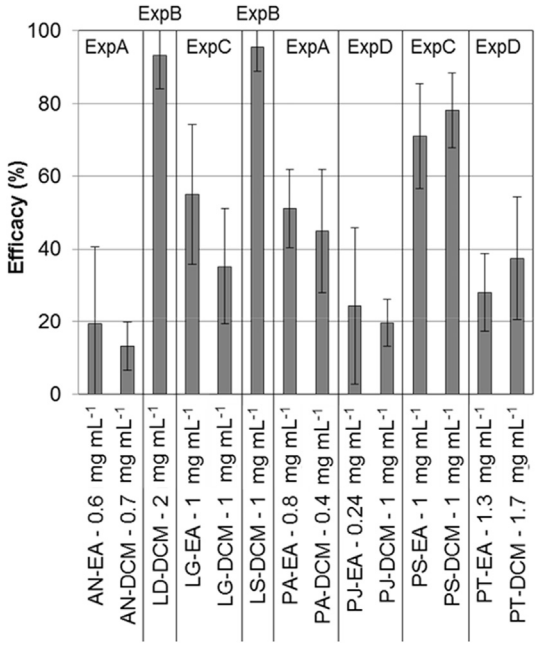

Fig. 2. Efficacy of ethyl acetate (EA) and dichloromethane (DCM) extracts from the bark of eight different tree species *Plasmopara viticola* on grapevine seedlings under semi-controlled conditions. Figures show means ± SD (n = 6). Extracts were tested in four distinct experimental sets (Exp A, B, C, D). Mean disease severity of the non-treated control in the four experimental sets was 86% ± 2%, mean efficacy of a copper control was 94% ± 5% (0.03 mg mL^{-1} Cu^{2+}) and 76% ± 12% (0.003 mg mL^{-1} Cu^{2+}). AN *Abies nephrolepis*, LD *Larix decidua*, LG *Larix gmellini*, LS *Larix sibirica*, PA *Picea abies*, PJ, *Picea jezoensis*, PS *Pinus sylvestris*, PT *Populus tremula*.

at the lower tested concentration (40–60% efficacy at 0.25 mg mL^{-1}) (Fig. 1B and C). Efficacies of *P. jezoensis* EtOAc and CH_2Cl_2 extracts were comparable to *P. sylvestris* extracts in a first experiment (Fig. 1B and C), but results could not be confirmed in the second experiment (Fig. 2). *P. tremula* EtOAc and CH_2Cl_2 extracts consistently showed significant, but relatively low efficacy against downy mildew, with efficacies between 30% and 60% at 1–1.7 mg mL-1 (Fig. 1B and C, 2).

In order to identify active ingredients in the most promising extracts (*Larix* sp., *P. sylvestris*, and *P. abies*), extracts were characterised phytochemically (Supplementary material S2) and nine compounds available in significant amounts (50–100 mg) were evaluated in the grapevine-downy mildew bioassay. Structures are shown in Fig. 4. Four compounds isolated from *Larix* sp., larixol (**1**), larixyl acetate (**2**), lariciresinol (**3**) and lariciresinol acetate (**4**), were found to be very efficient against grapevine downy mildew, with efficacies between 90% and 100% at the highest tested concentration (1 mg mL^{-1}) (Fig. 3A). The most efficient compound, larixyl acetate (**2**), still showed 70% efficacy at 0.1 mg mL^{-1}.

Of the three tested pure compounds isolated from *P. sylvestris*, 15-hydroxydehydroabietic acid (**5**) showed a dose-response comparable to compounds **1**, **2** and **3** isolated from *Larix* sp., with 99% efficacy at 1.4 mg mL^{-1}. The two other compounds, 7-oxo-15-hydroxydehydroabietic acid (**6**) and 7α,15-dihydroxydehydroabietic acid (**7**), showed efficacies of 72%–73% at 1 mg mL^{-1} and efficacies of 94–96% at 2 mg mL^{-1} (Fig. 3B).

The two tested compounds isolated from *P. abies*, rhaponticin (**8**) and piceatannol-5-*O*-glucopyranoside (**9**), were less active than the compounds from the other two species, with efficacies of only 62% (rhaponticin) and 26% (piceatannol-5-*O*-glucopyranoside) at 1 mg mL^{-1}.

4. Discussion

The present study aimed at the evaluation of the potential of bark extracts from important European forestry species to develop new, sustainable plant protection products against *Plasmopara viticola*. Efficacies of some of the non-formulated less polar bark extracts, particularly extracts of *Larix* sp., were very promising at concentrations of 1 mg mL^{-1}. Comparable or much higher concentrations have been reported to reach sufficient efficacies *in planta* experiments for many other crude, non-formulated plant extracts against various pathogens. For example, 5 or 10 mg mL^{-1} of a non-formulated extract of licorice (*Glycyrrhiza glabra*) were necessary to reach 50% efficacy against bean rust on potted beans or

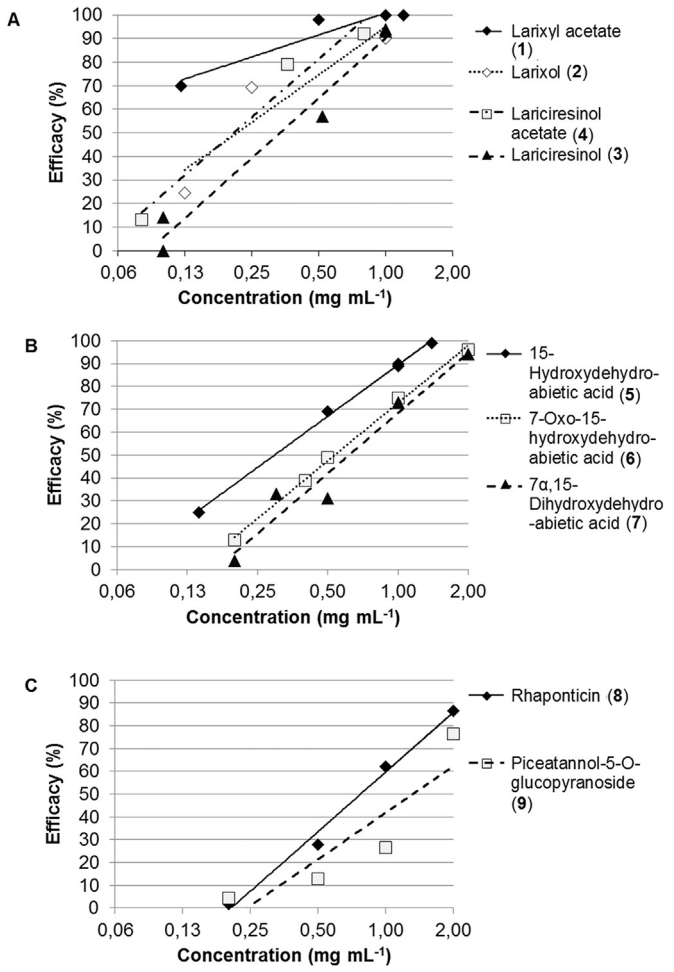

Fig. 3. Dose-response curves of compounds isolated from bark extracts of *Larix decidua/Larix gmellini/Larix sibirica* (A) *Pinus sylvestris* (B) or *Picea abies* (C) against *Plasmopara viticola* on grapevine seedlings under semi-controlled conditions. Each data point represents the mean of six replicate plants. The total of 36 data points originates from six distinct experimental sets, with a mean disease severity of the non-treated control of 89% ± 4%, and mean efficacy of a copper control of 97% ± 2% (0.03 mg mL^{-1} Cu^{2+}) or 78% ± 10% (0.003 mg mL^{-1} Cu^{2+}), respectively. The figure shows log-linear curve fits, with R^2 = 0.998 (15-Hydroxydehdroabietic acid (**5**)), R^2 = 0.997 (7-Oxo-15-hydroxydehydroabietic acid (**6**)), R^2 = 0.950 (7α,15-Dihydroxydehydroabietic acid (**7**)), R^2 = 0.909 (Larixyl acetate (**2**)), R^2 = 0.848 (Larixol (**1**)); R^2 = 0.963 (Lariciresinol acetate (**4**)), R^2 = 0.973 (Lariciresinol (**3**)), R^2 = 0.989 (Rhaponticin (**8**)); R^2 = 0.807 (Piceatannol-5-O-glucopyranoside (**9**)).

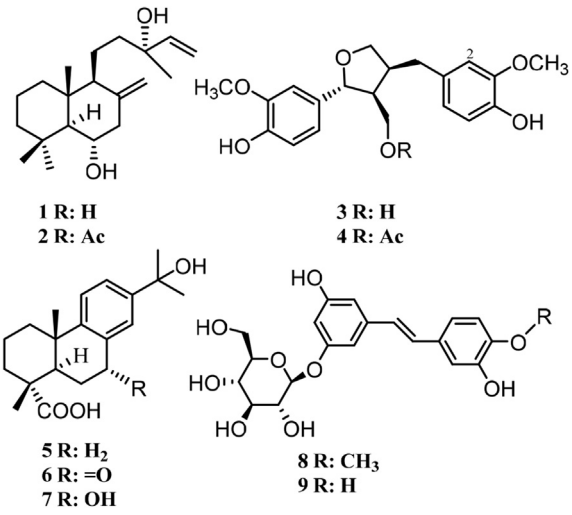

Fig. 4. Structures of pure compounds screened against *Plasmopara viticola* on grapevine seedlings.

cucumber downy mildew, respectively (Scherf et al., 2012; Schuster et al., 2010) and 50 mg mL^{-1} were necessary for 100% efficacy of a *Yucca schidigera* extract against apple scab under controlled conditions (Bengtsson et al., 2009). For an extract of *Inula viscosa*, ED_{90} were between 6.5 and 10 mg mL^{-1} against downy mildew of cucumber, powdery mildew on wheat and rust on sunflower, and 1.25 mg mL^{-1} or below against grapevine downy mildew (Cohen et al., 2006; Wang et al., 2004). Low solubility of less polar extracts in water as well as non-optimised extraction processes may lead to an underestimation of the potential of an extract in early stages of product development. For example, efficacy of a *Reynoutria sacchaliensis* extract against powdery mildew of tomato was much higher when applied as a formulation (Konstantinidou-Doltsinis et al., 2006) and Bowers and Locke (2004) report a significant impact of formulation on efficacy of various plant extracts against *Phytophthora nicotianae*. Development of novel plant protection products follows a tierd approach. To save material, money and time, formulations are often only developed for at least partially optimised extracts. Extraction processes have to be optimised to yield extracts with high amounts of the active compound(s) while using cost-efficient, upscalable extraction methods. Therefore, EC_{50} values of promising candidates should be evaluated in a later stage of product development with a (preliminary) formulation of an at least partially optimised extract.

In the present study, we have identified active compounds in the most promising extracts. The compounds with best efficacies included larixyl acetate (**1**), larixol (**2**), lariciresinol (**3**), lariciresinol acetate (**4**) (from *Larix* sp.), and 15-hydroxydehydroabietic acid (**5**) (from *P. sylvestris*). Most of the tested compounds, or closely related compounds, are known for one or several bioactivities, including anti-inflammatory activities (Demetzos et al., 2001., Chinou, 2005) anti-ulcer activity (Sepúlveda et al., 2005), selective interaction with specific cation channels (Urban et al., 2016), activity against human pathogens (bacteria and fungi like *Candida albicans*) (Salem et al., 2016; Savluchinske-Feio et al., 1997., Savluchinske-Feio et al., 2006; San Feliciano et al., 1993) activity against storage fungi of crops and food (e.g. *Penicillium* sp., *Aspergillus* sp. or *Rhizopus* sp.) (Salem et al., 2016; Savluchinske-Feio et al., 1997) or activity against wood decay fungi (Woodward and Pearce, 1988). In contrast, to our knowledge, this is the first report on activity of the main active compounds (**1**–**5**) against plant pathogenic oomycetes (Mulholland et al., 2016) a phylogenetic group completely unrelated to fungi (Beakes et al., 2012). Toxicological studies on these compounds are necessary before development of these compounds commercially as plant protection products.

In conclusion, we have shown that extracts of several important European forestry species have promising activity against *Plasmopara viticola*. Taken together with the fact that the raw material to produce these extracts is a fast growing, renewable resource available in large amounts at relatively low prices, there is a high potential for a further development of new, sustainable plant protection products against grapevine downy mildew.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cropro.2017.08.018.

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RESEARCH PAPER OPEN ACCESS

Assessment of the risk factors and various patient related attributes influencing hemodialysis

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Key words: Hemodialysis, Renal failure, Intradialytic complications, Quality of life, Kidney transplant.

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Abstract

Renal failure is associated with a variety of comorbid conditions and negatively affects the patients' quality of life. The aim of current study was to assess various patient related attributes effecting on the efficiency of hemodialysis accompanied by vital parameters such as predominant cause of end stage renal disease, intradialytic complications, determination of diet plan impact on hemodialytic patients and analysis of hemodialysis as only treatment of choice in renal failure except kidney transplant. Data of 50 patients were collected from Sheikh Zayed hospital dialysis unit. Statistical analysis was done by SPSS version 22. About 40% patients presented a family history of renal disorders, 70% patients undertook peritoneal dialysis prior to hemodialysis, A-V fistula at lower arm was most recommended location for vascular access, 10% patients used heparin during hemodialysis, 60% patients were on iron and vitamin intake, 80% patients were on limited intake of sodium and fluid, 76% patients were taking potassium and calcium supplements and 80% patients were taking albumin and proteins. About 96% patients were taking Eprex injection and 80% patients were vaccinated. Joint pain and muscular weakness were major complications and 60% patients showed intension of kidney transplant to improve their quality of life. Hereditary factors, diet, fluid intake and lack of awareness play a key role in the incidence of renal failure. If awareness of renal disorders and hemodialysis amongst population could be developed then early diagnosis and better treatment of renal failure will be done along with improvement in the patient's quality of life.

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Introduction

Hemodialysis is considered a cleansing process in which a dialysate similar in composition as blood plasma is used to remove waste products from blood (Carter *et al.,* 2000). The incidence of renal failure is associated with a variety of comorbid conditions like hypertension, diabetes and other cardiovascular diseases (Ritz *et al.,* 1999). It is reported that in young blacks there is an increase rate of end stage renal disease (ESRD) due to diabetes, hypertension and renovascular diseases. The survival rate of ESRD has been improved due to gradual improvements in hemodialytic complications (Foley and Collins, 2007). Hypertension is one of the major factors that lead to renal failure (Wright Jr *et al.,* 2002). Anabolic steroids are considered a secondary cause of renal failure especially in athletes and bodybuilders (Herlitz *et al.,* 2010). Although survival rate has been remarkably increased due to hemodialysis, there are certain complications which arise during hemodialytic procedures including cardiovascular and non-cardiovascular complications. Reasons of the cardiovascular complications are increased arterial stiffness and decreased diastolic blood pressure (Blacher *et al.,* 1998). There is a significant association between nutritional status and hemodialysis efficiency (Qureshi *et al.,* 2002). Major causes of mortality during hemodialysis are hypertension and other cardiovascular diseases, old age, diabetes, infection and malnutrition (Brunner and Selwood, 1992).

In renal failure and hemodialysis, the vitamin balance get disturbed and it may lead to metabolic disorders. However, the use of antibiotics and other agents in hemodialysis to treat infections due to impairment of immune response may also exaggerate hypovitaminosis. These antibiotics also cause the termination of vitamin producing intestinal flora (Kosmadakis *et al.,* 2014). It is suggested that peritoneal dialysis should be done prior to hemodialysis. This is because, in the initial stages of treatment, complete information of the patient disease profile is not available. So, it is safer to undergo peritoneal dialysis during the first two years of dialysis treatment prior to the patient's transfer to hemodialysis (Heaf *et al.,* 2002). Serum albumin level plays an important role in hemodialytic procedures as it is a predictor of nutritional status. Nutritional state of the patient can be determined by body weight, plasma insulin and serum albumin levels. Studies have shown that a low albumin level is associated with an increased death rate (Ikizler *et al.,* 1994).

Vaccination prior to hemodialysis is necessary because the immune system gets weaker in chronic renal failure. Patients on hemodialysis show impaired vaccination response against various infections (Krüger *et al.,* 2001). Data provided in another study has elaborated the significance of vaccination in long term hemodialysis. Findings showed the efficiency of influenza vaccines and support annual vaccination in hemodailytic patients (Scharpé *et al.,* 2009).

Location of fistula is also very important regarding patient's comfort and efficacy of hemodialysis. Bay W.H and coworkers surveyed staff members including dialysis unit nurses, surgeons, technicians and nephrologists regarding their preference in hemodialysis vascular access. This survey showed that A-V fistula was the most preferred access for hemodialysis (Bay *et al.,* 1998).

The preferred treatment for end stage renal disease patients is kidney transplantation. Hemodialysis is a temporary treatment. Several studies were conducted to determine which dialysis method is best for ESRD patients (Fenton *et al.,* 1997). In the United States, hemodialysis is the preferred therapy for end stage renal disease patients. Dialytic technology has greatly extended the life span of ESRD patients (Block *et al.,* 2004). Renal transplant is considered as most satisfactory and promising treatment for renal failure patients. Patients who have undergone renal transplant experience an improvement in quality of life (both physical and social activities) as compared to the patients on hemodialysis (Fujisawa *et al.,* 2000). However, some studies showed that patients who suffered from failed kidney transplant undergoing hemodialysis developed chronic inflammation, erythropoietin resistance and worsened anemia (López-Gómez *et al.,* 2004).

The aim of present study was to assess various patient related attributes effecting on the efficiency of hemodialysis accompanied by vital parameters such as predominant cause of end stage renal disease, intradialytic complications, determination of diet plan impact on hemodialytic patients and analysis of hemodialysis as only treatment of choice in renal failure except kidney transplant.

Material and methods

Data were collected from the fifty patients with end stage renal disease undergoing hemodialysis in Sheikh Zayed Hospital, Lahore. It was a retrospective study in which direct questions were asked from the patients. A questionnaire was developed to gather the data about hemodialysis. Questions regarding history, medications, causes, vaccination, heparin usage, frequency of hemodialysis and Intradialytic complications were asked. Statistical analysis was done by using SPSS version 22.

Results and discussion

Results of duration of hemodialysis have shown (Fig. 1) that 30% patients were on hemodialysis up to 10 years, 50% patients undergoing hemodialysis up to 5 years and 20% were on hemodialysis for 2 years or less. Family history of renal failure has exhibited (Fig. 2) that 40% patients have a family history of renal failure whereas 60% have no family history.

Studies also indicated that hereditary factors play important role in the incidence of renal failure (Freedman *et al.,* 1993). Peritoneal dialysis before hemodialysis results have illustrated in Fig. 3. Approximately, 70% of the patients have undergone peritoneal dialysis prior to hemodialysis as this has more survival advantages due to low incidence of co-occurring disorders (Murphy *et al.,* 2000). It is suggested that peritoneal dialysis should be done prior to hemodialysis.

This is because at the beginning of the treatment complete information about patient disease condition is not available (Heaf *et al.,* 2002).

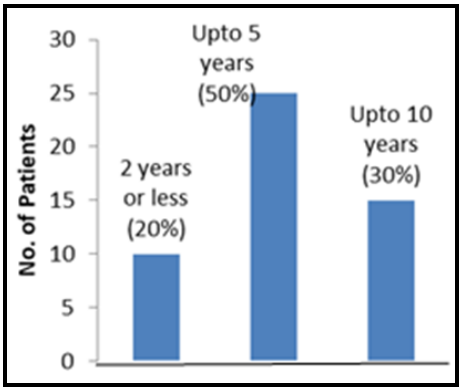

Fig. 1. Duration of hemodialysis.

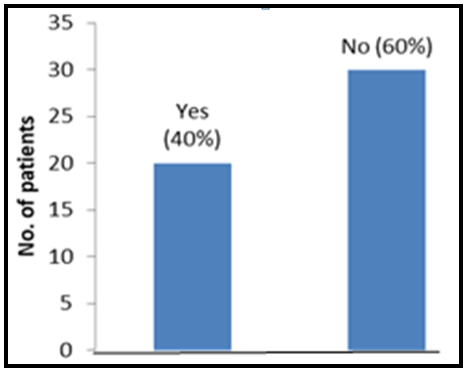

Fig. 2. Family history of renal failure.

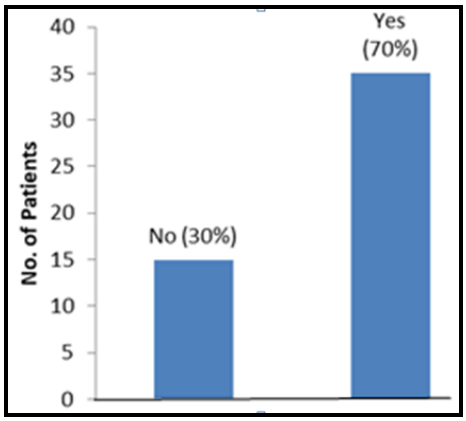

Fig. 3. Peritoneal dialysis before hemodialysis.

There are various factors which are responsible for renal failure. Causes of renal failure are shown in Fig. 4, about 50% have diabetes, 40% are associated with hypertension and 10% of the patients have a history of using the steroids. According to some studies, survival rate of renal impaired patients having diabetes are remarkably low (Ritz *et al.,* 1999).

Many studies have suggested different mechanisms and hypotheses regarding glucose mediated renal damage which include over production of free radicals by mitochondria in hyperglycemic situations

and activation of growth factors present in the kidney due to high levels of glucose (Brownlee, 2001). In 40% of the patients leading cause of renal failure was hypertension. Studies have also reported that hypertension as one of the major factors associated with renal failure (Wright Jr *et al.,* 2002). Furthermore, in 10% of patients steroids contributed largely in the progression of renal failure.

The reason for this progress could be due to increase in body mass and nephrotoxic effects of anabolic steroids (Herlitz *et al.,* 2010). Frequency of dialysis per week results has showed that the 60% patients have undergone hemodialysis twice a week, whereas 40% have gone through hemodialysis thrice a week (Fig. 5).

Conventional hemodialysis is preferred over frequent hemodialysis (frequency of hemodialysis is 5 to 6 times per week) as the later may lead to many complications such as vascular access interventions, imbalance of albumin level, patient depression and cost intensive treatment (Group, 2010).

Results of Heparin used during hemodialysis have demonstrated that 10% patients used heparin during hemodialysis whereas 90% did not use heparin during hemodialysis (Fig. 6). Heparin is used in hemodialysis to prevent clot formation.

Some studies suggested the use of lower effective dosage of heparin than unfractionated heparin as this leads to reduction in excessive bleeding in hemorrhagic complications (Lai *et al.,* 1996).

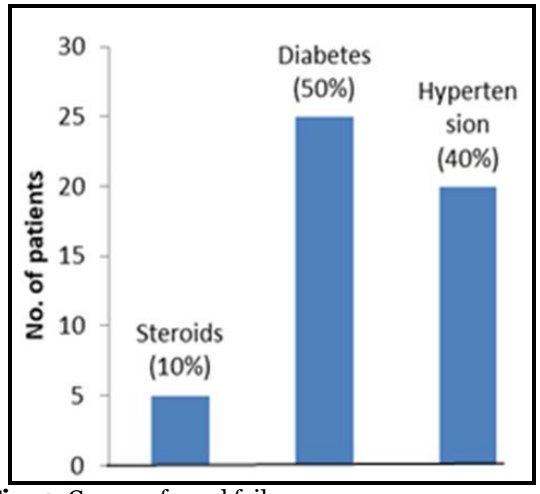

Fig. 4. Causes of renal failure.

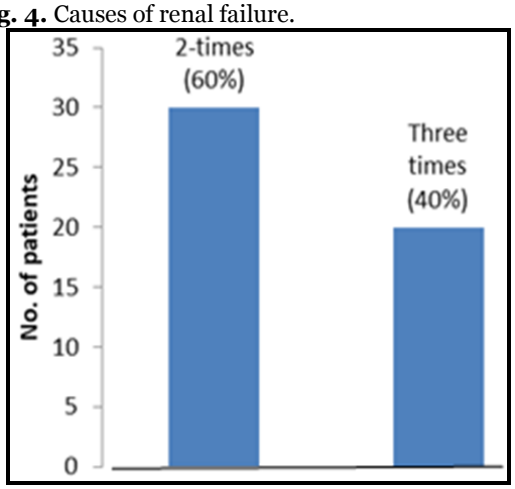

Fig. 5. Frequency of dialysis per week.

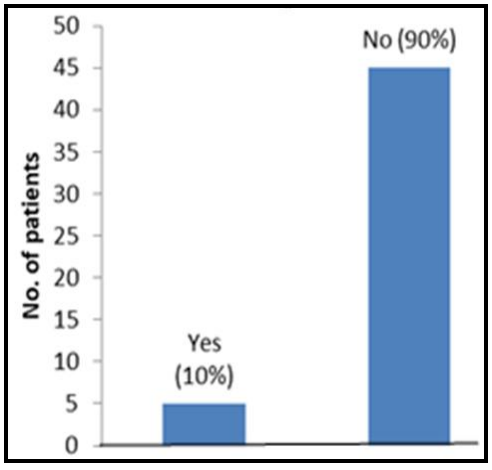

Fig. 6. Heparin used during hemodialysis.

In current research as only 10% patients used heparin while 90% patients did not use any anti-coagulants is may be due to increased risk of prolonged bleeding and clotting time after removal of dialysis needles (Cronin and Reilly, 2010). Location of fistula results (Fig. 7) have exhibited that in 76% patients' fistula were located on lower arm, in 16% patients on

forearm and in 8% patients location of the fistula was on jugular vein. A-V fistula at lower arm is the most recommended location by nephrologists though On the contrary patients prefer forearm vascular access (Bay *et al.,* 1998). Moreover Jugular vein is recommended as temporary vascular access (Fenton *et al.,* 1997). Folic acid, iron and vitamin intake results (Fig. 8) have shown that 60% patients were taking iron, folic acid and vitamins whereas 40% were not taking these supplements. The use of iron is necessary for erythropoietin activity. So, oral ferrous sulfate and intravenous dextran injections are given to compensate iron deficiency. Intake of antioxidant vitamins is also necessary because hemodialysis may generate reactive oxygen species that may lead to vascular disorders.

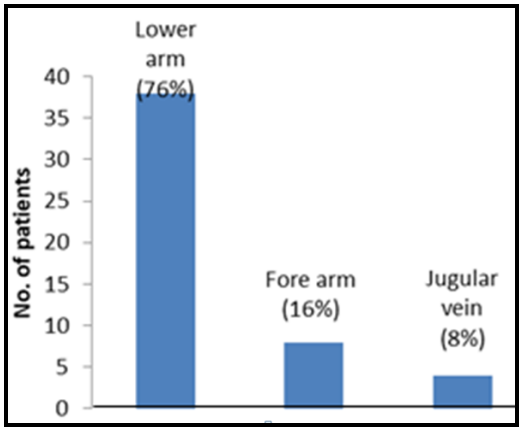

Fig. 7. Location of fistula.

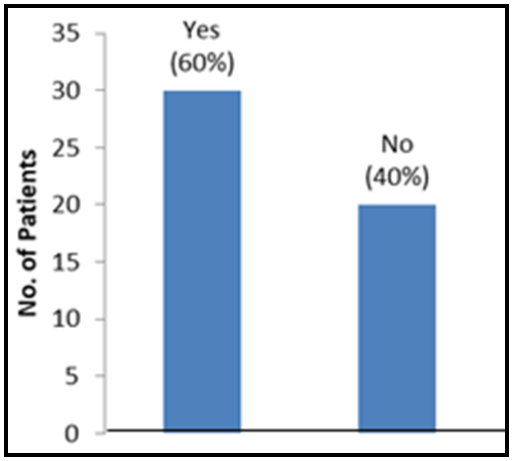

Fig. 8. Folic acid, iron and vitamin intake.

Deficiencies of vitamin C and B complex were particularly reported in patients with renal pathology (Snyder *et al.,* 2004). End stage renal disease (ESRD) is characterized with electrolyte imbalance. That's why potassium and calcium supplements are given to patients on hemodialysis. About 76% of patients were taking limited intake whereas 24% of patients were taking excessive intake of potassium and calcium (Fig. 9). Hyperkalemia is considered as most fatal condition for hemodialytic patients, according to new research hypokalemia is equally fatal and it's responsible for mortality in hemodialytic patients. Hypokalemia occurs due to malnutrition, medications or diarrhea (Choi and Ha, 2013). But calcium supplements are commonly use in hemodialysis as increase concentration of calcium combat Intradialytic hypotension (Maynard *et al.,* 1986). Results of the fluid and sodium intake (Fig. 10) have demonstrated that 80% of patients taking limited intake whereas 20% of patients taking excessive intake of fluid and sodium. Sodium and fluid intake is necessary because hyponatremia occurs in patients on hemodialysis and according to studies lower serum concentration of sodium and fluid lead to patient death (Waika *et al.*, 2011). Protein and albumin intake(Fig.11) have suggested that 80% of patients taking albumin whereas 20% of patients were not taking protein and albumin. During hemodialysis there was a marked decrease in the serum levels of amino acids and proteins.

This decline in concentration of amino acids and proteins may be associated with malnutrition or anorexia. Loss of amino acids and albumin during hemodialysis, using larger pore size membranes, has also been reported by various studies so it is essential for hemodialytic patients to take albumin and protein rich diet (Ikizler *et al.*, 1994).

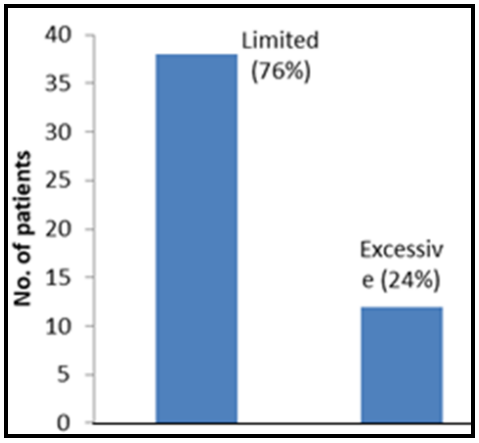

Fig. 9. Potassium and calcium intake.

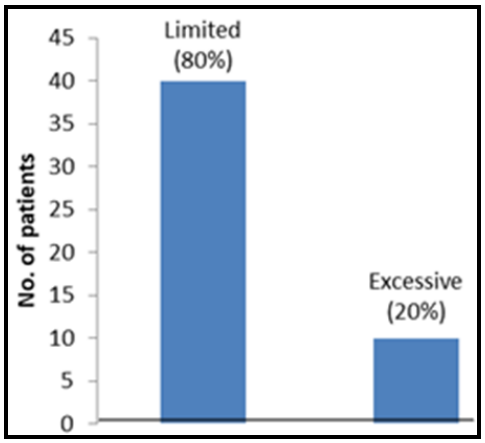

Fig. 10. Fluid and sodium intake.

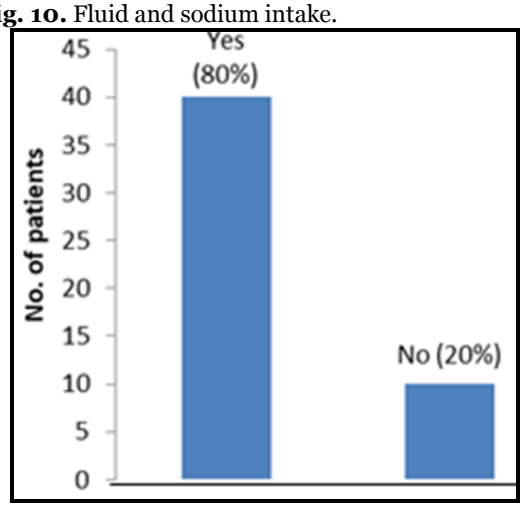

Fig. 11. Protein and albumin intake.

Medication accompanying hemodialysis exhibited that 80% of patients were taking medicines whereas 20% of patients were not taking medicines accompanying hemodialysis (Fig. 12). Data about the injection Eprex given for blood deficiency has exhibited (Fig. 13) that 96% of patients received Eprex injection for blood deficiency whereas 4% of patients did not receive Eprex injection. These include medicines for hypertension and oral anticoagulants. Most common side effect that arises during hemodialysis is anemia because in renal failure kidneys fail to secrete hormone "erythropoietin" (Snyder *et al.,* 2004) and for this reason synthetic erythropoietin is given through injections to patients on hemodialysis.

In present study 96% of patients were taking Eprex injection (alfaepoetina, 4000UI/0,4ml) to manage their hemoglobin level. Now a day's recombinant human erythropoietin is also used for the management of anemia (Fishbane and Berns, 2005).

Renal failure is characterized with impairment of immune system. So, patients of renal failure need to be vaccinated prior to hemodialysis against various infections like tetanus, diphtheria, hepatitis etc. Hemodialysis is considered as reservoir of hepatitis as it is transmitted through blood transfusion not only to patients but also to staff members (Krüger *et al.,* 2001). The current study showed that almost 80% patients were vaccinated prior to hemodialysis as shown in Fig. 14. However, it was indicated that 20% patients showed symptoms of muscular weakness and vomiting while 30% of patients complained about joint pain, 14% presented symptoms of hypotension whereas 10% and 6% of patients had symptoms of hepatitis and stomach upset respectively as shown in Fig. 15. High incidence of hepatitis during hemodialysis is mainly due to blood transfusion procedures. Hepatitis virus is not only transmitted to patients but practitioners are also at high risk (Alter *et al.,* 1986). Preventive measures should be done either by isolating hepatitis patients or through vaccination (Stevens *et al.,* 1984).

Muscular weakness particularly in extremities occurs due to decrease blood pressure, decrease blood volume and disturbances in electrolyte balance. About 14% of patients showed complain of hypotension during hemodialysis due to weight loss, trauma, bleeding disorders and use of antihypertensive medicines. Approximately 20% of patients suffer from nausea and vomiting during hemodialysis due to

decrease in blood pressure and disequilibrium syndrome. Arthritis is considered as most common complication in hemodialysis.

Shoulders, hips and wrist are most commonly affected joints accompanied with stiffness and pain (Kleinman and Coburn, 1989) and affects negatively on quality of life (Kanwal *et al.,* 2017). In addition to the above mentioned complications gastrointestinal irregularities were also commonly reported in patients on hemodialysis. These include abdominal pain, irritable bowel syndrome, constipation and diarrhea. Gastric dilatation due to intestinal pseudo obstruction was also reported during hemodialysis in some studies (Shinoda *et al.,* 1989). Nearly 40% of patients showed the intentions of renal transplantation (Fig. 16), as the renal transplantation is most promising treatment for renal failure (Simmons *et al.,* 1984). However, 60% of patients were not interested and did not prefer renal transplantation as just in case of failure of renal transplantations severe complications were observed like chronic inflammation, infection, anemia etc. (López-Gómez *et al.,* 2004) which ultimately changed the patient's choice of treatment.

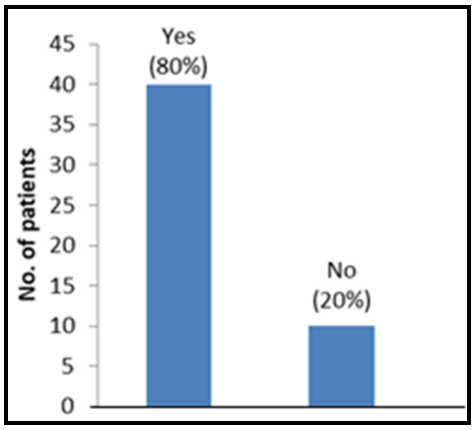

Fig. 12. Medication accompanying hemodialysis.

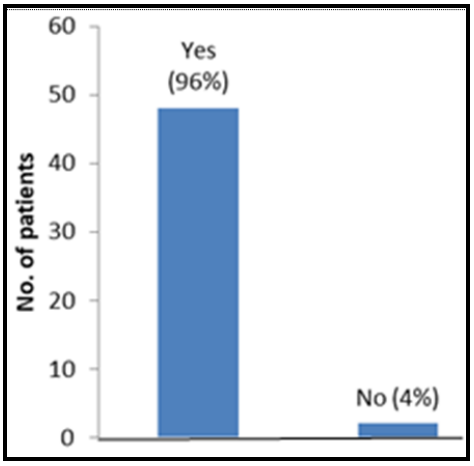

Fig. 13. Injection Eprex given for blood deficiency.

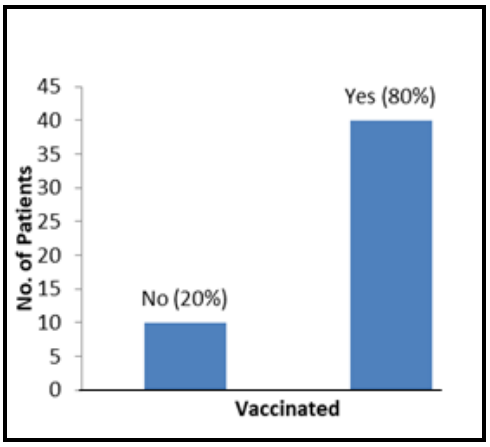

Fig. 14. Vaccinated patients.

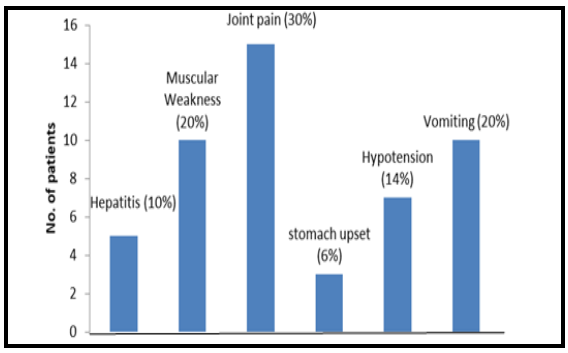

Fig. 15. Complications associated with hemodialysis.

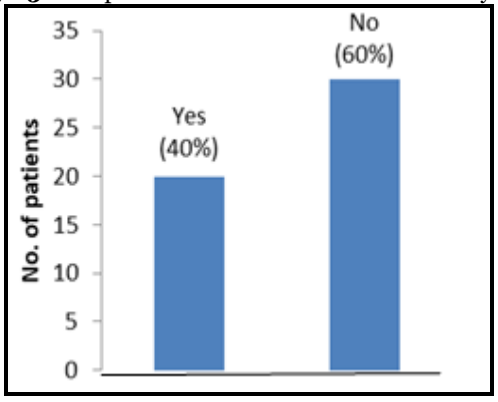

Fig. 16. Intensions for kidney transplantation.

Conclusion

Renal failure is associated with a variety of comorbid conditions. Hereditary factors, diet, fluid intake and awareness play key role in high incidence of renal failure. It is beneficial to undergo peritoneal dialysis in initial stages of the therapy prior to hemodialysis. Furthermore Iron, vitamins, potassium, calcium, sodium and fluid intake are also recommended in hemodialysis depending upon renal status of individual patients. It is suggested that there is still need to develop awareness regarding renal disorders and hemodialysis amongst the population so that prior diagnosis of renal failure and early intervention of kidney malfunction could be done along with improvement in the patients' quality of life.

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Conflict of interest

There is no conflict of interest among authors.

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A COMPREHENSIVE REVIEW ON PHARMACOLOGICAL AND PHYTOCHEMICAL POTENTIAL OF *CASSIA FISTULA LINN*: A MAGICAL HERB

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ABSTRACT

The importance of medicinal plants in treatment of various disorders is undeniable owing to their efficacy, fewer adverse effects and cost effectiveness. *Cassia fistula Linn* is a magical herb and used worldwide for treatment of various pathological conditions. The current article aims to provide a comprehensive review on pharmacological activities and phytochemical constituents present in *Cassis fistula Linn.* Related articles published between 1995 and 2018 were reviewed with help of different database including PubMed, Springer Link, Medline, Google scholar and Science direct. In order to ensure credibility and accuracy of data only those articles were considered which are published only in index journals. *Cassis fistula Linn* is a deciduous tree with grey bark and beautiful yellow flowers. It is naturally distributed in various parts of different countries including Pakistan, India, West Indies, China, South Africa and Brazil. This plant is enriched with numerous therapeutically important phytochemicals such as polyphenols, polysaccharides, flavonoids, tannins, glycosides, anthraquinones and amino acids exhibiting antifungal, hepatoprotective, antimicrobial, anti-inflammatory, analgesic and nephroprotective activities. Various phytochemical investigations and numerous pharmacological studies have demonstrated its significance as an important medicinal plant in cure of various ailments.

Keywords: *Cassis fistula Linn*, Phytochemicals, Pharmacological activities, Polyphenols, Tannins

INTRODUCTION:

In many countries, traditional use of medicinal plants is becoming popular than their allopathic alternatives because of their availability and cost effectiveness [1]. Europeans are also using traditional medicines especially Indian Ayurvedic therapies for treatment of long term diseases. Traditional medicines always have an edge over conventional medicines as later cause dependency in patients and have more undesirable effects. Hence traditional medicines can play an important role in improving patient quality of life by reducing their health issues and sufferings [2].

World Health Organization has included Japanese, Chinese and Ayurvedic traditional medication systems in disease control program due to effectiveness, availability and inherited practice of traditional drugs [3].

Many therapeutically beneficial compounds are being isolated from different herbs and used in treatment of chronic diseases. They are also used as pesticides [4]. According to research, approximately 70-80% of population in developing countries is using herbal drugs for treatment of their ailments and 25% of commercial medicines are synthesized from medicinal herbs [5].

Phytochemicals are chemical moieties that are present in plants naturally. These Phytochemicals are being increasingly used as therapeutic agents as they are capable to produce different pharmacological effects in living organisms. There are various classes of Phytochemicals depending upon their chemical structure and biological action. These include phenols, alkaloids, lipids, proteins, flavonoids and carbohydrates [6].

Plants use secondary metabolites and other bioactive molecules as a shield against vegans and fungi. Plants produce antifungal protein enzymes that kill fungi by hydrolyzing their cell wall. Plants also synthesize certain antifungal proteins which act by combining with membrane constituents of fungi. For example napins are proteins which are not only big source of nitrogen in plant seeds, it also contain certain enzymes like protease inhibitors that protect plants against insects and fungi [7].

Vernacular names:

English: Golden shower, Golden rain tree

Hindi: Amaltas

Marathi: Bahava

Guajarati: Garmala

Tamil: Konai

Urdu: Amaltaas

Botanical description of *Cassia fistula Linn*:

Botanical name: *Cassia fistula*

Kingdom: Plantae
Order: Fabales
Family: Fabaceae
Genus: *Cassia*
Species: *fistula*

Description:

Cassis fistula Linn is a deciduous tree with grey bark and beautiful yellow flowers. Its fruit is cylindrical in shape containing seeds. Seeds are separated by transverse partitions. The diameter and length of fruit pod is 20-27mm and 40-70 cm respectively. Fruit pod is slightly curved and rounded at distal ends [8]. It is decorative, medium sized and rapidly growing plant that shed its leaves at end of season [9].

Habitat:

Cassia fistula Linn is an herb, naturally distributed in various parts of different countries including Pakistan, India, West Indies, China, South Africa and Brazil [10]. *Cassis fistula Linn* is a semi-wild Indian Labernum, commonly known as Amaltas [11]. The main habitat of *Cassia fistula Linn* is Caribbean islands and tropical forests of West Indies [12].

Traditional uses:

Traditionally *Cassia fistula Linn* is used to treat fungal infections. In Indian tribal areas it is also used to cure nasal infections. Its fruit pulp is used as antifungal and has light cathartic and laxative actions. In Asian countries, all parts of plants are used to treat various ailments. It is used as an anti-inflammatory, emollient, cathartic and antipyretic. Plant is also used to cure respiratory tract infections, cardiovascular and liver disorders. *Cassia fistula Linn* also manifests wide range of anti microbial activity and found effective against various skin diseases [10].

PHYTOCHEMICAL CONSTITUENTS:

Cassia fistula Linn contains numerous amounts of primary and secondary metabolites. These metabolites are important for its pharmacological and biological activities. Primary and secondary metabolites include polyphenols, polysaccharides, flavonoids, tannins, glycosides, anthraquinones and amino acids. Decline in concentration of amino acids and proteins can lead to various health hazards [13]. These are present in stem, bark, flowers, roots and fruits of *Cassia fistula Linn* [14].

Bahorun and coworkers in 2005 gave a detailed account on phytochemicals present in *Cassis fistula Linn*. According to their study glycerides and fatty acids are found in abundance in seeds. Among fatty acids, palmitic acid and linoleic acid are present in surplus whereas myristic and caprylic acid occur in traces. Seeds of *Cassia fistula Linn*

are also rich source of proteins and globulins. The same study also reported the presence of Phospholipids and carbohydrates in *Cassia fistula Linn* seeds. Among carbohydrates, a polysaccharide, galactomannan is found in abundance.

Stem bark of *Cassia fistula* is enriched with triterpenoids and phytosterols. It was reported that lupeol and beta sitosterols was found in abundance in stem bark of *Cassia fistula Linn* [15]. Topical use of these steroids can stimulate Hirsutism in young females [16]. Bark and stem are also good source of flavonoids. Fistulaflavonoid B and C are two newly discovered flavonoids from stem and bark of *Cassia fistula*. Their structures were also elucidated using NMR spectroscopic technique. These compounds were found useful against Mosaic virus of plants [17].

A study confirmed the presence of proteins (12%) along with free amino acids such as Glutamic acid, methionine and pyroline and in flower's pollen of *Cassia fistula Linn* [15]. Presence of anthraquinone glycoside was also confirmed in flowers especially rhein which possess excellent anticancer activity [18].

Presence of minerals such as manganese, calcium, potassium and iron was reported in edible fruit of *Cassia fistula Linn* and findings showed that it was good source of minerals as compare to other fruits like orange, apple and peach [15]. Another study confirmed the presence of isoflavone biochanin A, in fruit of *Cassis fistula Linn* and this compound was found effective in treatment of Leishmaniasis [19].

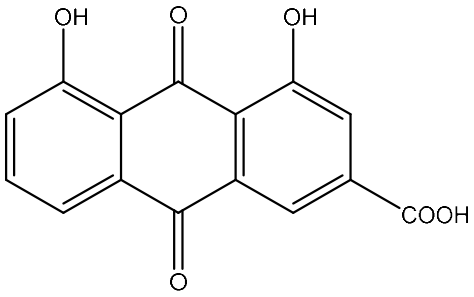
Various studies were conducted to find out nature of phytochemicals present in *Cassia fistula Linn* leaves. Panda and coworkers carried out sequential extraction technique by using solvents of different polarity and investigated various types of primary and secondary metabolites in *Cassia fistula Linn* leaves. According to their study *Cassia fistula Linn* leaves are enriched with alkaloids, carbohydrates, phenolic compounds, tannins, glycosides, proteins, flavonoids, saponins and triterpenoids. The same study also manifested solubility of these phytochemicals in their respective solvents such as concentration of alkaloids, carbohydrates, glycosides and proteins was found maximum in alcoholic and aqueous extracts. Triterpenoids were abundant in petroleum ether, methanol and ethanol extracts whereas phenolic compounds, tannins were found soluble in chloroform, methanol and ethanol [20]. Another study confirmed the presence of alkaloids, anthraquinones, reducing sugars, coumarins

and steroids in air dried powder of leaves [21]. Leaves and pods of *Cassia fistula Linn* was found enriched with anthraquinone glycosides like rhein, aloe-emodin, sennosides and chrysophanic acid especially rhein showing excellent laxative properties [22]. Another study confirmed the presence of flavonoids, phenols, tannins, saponins and alkaloids in leaves of *Cassia fistula Linn* [11].

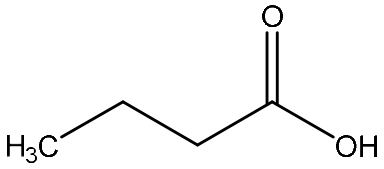
In one study presence of valuable Antineoplastic compounds were reported in pulp and seeds of *Cassis fistula Linn*. These cytotoxic compounds include thymol, oleic acid, furanone and rhein. Moreover butanol extract of *Cassis fistula Linn* seeds is enriched with palmitic acid and inositol. Whereas butanol extract of pulp also contain pyrrolidine [23].

Danish and coworkers gave a comprehensive review on primary and secondary metabolites present in different parts of *Cassia fistula Linn* [8]. These phytochemicals and their respective plant parts are summarized in Table 1.

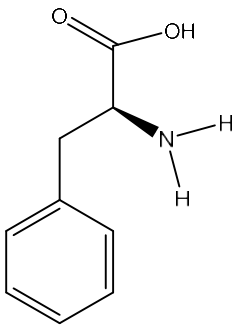
A comparison of total phenols, flavonoids and proanthocyanidins was done in different parts of *Cassia fistula Linn*. Results showed that pods of plant contain highest concentration of total phenols, flavonoids and proanthocyanidins [15]. A graphical representation is given in Figure 1.



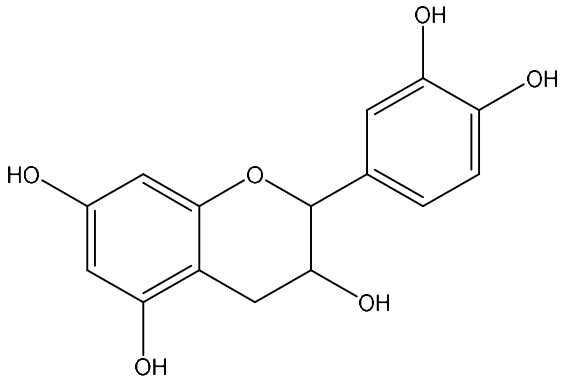
Rhein



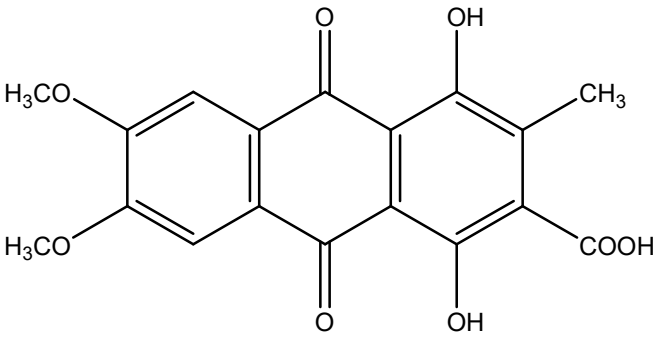
Butyric acid



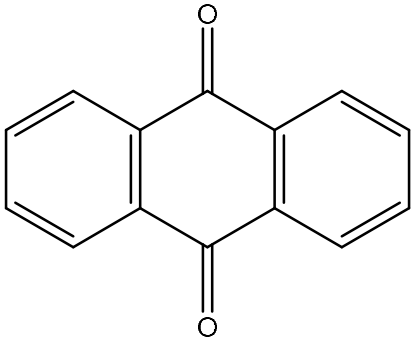
Phenylalanine



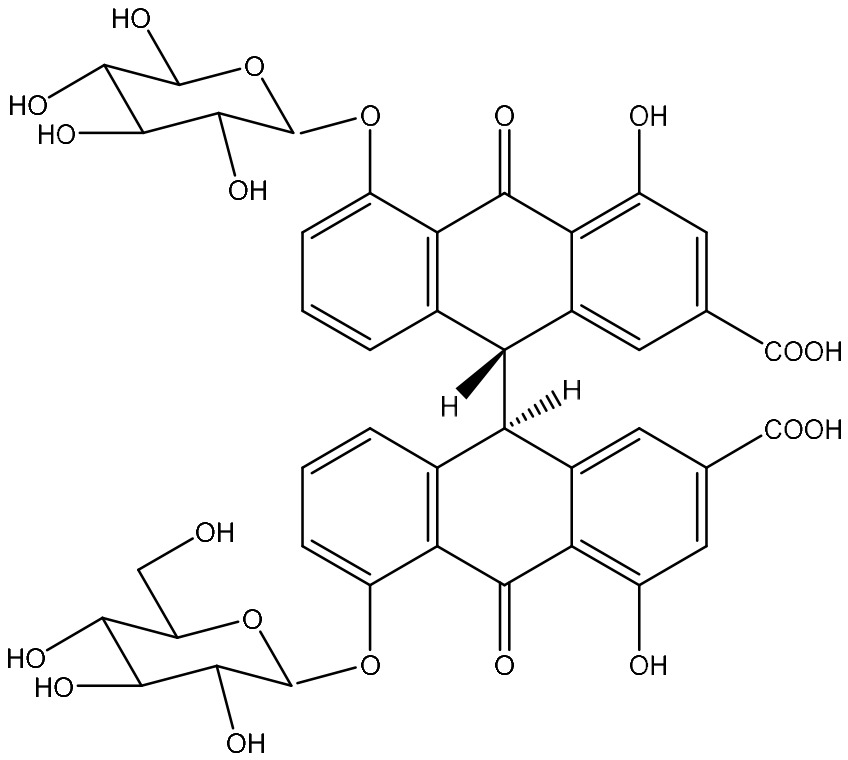
+, - Catechin



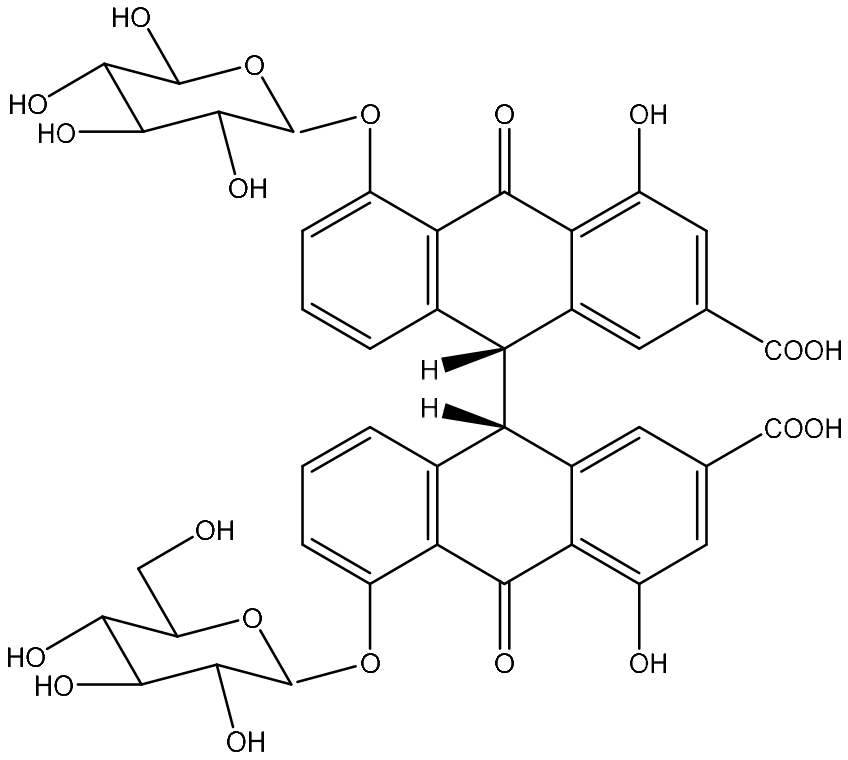
Fistulic acid



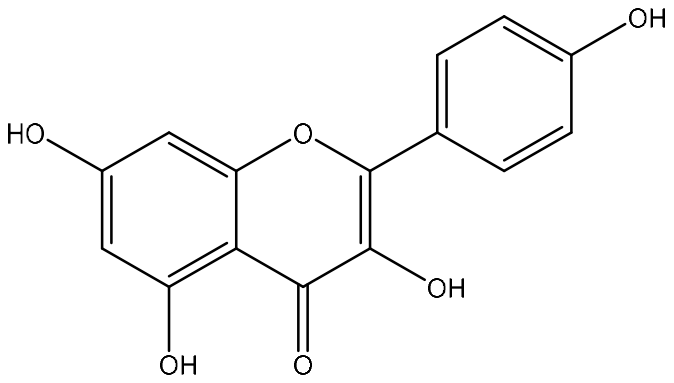
Anthraquinone



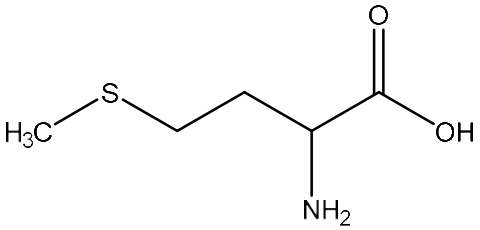
Sennoside A



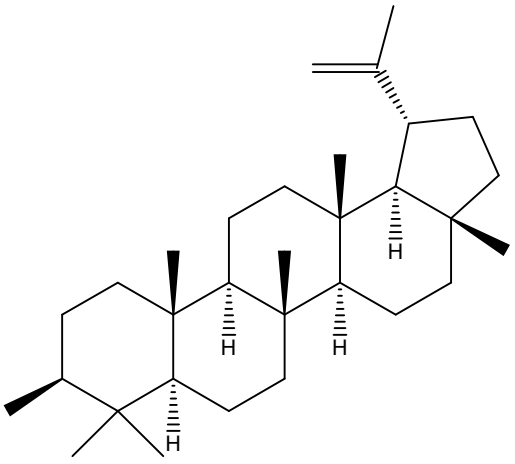
Sennoside B



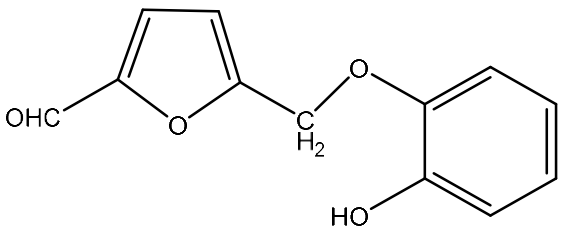
Kaempferol



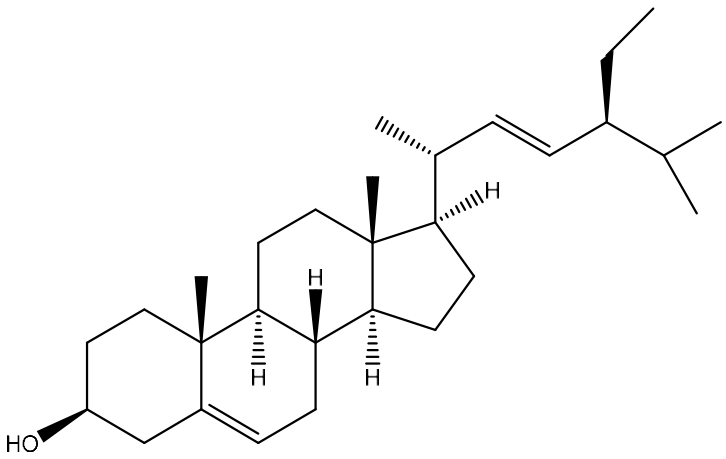
Methionine



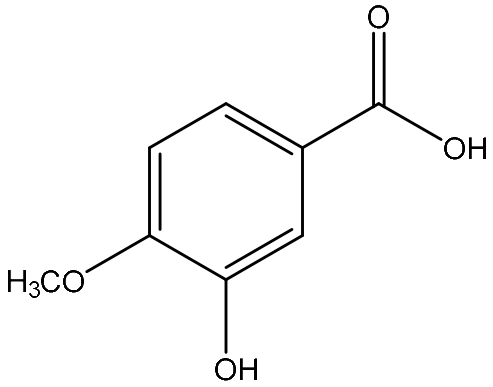
Lupeol



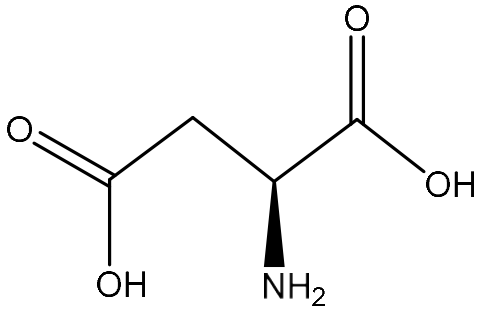
5-(2-hydroxyphenoxymethyl) furfural



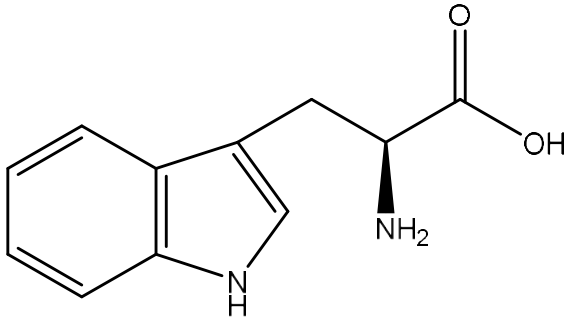
Stigmasterol



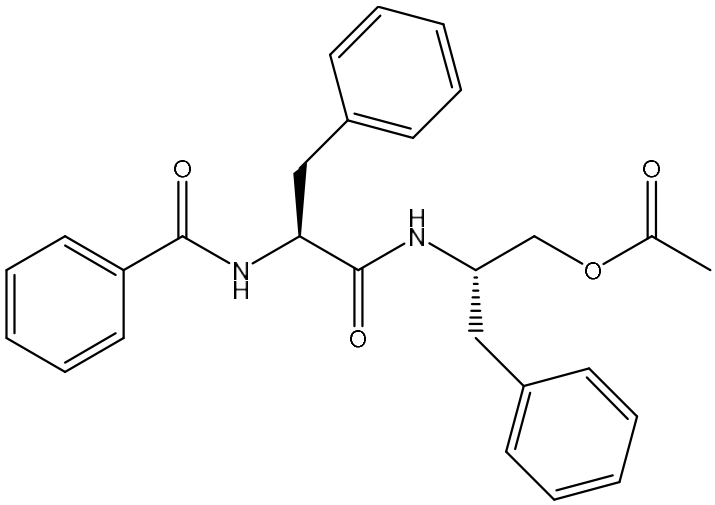
Isovanillic acid



Aspartic acid



Tryptophan



Aurantiamide acetate

Structures of some Phytochemicals of *Cassia fistula Linn*.

Table 1: Phytochemicals in different plant parts of *Cassis fistula Linn*.

Cassis fistula (parts)	Primary and Secondary Metabolites
Seeds	Amino acids, galactomannan, Kaempferol, fistulin, triglycerides, vernolic acid, stetculic acid, furfural derivatives, oxyanthraquinones, galactomannan free sugars and amino acids.
Leaves	Sennoside A and B, Rhein, Tannins, nerolidol, hexadecanone, phytol, Volatile oils.
Flowers	Bianthraquinone glycosides, ceryl alcohol, aurantiamide acetate, rhein and volatile oils.
Pulp	Gluten Oxalates, oxyanthraquinones, albuminous starch, sugar, gum, astringent matter.
Root bark	Tannins, phlobaphenes, betulinic acid, rhamnetin 3-*O*-gentiobioside, oxyanthraquinone, 7-methylphyscion.
Pod	Sennoside A and B, Oxalic acid, rhein, 5-nonatetracontanone, anthraquinones derivatives.
Stem bark	Flavonol glycosides, Xanthone glycosides, dimethoxyflavone arabinopyranoside.
Fruit	Methionine, aspartic acid, leucine, catechin, 1,8-dihydroxy-3-methyl anthraquinones, Glutamic acid, 5-nonatetracontanone, triacontane.
Aril part	Isovanillic acid, palmitic acid, Oleic acid, sterols, stigmasterol, lupeol, emodin, ziganein, scopoletin.

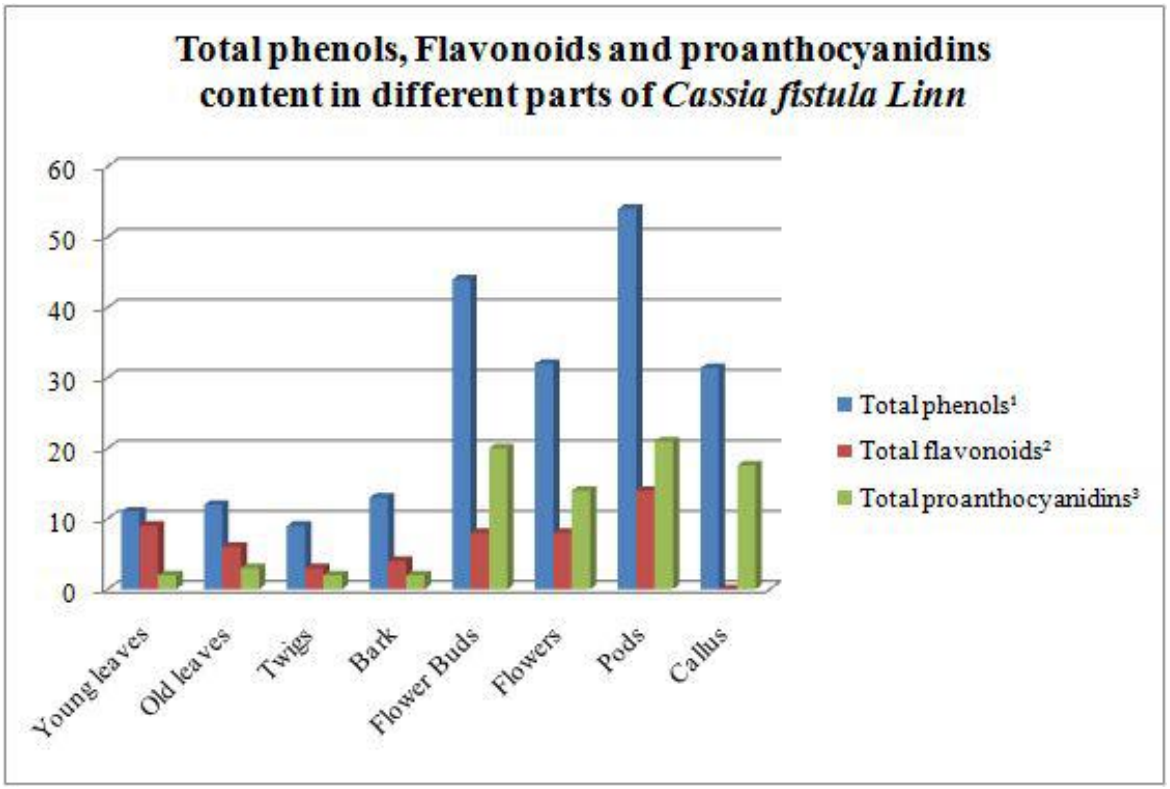


Figure 1: Graphical representation of Total phenols, flavonoids and proanthocyanidins contents in different parts of *Cassia fistula Linn*. Concentration of phenols, flavonoids and proanthocyanidins was found maximum in pods.
[1] = mg gallic acid equivalent/g dry weight
[2]= mg quercetin equivalent/g dry weight
[3]= mg cyaniding chloride equivalent/g dry weight

PHARMACOLOGICAL ACTIVITIES:

Anti oxidant activity:

Cassia fistula (Linn) flowers showed excellent antioxidant activity when its aqueous extract was used in alloxan induced diabetic Albino rats. It not only decreased the levels of harmful free radicals like peroxides, hydroperoxides but also normalized low

levels of catalase, glutathione reductase and superoxide dismutase which are key antioxidant enzymes [24]. These reactive oxygen species can cause mitochondrial damage and inhibition of energy producing cycle [25].

A comparison of antioxidant activity was done between sexual and asexual parts of *Cassia fistula Linn*. Antioxidant activity is strongly associated with presence of phenols and flavonoids contents. It was reported that sexual parts of *Cassia fistula Linn* showed good antioxidant activity than asexual parts as the former had higher levels of phenol and flavonoids contents [26].

Cassia fistula Linn bark also posses significant antioxidant and anti-inflammatory activities. Aqueous and methanolic extracts of plant bark manifested excellent anti-inflammatory activity both *in vitro* (Hydroxyl and nitric acid) and *in vivo* (CCl_4 and $FeSO_4$) models. Experiments also showed that *Cassia fistula Linn* bark is non toxic even at higher doses [27].

Alcoholic extracts of *Cassia fistula Linn* pulp, leaves, flowers and stem bark also exhibit good antioxidant activity. Significant antioxidant activity was reported in stem bark followed by leaves and flowers while pulp showed minor activity as level of phenolic constituents was found low in pulp [28].

Cough Suppressant Activity:

Cassia fistula Linn leaves were tested for antitussive activity by developing induced cough model in mice. Findings showed that methanolic extracts of leaves manifested excellent activity and results were equivalent to other commercially available cough suppressant drugs [29].

CNS Depressant and Analgesic Activity:

Cassia fistula Linn seeds also possess various pharmacological activities. Among these most prominent is central nervous system depressant activity. It exerts its CNS depressant action by acting synergistically with benzodiazepines and other sedatives. Moreover methanolic extract of seeds also intensify analgesic actions of drugs [30].

Antipyretic Activity:

Cassia fistula methanolic extracts has ability to alleviate high body temperature. Its temperature alleviating effect was tested on two groups of rats. In one group effect on normal body temperature was measured. In second group pyrexia was instigated by yeast. Results showed that *Cassia fistula Linn* shoot methanolic extract decrease normal body temperature up to 3hrs at dose of 200mg/kg whereas at dose of 400mg/kg antipyretic effects was observed up to 6hrs.

In yeast instigated fever group it was observed that decrease in elevated temperature is correlated with dose of extract.

Purgative activity:

Laxative and purgative effects of *Cassia fistula Linn* was evaluated on guinea pig intestine. It was reported that *Cassia fistula Linn* pods infusion show excellent purgative action and it can be comparable with Senna leaves. Toxicity profile of *Cassia fistula* pods was also analyzed and findings showed that it does not possess any toxic effects even at high dose of 6600mg/kg [8].

Anti Hepatotoxic Activity:

Leaves of *Cassia fistula* were found to be effective in treatment of liver damage. In order to investigate hepatoprotective activity, *in vivo* model consisting of Albino rats was developed. Liver toxicity in these rats was induced using diethyl nitrosamine. To these rats ethanolic extracts of *Cassia fistula Linn* leaves were administered orally for 30 days. Results proved that *Cassia fistula* leaves are indeed beneficial to cure liver damage and liver injuries [31].

Antineoplastic Activity:

Seeds of *Cassia fistula Linn* possess variety of pharmacological activities. Methanolic extract of *Cassia fistula Linn* seeds demonstrated remarkable anticancer properties especially against ascites tumor in mice (this tumor is commonly known as Ehrlich cell carcinoma) by decreasing number of cancerous cells. Its exact mechanism of action is unknown. But it is believed that it exerts is Antineoplastic action by formation of membrane vesicles and by declining the rate of cell division of cancerous cells. Antineoplastic studies were also performed on cancer inflicted mice by administering doses of *Cassia fistula Linn* seed extract. It was observed that at dose of 100mg/kg not only hematological profile of these rats improved but also they lived longer comparative to other cancer bearing rats that were not treated with *Cassia fistula Linn* seeds [32].

Apart from seeds, *Cassia fistula Linn* bark also manifested excellent Antineoplastic and anti cancer activities. To investigate these effects animals were treated with a strong carcinogen and powerful immunosuppressant, dimethyl benzanthracene that provoked Hamster Buccal Pouch Cancer in animals. These animals after induction of cancer were treated with oral doses of *Cassia fistula Linn* bark extracts. Results revealed that bark extracts inhibit the development of skin cancer specially epidermis squamous cell carcinoma. It is thought that *Cassia fistula*

Linn bark exerted this action through its antioxidant and toxin removing action [8].

Antifungal activity:

Cassia fistula Linn found to possess promising antifungal properties as well. Leaves of *Cassia fistula* has been tested against various fungal species including *Candida albicans*. *Cassia fistula Linn* leaves extracts were prepared by using solvents of different polarity namely methanol, acetone and diethyl ether. Among all these extracts methanolic extract of *Cassia fistula Linn* leaves manifested excellent antifungal activity and its effect was similar to that of commercially available antifungal agents [33].

Cassia fistula Linn flowers are found effective not only against fungi but also against a variety of gram negative and gram positive bacteria. Assay of different extracts of *Cassia fistula Linn* were analyzed for its anti microbial activity. All extracts especially of chloroform, methanol and water showed good activity. *Pseudomonas aeruginosa* was found very liable to these extracts. In ethyl acetate crude extract, compound responsible for anti microbial activity was 4-hydroxy benzoic acid; its structure was elucidated using X-ray crystallography X-ray crystallography techniques. This compound was effective against various pathogenic species of fungus Trichophyton and Epidermophyton [10].

Antileukotriene Activity:

Cassia fistula Linn also exhibit anti allergic activities by inhibiting production and secretion of leukotrienes. Mechanism behind this anti allergic activity was oxidation reduction reactions causing inactivation of 5-lipoxygenase that ultimately leads to inhibition of leukotrienes production [34].

Anti-inflammatory Activity:

Cassia fistula leaves also demonstrate outstanding effects to alleviate inflammation such as gout which have negative impact on patient quality of life [35, 36]. *In vivo* model of albino rats were used to evaluate anti inflammatory activity of leaves extracts. Oedema was induced in these rats using carrageenan and dextran. *Cassia fistula Linn* leaves extract showed significant anti inflammatory activity [37].

Cassia fistula Linn bark was analyzed for its antioxidant and inflammation alleviating activity *in vivo* using two groups of Albino rats' namely acute and chronic groups. Inflammation is induced in these two groups using carbon tetrachloride and ferrous sulphate. Methanolic and water extracts demonstrated excellent anti inflammatory activity. This activity is due to suppressing peroxidation of lipids. Factors that affect the

anti inflammatory activity include dose/ conc. of extracts and production of oxidative specie. Toxicity studies of bark extracts were also performed. It was found out that bark extracts have very low levels of toxicity even at higher doses [27].

Another study demonstrated anti inflammatory action of *Cassia fistula Linn* bark. To analyze these effect acute inflammatory models of albino rats were used using aqueous and methanolic extracts. Both extracts show outstanding anti inflammatory activity especially against granuloma induced by implantation of cotton ball. Mode of action involves decrease in concentration of serum enzymes like alkaline phosphatase and acid phosphatase. Anti inflammatory activity produced by these extracts was equivalent to effect produced by commercially available standard anti inflammatory agent like Diclofenac [8].

Antimicrobial Activity:

Antimicrobial activities of *Cassia fistula Linn* were compared with other herbal extracts like *M. ferrea*. It was found out that *Cassia fistula* demonstrated more promising antimicrobial activities including both antifungal and antibacterial properties. Compounds responsible for this activity were isolated and found effective against various gram positive and gram negative bacteria.

Different proteins were isolated from seeds of *Cassia fistula Linn*. After purification these proteins they were employed against various streptococcus species and were found effective against most of strains [38].

Cassia fistula Linn extracts also exhibit pesticidal activity as it is found useful against a variety of parasitic nematodes. Death rate of nematodes was reported 100%, 48hours and 72 hours after administration of *Cassia fistula Linn* extracts. Encouraging results were not obtained after 24 hours as death rate of parasite was reported minimum [39].

Stem bark of *Cassia fistula Linn* possess outstanding antimicrobial properties. Alcoholic and aqueous extracts were found most effective. Both extracts showed excellent activity against *Streptococcus aureus*. Although alcoholic extract show better antibacterial activity than aqueous extract. Even *S. aureus* that were unaffected by chloramphenicol were also liable to alcoholic extract of *Cassia fistula Linn* stem bark extract [40].

Larvicidal and Ovicidal Activity:

Leaves of *Cassia fistula Linn* also found to possess pesticidal activity. When leave extract of varying concentrations applied topically, they not only inhibit hatching of eggs but also makes them non functional to produce any disease [8].

In another study larvicidal activity of *Cassia fistula Linn* leaves methanolic extract was tested against *Culex quinquefasciatus* and *Anopheles stephensi*. The methanolic leaf extract show more activity against *A. stephensi* at larvae stage. Less larvicidal activity was reported against *C. quinquefasciatus*. Thus it was proved that *Cassia fistula Linn* does possess good larvicidal activity [41].

Lipid Lowering and Hypoglycemic Activity:

Studies have revealed that *Cassia fistula Linn* posses outstanding lipid lowering and antidiabetic activities. To evaluate its antidiabetic activity, n-hexane extract of bark was administered in varying doses (0.15, 0.30, 0.45g /kg of body weight) to albino rats for one month. Diabetes was induced in these rats by intraperitoneal injection of streptozotocin. Results showed that blood glucose level of those diabetic rats was remarkably reduced. Lipid profile of these diabetic rats was also evaluated. It was reported that lipid profile remarkably improved at dose of 0.45g/kg body weight. It is thought that hypoglycemic and hypocholestrolemic action of *Cassia fistula Linn* was due to presence of ploy phenols and antioxidant constituents [42].

Wound Alleviating Activity:

Wound healing potential of *Cassia fistula Linn* was explored by using its methanolic leaves extract in different *in vivo* wound models in rats. Leaves extract in 5 and 10% w/w concentration was incorporated in ointment base. In these concentrations the ointment was found to be effective in treating both types of wounds. The wound healing effect was equivalent to standard control drug nitrofurazone in every aspect [29].

Wound healing activity of *Cassia fistula Linn* was demonstrated in another study using albino rat model. Ointment base formulation of alcohol leaves extract was prepared and wound healing effect was analyzed on wounds infected with *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It was observed that wounds treated with *Cassia fistula Linn* ointment showed faster healing, better tissue reanimation and rapid wound reduction rate. These findings provided a scientific proof of traditional use of *Cassia fistula Linn* in wound management [43].

Antidiabetic Activity:

A study was conducted to explore antidiabetic effects of *Cassia fistula Linn* and to identify its mechanism of action. For this purpose hydroalcohlic extract of *Cassia fistula Linn* was used in *in vivo* model of alloxan induced diabetic rats. The antidiabetic effect was analyzed at dose

levels, 200 and 400mg/kg. Glibenclamide was used as standard control. In parallel antioxidant (*in vitro* model) and lipid profile (*in vivo* model) of this extract was also evaluated. It was reported that the extract showed marked decrease in blood glucose level in fasting rats. Extract also decrease the level of free radical species lipid profile of diabetic rats was also improved [44].

Antidiabetic potential of *Cassia fistula Linn* roots was evaluated using alpha amylase inhibition and glucose diffusion assay as *in vitro* models. For this purpose root extracts of n-hexane, ethanol and ethyl acetate were prepared. Among this ethanol root extract showed outstanding results in inhibiting the activity of alpha amylase. Ethanol root extracts also manifested significant antidiabetic potential in glucose diffusion assay as compare to ethyl acetate and n-hexane extracts [45].

Different parts of *Cassia fistula Linn* plant were subjected to comparative analysis of antidiabetic potential. For this purpose, aqueous extracts of all parts of plant were prepared. An *in vivo* model of streptozotocin induced diabetic rats was developed. These diabetic rats were treated for 21 days with extracts of different plant parts at dose levels of 250 and 500mg/kg. It was reported that bark and leaves methanolic extract showed significant decrease in blood glucose levels than other plant parts [46].

Hypoglycemic and pain reducing potential of ethanolic extract of *Cassia fistula Linn* stem bark was evaluated using *in vivo* models of rats and mice. For hypoglycemic activity albino rat model was selected and for analgesic activity *in vivo* model of mice was chosen. Writhing test method was adopted to evaluate analgesic effect. In this method, body contortions movements of rats like twisting and squirming were observed using Diclofenac as standard control. For evaluation of hypoglycemic potential, diabetes was induced by alloxan and glucose tolerance test was adopted using Metformin as standard control. Results revealed that ethanolic extract of *Cassia fistula Linn* stem bark appreciably reduced blood glucose levels in alloxan induced diabetic rats. Contrarily, for analgesic effect, ethanolic extract reduced contortions movement of rats up to 60% but results were not comparable to the standard control [47].

Antidiabetic potential of *Cassia fistula Linn* whole fruit was determined using its petroleum ether extract in *in vivo* rat model. Toxic profile of *Cassia fistula Linn* fruit petroleum ether extract was evaluated and it was found out that extract was safe and did not produce any signs of toxicity. Diabetes

was induced using Streptozotocin. It was reported that petroleum ether extract of *Cassia fistula Linn* fruit significantly reduced blood glucose levels in diabetic rats [48].

In vitro antihypertensive activity of *Cassia fistula Linn* was also tested using alpha amylase inhibition assay. The enzyme alpha amylase cause hydrolysis of starch and glycogen and convert them into monomers like maltose and glucose. So, alpha amylase inhibition is very effective criteria to measure antidiabetic potential of any sample. Results of this assay showed that *Cassia fistula Linn* possessed excellent antidiabetic potential [49].

Cassia fistula Linn bark also exhibit outstanding antidiabetic potential. To evaluate antihyperglycemic activity of *Cassia fistula Linn* bark, its extracts were prepared in alcohol and ethyl acetate. *In vivo* albino rat's model was developed and diabetes was induced by using alloxan. Results revealed that there was marked reduction in blood glucose levels of ethyl acetate extract treated diabetic rats. Moreover Cassia *fistula Linn* bark also improved lipid profile of these diabetic rats [50].

In another study antidiabetic potential of *Cassia fistula Linn* bark was reported. To evaluate its antihyperglycemic activity aqueous and alcoholic extracts of *Cassia fistula Linn* bark (400mg/kg) was administered to alloxan induced diabetic rat model. The study revealed that both aqueous and alcoholic extracts of *Cassia fistula Linn* bark tremendously reduced blood glucose levels of diabetic rats. These findings provide scientific proof of traditional use of *Cassia fistula Linn* for treatment of diabetes related ailments [51].

Due to threatening increase in prevalence of type 2 diabetes, use of medicinal plants is gaining popularity in treatment of type 2 diabetes. For this purpose, a study was carried out to evaluate antidiabetic potential of stem bark of *Cassia fistula Linn* stem bark against type 2 diabetes. Results showed that *Cassia fistula Linn* stem bark significantly decrease blood glucose level without having any harmful effects on urea and creatinine levels [52].

CONCLUSION:

For centuries herbal remedies have been used for prevention and management of diseases. In rural areas people still rely on medicinal herbs for treatment of their ailments. In this regard *Cassia fistula* is considered one of the most important herbs and it is widely used in traditional medicinal systems of India, China and Japan. It is also found to possess antibacterial, antipyretic, anti-inflammatory, antidiabetic, antioxidant, antitussive, wound

healing and antifungal properties. Phytochemical profile of *Cassia fistula Linn* showed that it is rich source of primary and secondary metabolites such as lipids, proteins, carbohydrates, tannins, phenols, flavonoids, glycosides, volatile oils and essential oils. The current review has summarized pharmacological activities and phytochemical constituents of almost all parts of *Cassia fistula Linn* including leaves, stem, stem bark, roots, seeds and flowers. It was found that less attention has been paid on fruit wall of plant. No study has been conducted to explore phytochemical and pharmacological potential of fruit wall of *Cassia fistula Linn*. Moreover there is need to standardize herbal medicines to ensure safety and efficacy.

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REVIEW PAPER OPEN ACCESS

Current situation of breast cancer in Pakistan with the available interventions

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Key words: Breast, Cancer, Pakistan, WHO, Health burden.

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Abstract

The aim of the current review is to demonstrate and indicate the lack of resources and strategies for the diagnostic and palliative care of the patients suffering from breast cancer. As, cancer is a major disease worldwide, it is presiding the errand of medics. In all cancers, breast cancer is a pronounced issue in females all over the world, including Pakistan. It is at the topmost of the list of both genders. There are some institutes working as the registry of cancers in Punjab and Karachi, but are insufficient and its working should be expanded to all provinces of Pakistan to meet the required cancer statistics inclusion nationwide. There are major concerns in collection of the data like; government negligence, lack of awareness, ignorant attitude towards disease management and much more. For the prevention and reduction in the prevalence of disease, the health official must ponder over current state seriously by developing the proper institutes, organized system and implementation of awareness programs to educate people to undergo regular examination for early detection of disease throughout Pakistan.

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Introduction

Cancer is a chief concern and a leading cause of mortality worldwide. Cancer is a non-communicable disease characterized by uncontrolled abnormal division of cell (Shewach and Kuchta, 2009). In the past few years, an upward trend was seen in health burden due to prevalence of non-communicable diseases (Ghoncheh *et al.*, 2016). This is in turn has adversely effected the quality of patient's life (Ashiq *et al.*, 2017). In Asiatic countries like Pakistan there is an ongoing increase in the progression of breast cancer and it has become one of the prominent causes of death (Agarwal *et al.*, 2007). Annually, about 3 million new cancer cases are recorded and so far more than 2 million deaths due to cancers have been reported only in Asia. If current disease advancement is continued and existing preventive measures are not provided, then it is estimated that the number of new cases in Asia will be raised to approximately 7.1 million continually till 2020 (Park *et al.*, 2008). According to the global report generated by WHO in 2016, 56.9 million deaths were reported among which 15.2 million deaths occurred due to ischemic coronary illness and stroke, comprising almost 54% of the total mortality rate recorded. However the remaining 3.0 and 1.7 million deaths occurred in different time frames i.e. in 2016 and 2018 respectively, due to chronic obstructive pulmonary infection and lung cancer (alongside trachea and bronchus malignancies) separately. Furthermore, in the United States in 2017 almost 1,688,780 new cancer cases were reported, out of which roughly 6, 00,920 cases were pronounced dead (Abbosh *et al.*, 2017).General trend states that almost half of the cancer patients reside in developing countries as they contribute more towards the prevalence of cancer than any other developed nations since the resources required to combat the disease are meager (Parkin *et al.*, 1993). According to cancer statistics breast cancer contributes to the second highest prevailing cancer and it cause hormonal imbalance that can lead to abnormal growth of facial hair, a condition known as Hirsutism (Mahmood *et al.,* 2011). Breast cancer is one of the major causes of mortality after Lung cancer that comes first as the leading cause of death (Ghoncheh *et al.*, 2016). The proportion of the incidence of breast cancer is quite high in developed and under developed nations. Furthermore, data suggests it is the most frequent type of cancer diagnosed in women since each 1 in 10 cancer cases belongs to the breast cancer. It is seen that worldwide each year over a pair of million women is square diagnosed with breast carcinoma (Ferlay *et al.*, 2010; Ginsburg *et al.*, 2017). An increased trend of occurrence in breast cancer prevalence is mostly seen in the women of age group between thirty to thirty nine years old (Usmani *et al.*, 1996). Chemotherapy used in treatment of breast cancer can lead to renal failure which is associated with variety of comorbid conditions and negatively affects patient's quality of life (Tanveer *et al.*, 2019). There are varying indicative factors that are responsible for contributing to the advancement of the etiology of breast carcinoma such as genetic science, diet, chemicals, and environmental factors (Hafeez *et al.,* 2009). Nanoparticles toxicity is also one of the major causes of genetic mutations that can prove to be carcinogenic as these nanoparticles are present in smoke, paints and even in air (Tanveer *et al.*, 2014).

Current situation in pakistan

Pakistan, the 6th most crowded nation on the globe and is a republic in south central Asia. It shares universal topographical limits and social similitudes with India in the east and southeast, Iran and Afghanistan on the west and northwest and China and Soviet Central Asian Republics in the north. Political unsteadiness and economic destruction have ruined our establishments in general and health department specifically (Bhurgri *et al.*, 2006; Hanif *et al.*, 2009). Pakistan is facing many plights especially financial constraints being a lower middle income state of South East Asia (Khan, 2017). In Pakistani population there is an upward trend in the predominance of cancer and has effected all genders (Sarwar and Saqib, 2017). Thus, the diagnosis of breast cancer is obtained almost a decade earlier in Pakistan as compared to other western countries (Somoro *et al.*, 2018). Almost 30 cancer hospitals are currently operative In Pakistan and are providing

their services to patients effectively. This includes11 cancer hospitals in Sindh, 7 in Punjab and Khyber Pakhtunkhaw, 3 in Capital city Islamabad and one in Baluchistan, Gilgit and Baltistan each. Conversely, there is no cancer hospital in Kashmir (Pak info medics, 2018). There is Pakistan being a developing nation faces a twofold weight of diseases with a noteworthy occurrence of cancers and there is a continuous rise in the pattern of risk elements, profile and frequency of cancer (Bhurgri *et al.*, 2006; Hanif *et al.*, 2009). The data of breast cancer statistics in Karachi alone illustrate the proportion of breast cancer to be 69.1 per 1 million out of which most of the cases presented were in stages of III and IV (≥ 50%) (Ahmad *et al.*, 2006).According to the study conducted in the Baluchistan region of Pakistan breast cancer came out to be quite common among the Pushtoon ethnic group with age ranges 41-50.Among these the most prevalent form observed was invasive ductal carcinoma followed by invasive lobular carcinoma (Baloch *et al.*, 2012).

In an investigation, it was estimated that a total of 28,740 patients, cancer was detected and subjects got registered at INMOL during the period from 1st January, 2000 to 31st December, 2009. Among those almost 6,718 patients reported having breast cancer. The proportion of occurrence of breast cancer among women was 41% (38% in the first five years and 42% in the later five years). The ratio among the female and male counterpart was 100:2.

As far as regional statistics is concerned Lahore came out to be the most cancer prevailing city (Table 1) with almost 46% of patients with small number residing in adjacent cities.

Table 1. Breast cancer statistics in different cities of the Punjab (Khoker *et al.,* 2012).

Cities	Percentage of patients with breast cancer
Lahore	46%
Gunjranwala	7%
Sialkot	6%
Sargoda	4%
Shiekhupura	4%
Kasur	3%
Okara	3%
Sahiwal	3%
Faisalabad	3%
Gujrat	3%

Only 7% of patients were from Gujranwala, 6% of Sialkot, 4% each of Sargodha and Sheikhupura and 3% were from each Kasur, Okara, Sahiwal, Faisalabad and Gujrat (Khoker *et al.,* 2012). Registering a disease that has any association with the cancer is quite challenging here. Thus, no national information is accessible on frequency of cancer in Pakistan. Therefore, there is an upward trend in the prevalence of breast cancer which is occurring at the increment of 150K cases every year with 50-60% deceased rate (Shabbir *et al.*, 2019). Breast cancer constitutes 33% of all cancers in women admitted at Nuclear Medicine, Oncology and Radiotherapy Institute (NORI) Islamabad (NORI Annual Report 2010-2012). Survival strategies for breast cancer are quite divergent and vary broadly according to numerous factors. Formation of metastases is one major causative factor for short survival in breast cancer (Rezaienzadeh *et al.*, 2012). Some initiatives are now being taken by the Government of Pakistan to control the current situation. One such initiative is taken by Pakistan health research committee (PHRC) working under service of national health administrations, control and coordination, Government of Pakistan, i.e. the intention of building up a cancer registry by affiliating and bridging all real open and private

division hospitals of the nation. PHRC is likewise dealing with awareness and mindfulness of cancer in public by leading distinctive exercises and commending disease days like strolls for breast cancer, in addition to this, dissemination of mindfulness material would be like wise done throughout the country (PHRC, 2018). Moreover, there was also another such cancer record maintaining entity that was formed in 1966 named as Karachi Cancer Registry (KCR) which later on became the main perceived populace-based cancer registry in the region. Nationwide considering Karachi only, south region of Pakistan, records for less than 1% of the aggregate populace of the country. Dr. Yasmin Bhurgri chief of KCR was an efficient principle researcher who worked and gathered major information on cancer statistics but departed around 2 years prior hoping that her work will be preceded. Currently KCR is working with joint efforts of GICR, IARC and ENCR (IACR, 2018). Over the years, some other cancer treatment offices have endeavored to advance cancer enrollment in the district. One such focus is the Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH and RC), Lahore, Pakistan, which has a hospital-based cancer registry presently working for around 19 years. World Health Organization (WHO) provides an organized framework that provides global guidelines on cancer enlistment and restorative coding data. The SKMCHRC cancer registry is one of a single archive of the whole nation that follows all these WHO guidelines and maintains records of this restorative coding data. Thus, SKMCH and RC has been able to provide this Information to hospital experts help them assess childhood cancer in Lahore region efficiently (SKMCH&RC, 2018). Furthermore, the Punjab Cancer Registry (PCR) was set up in February 2005 for taking decisions on tumor insights in the locale at general mass level. At first, endeavors were made to gather data from cancer patients in the region of Punjab and ultimately got successful on July 1, 2008 in executing the collection of information on cancer analysis and treatment among the inhabitants. In 2014, the registry expanded its operation in four different regions of Punjab including Faisalabad, Sheikhupura, Kasur, and Nankana Sahib. In 2016, this registry expansion was further progressed by the inclusion of Sialkot and Narowal locale. Currently, the registry has around 39 individuals to exhibit who are part of more than 20 foundations. The Central Office of the Registry is situated inside the Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH and RC), Lahore, Pakistan. Thus the running of the registry is likewise supported by SKMCH and RC (PCR, 2018). PCR data has a profound importance as it has been used to provide cancer estimates for Pakistan in GLOBOCAN 2012 report in response to a call for data by the International Agency for Research on Cancer (IARC) (GLOBACAN, 2012). Although a number of studies have been done worldwide to estimate survival of breast cancer patients with regard to demographics and clinic pathological features but no such study has been done in Pakistan (Humera *et al.*, 2015). The reason for this could be attributed to inability of reaching out to those cancer patients who doesn't seek medical treatment. Cancer treatment is quite costly and only few hospitals have managed to provide free of cost detailed treatment designs which include Shaukat Khanum Memorial Cancer Hospital (SKMCH), Bait-ul-Sukoon Cancer Hospital and Children Cancer Foundation Hospital. These hospitals do offer free/sponsored treatment designs but through zakat subsidizes or Bait ul Maal nevertheless gaining treatment from these channels is an extensive and tedious process as candidates are more than government's liability (Begum, 2018). Poor implementation of policies leads to the increased prevalence of disease. There is a need to promote awareness about the disease to the local masses so that earlier diagnosis and treatment of disease can be made possible with their timely inclusion at hospital which would in turn help in maintaining cancer statistics at hospital registry (Ashiq *et al.*, 2018). Although a number of studies have been done worldwide to estimate survival of breast cancer patients with regard to demographics and pathological features but no such proper investigation has been done in Pakistan. Contrary to Europe and America, in Pakistan more than 60% of breast cancer

patients exist at an advanced stage of the disease. This means the biological behavior and disease etiology of breast cancer in Pakistani population is diverse (Humera *et al.,* 2015). Free cancer screening, maturity advantages and healthcare, construct of Medicare and Medicaid-like programs, and sponsored pharmaceutical drug programs have been enforced. During this, background the National Cancer Control Program (NCCP) developed as a part of the National Action (Fig. 1) to set up an evidence-based way for the timely detection, management, cure and palliation as suggested by the World Health Organization (Bhurgri *et al.*, 2006).

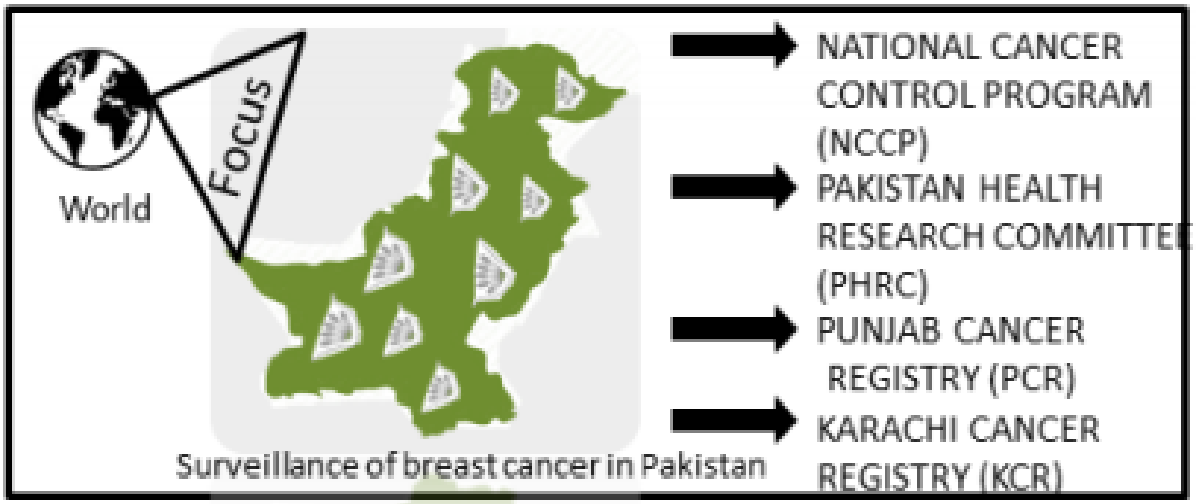

Fig. 1. Surveillance of breast cancer in Pakistan.

Conclusion

Cancer is still a huge issue in both developed and emerging countries, especially breast cancer. In Pakistan, breast cancer is found to be a chief form among all other types of cancers. There is an upward trend in progress and prevalence of breast cancer due to lack of facilities and awareness among the patients.

Currently no authentic data is available regarding morbidity and mortality of breast cancer which could be due to lack of patients' follow up. Besides this, even though cancer registries have been developed and our functional but they seem to be in their preliminary stage for designing the protocols for diagnosis and treatment of the cancer and are not adequate to provide complete statistics on breast cancer for early disease prevention. For the deterrence in the prevalence of disease, the health official must ponder over the current situation seriously by developing the proper institutes, organized system; implementation of awareness programs to educate people for regular checkup for early detection of disease all over Pakistan.

Conflict of interest

There is no conflict of interest.

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A comprehensive review on anti-cancer medicinal plants

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Abstract
Cancer is a major health concern and one of the leading causes of death around the globe. Medicinal plants contain numerous phytochemicals and their usefulness for the treatment of cancer has been proven scientifically. The current review is aimed to provide a comprehensive knowledge about the herbal plants with established anti-cancer activity. For this study, different databases were used, including: PubMed, Google Scholar, Scopus and MEDLINE and literature search were done without any year limit. Studies have reported that numerous classes of phytochemicals have tumor inhibitory effect and these could be used for the cure of cancer. In this era, where the drug development process and its subsequent marketing and surveillance often take decades, the emerging evidence of the beneficial anti-cancer properties of plants have proved to be a mercy. There is need to explore more about the mechanism of action of phytochemicals having anti-cancer properties and further to ensure the medicinal plants safety and efficacy to justify their rational use for the treatment and management of the cancer.

Keywords: cancer, chemotherapy, medicinal plants, phytochemicals, tumor

1. Introduction

Cancer has been designated worldwide as a second leading cause of death. The prognosis of cancer, despite concerted efforts in innovating and improving current cancer therapies, remains dismal.In Asiatic countries, there is an ongoing increase in the progression of breast cancer and it has become one of the prominent causes of death. Annually, about 3 million new cancer cases are recorded and sofar more than 2 million deaths due to cancers have been reported only in Asia [1]. A limited or sporadic response has been associated with highly specific blockage of the single signaling pathway. Thus, a new paradigm for anticancer therapy that targets multiple signaling pathways has emerged by using targeted therapies [2]. Over the last decade, a significant change in the treatment of cancer has been viewed owning to the emergence of small molecule inhibitors and monoclonal antibodies, together which are termed as Targeted Therapies. These therapies have taken an integral place in the treatment of a wide array of common malignancies, including pancreatic, colorectal, lung and breast cancers. Despite the fact that targeted therapies are associated with several adverse effects including cardiac dysfunction, thrombosis and hypertension, they are well tolerated than cytotoxic chemotherapy which is the reason for paving the replacement of this hallmark of medical treatment of cancer with new targeted therapies [3]. Moreover chemotherapy used in treatment of breast cancer can lead to renal failure which is associated with variety of comorbid conditions [4]. In the past few years, an upward trend was seen in health burden due to prevalence of these comorbid conditions. This is in turn has adversely affected the quality of patient's life [5]. Two major factors that determine the success as well as the effectiveness of a targeted therapy is firstly the target's nature and secondly, the targeting characteristics of the agent developed to focus the identified target [6]. Nonetheless, to arrest the insidious nature of this dreadful disease one should not merely focus on targeted therapies as they too are embodied with severe side effects. Growing evidence has revealed that the use of folk medicine plant preparations provides a suitable alternative for rationalized allopathic drugs. In recent years, the anti-tumor actions of various phytochemicals have been thoroughly investigated and being increasingly used as therapeutic agents as they are capable to produce different pharmacological effects in living organisms [7]. Hoping for a better cure options, more and more patients together with medical health personnel are turning towards complementary and alternative traditional healthcare systems.

Cancer is a debilitating disease characterized by the formation of lumps and masses of tissues referred to as tumors which are formed due to uncontrollable division of damaged cells. The normal physiology of circulatory, nervous and digestive system is compromised and disrupted by the uncontrolled tumor growth. Benign tumors tend to demonstrate limited growth and characteristically stay located in one spot. On the other hand, the dangerous malignant tumors show invasion of distant tissues, by moving through blood and lymphatic systems from their primary genesis location and also promote angiogenesis. These metastasized tumors create dangerous circumstances with very narrow therapeutic options [8]. Among various causes of cancer, nanoparticles toxicity is one of the major causes of genetic mutations that can prove to be

carcinogenic as these nanoparticles are present in smoke, paints and even in air [9].

Irrespective of its categories groups-herbs, shrubs or trees, the chemotherapeutic agents derived from natural botanical sources are attributed to being almost 60%. Recent research throws limelight over the fact that plants provide a paramount source of potential chemotherapeutic agents that are yet to be exploited. Significant therapeutic properties are possessed by numerous plants against common malignancies including colorectal, breast and lung cancers. Broadly, chemotherapeutic agents derived from plants are categorized into twelve major categories namely; alkaloids, phenylpropanoids, terpenoids, glycosides, aldehydes, lignans, lipids, unsaponified lipids, nucleic acids, polysaccharides, proteins and unidentified compounds. Since centuries, secondary metabolites isolated from plants have been used in folk medicine for the treatment of diseases including cancer. Some of the notable medicinal plants possessing anti-tumor activity are *Aloe vera, Helianthus annuus, Azadirachtaindica, Curcuma longa, Curcuma zedoaria,* and *Euphorbia tirucalli* [10].

Table 1: Active principles of Anti-Cancer Plants

Plant name	Botanical Origin	Family	Constituents	Properties
Aloe vera	*Aloe barbadensis*	Liliaceae	anthraquinonones	Strengthens the immune system and anti-tumor activity [11].
Sunflower	*Helianthus annus*	Asteraceae	Nevadensin	Anti-cancer agent [12]
Indian Lilac (Neem tree)	*Azadirachtaindica*	Meliaceae	Quercetin quercitrin	Potent Anti-Cancer activity [13].
Turmeric	*Curcuma longa*	Zingiberaceae	Curcumin	Anti-proliferative agent [14].
White turmeric	*Curcuma zedoaria*	Zingiberaceae	8,9-Dehydro-9-formyl-cycloisolongifolene, 6-ethenyl-4,5,6,7-tetrahydro-3,6-dimethyl-5-isopropenyl-trans-benzofuran, eucalyptol, and γ-elemene	Anti-cancer agents through the induction of apoptosis
Indian tree spurge	*euphorbia tirucalli*	Euphorbiaceae	Euphol	Cytotoxic effect on cancerous cell lines [15].
Hyptis fasciculata	*Hyptis fasciculata*	Labiatae	isoquercitin	Anti-tumorigenic action
Apple	*Malusdomestica*	Rosaceae	quercetin glycosides: hyperoside, isoquercitin, avicularin, rutin and a high concentration of quercitrin [16].	Chemopreventive & anti-cancer properties
Skullcap	*Scutellariabaicalensis*	Lamiaceae	Flavonoids [17, 18].	Tumor growth inhibition CDK1 Inhibitor
Bitter Orange	*Citrus aurantium L*	Rutaceae	phenethylamine alkaloids octopamine, synephrine, tyramine, hordenine and N-methyltyramine [19].	Chemopreventive& Anti-inflammatory actions
Pomelo	*Citrus maxima*	Rutaceae	Flavonoids (Naringin)	Tumor growth inhibition
Beet Root	*Beta Vulgaris*	Amaranthaceae	Betalains, phenolic compounds [20].	Anti-cancer & Anti-inflammatory
Kidney Breans	*Phaseolus vulgaris*	Fabaceae	polygalacturonic acid lectin [21].	Anti tumorigenesis& anti-inflammatory
Green tea	*Camellia sinensis*	Theaceae	Epigallocatechin [22].	Chemopreventive, anti-inflammatory& anti-tumorogenesis
Selfheal	*Prunella Vulgaris*	Lamiaceae	Phenolic compounds [23].	Anti- tumore proliferation & metastasis [24].

Citrus maxima

The habitat of *Citrus maxima* belonging to the family *Rutaceae*is Asian tropical areas. Neohesperidin and naringin are the two major flavanones isolated from the seeds of the citrus fruits and mediate anti-tumor and anti-inflammatory through its antioxidant activity by promoting free radical scavenging and reducing oxidative stress by counteracting reactive oxygen species in H_2O_2–treated HepG2 cells *in vitro*. On the contrary, flavonoids mediate a beneficial effect on signal transduction in cell proliferation and angiogenesis and thus, play a prophylactic role. As postulated by an experiment conducted by Kudusenand coworkers [25]. A decrease in tumor volume and an increase in the lifespan of nonviable tumor cell count is shown to be attributed to anintraperitoneal administration of 200 and 400 mg/kg BW of a methanolic extract of *Citrusmaxima* [26].*Citrus maxima contains an abundant concentration of naringin, a bioflavonoid, which has demonstrated significant anti-cancer potential through a dose& time dependent inhibitory effect on AGS cancerous cells [27]. Naringin is also actively* involved in the inhibition of FAK kinase activity, inhibition of FAK/mmps pathway, thus paving way for the suppression of cell invasion and apoptosis [28]. The mammalian enzyme activity is significantly influenced by flavonoids particularly protein kinase activity is modulated to a considerable extent. The interference of flavonoids with protein kinase activity is a major contributor to their anti-cancer potential [29]. The anti-tumorigenesis property of flavonoids is also linked to the biological activity of their active metabolites [30]. The methanolic extract of Citrus maxima leaves, in vitro, produces a twofold effect; a significant increase in life expectancy coupled with a leucocyte count decrease [25]. *Citrus aurantium* L.

The *Citrus aurantium* L of the family *Rutaceae*,has a spectrum of biologically active constituents, most importantly, phenethylamine alkaloids octopamine, synephrine, tyramine, hordenine and N-methyltyramine. Consumption of this citrus fruit has been associated with a lowering in the incidence of cancer, as evidenced by the lower cancer prevalence amongst the mediterraneans where

a considerable portion of diet is composed of Citrus aurantium[19].Anti-inflammatory, antioxidant, and anti-tumorproperties have long since been attributed to the Korean *Citrus aurantium* L. The flavonoids isolated from the specie mediate, in a dose dependent manner, the inhibition of HepG2 cell proliferation. Various downstream targets of phosphoinositide-3-kinase/Akt pathway – P-4EBP1 and P-p70S6K and pAkt levels are shown to be reduced by flavonoids isolated from Korean *Citrusaurantium* L. In addition, an increase ratio in the expression of Bax/Bcl-xL coupled with a decrease in Bcl-2 and Bcl-xL and an increase in the expression of cleaved caspase 3, Bax and Bak is exhibited by cells that have been treated with flavonoids extracted.In flavonoid treated Hep-G2 cells, there has also been observed a loss in the motichondrial membrane potential [31].*The complex low molecular weight polysaccharide known as citrus pectin, abundantly found in the peel and pulp of a number of citrus fruits including citrus maxima, characteristically possesses sugar carbohydrate residues abundantly. The citrus pectin, has anti-tumorigenesis properties that specifically target cancerous cells of the gastrointestinal tract through a Bcl-xL-mediated process which results in a causing an apoptosis dampening in susceptible cells [32]. In addition, the galactomannans, isolated from Citrus aurantiumalso have the ability to scavenge free radicals and mediate anti-cancer activity at a very low concentration [33].*

Scutellariabaicalensis

Scutellariabaicalensis of the family Labiatae is a popular Chinese herbal medicine that has been used since ancient times for its anti-influenza, anti cancer properties as well as for its ability to effectively combat oxidative stress. Recently, a study was conducted byJi Et.al to elucidate various biologically active therapeutic constituents which were isolated through the use of various column chromatography techniques and semi-preparative HPLC. The successfully isolated constituents were then identified by the utilization of the process of HRE-SIMS and NMR spectroscopic analysis. The utilization of MTS assay to detect the cytotoxic effects of the isolated and identified constituents against HepG2, SW480, and MCF7 human cancer cells revealed that a majority of the free flavones exhibited such activity with a 61.2% inhibition rate at 10 μM.This discovery further highlights the fact that flavones being an important effective constituent of most anti cancer plants can be used as chemical markers in order to ensure quality control of pharmaceuticals or herbal medicines containing these biologically active components [34]. Baicalein, a flavone isolated from *Scutellariabaicalensis, demonstrates a potent anti-cancer activity in pancreatic cancer cells through the inhibition of erastin induced ferroptosis [35]. Inaddition to neuroprotective and anti-inflammatory effects, baicalein also mediates an analgesic effect in eliminating chronic bone pain induced by cancer. The effect is thought to be associated with an inhibition of inflammatory cytokines TNF-alpha and IL-6 expression [36]. Baicalein has also shown to possess crucial ability of being a CDK1 inhibitor. The only CDK1 involved and thought to have a major contribution in the process of cell proliferation is cyclin dependent kinase 1. Thus, the activity of baicalein against CDK1 is of tremendous importance and poses as a new anti-cancer agent to be exploited [18].*

Malus Domestica

One of the most popular and widely cultivated fruit trees in the world, *Malusdomestica*contains phenolic compounds and flavonoids which are attributed to have strong anti-oxidant properties. The apple leaves have shown to contain quercetin glycosides: hyperoside, isoquercitin, avicularin, rutin and a high concentration of quercitrin [16]. The best known and described property of phenolic compounds is their anti-oxidant property. The cellular dysfunction characteristic of cancer and various other diseases is a result of highly reactive oxidant molecules that mediate their degenerative effects through the capture of electrons leading to chemical structure modifications. The quercetin glycosides are powerful anti-oxidant molecules that act by scavenging free radicals or reactive oxygen species, thus, the chemopreventive properties of quercetin glycosides is attributed to their anti-oxidant and oxidative damage prevention effects.By using the technique of cancer cell viability assays for a comparison between quercetin, hyperoside, isoquercitin, and quercitrin reveals that due to glycosylation, isoquercitin is a promising candidate for chemotreatment because it confers more advantageous pharmacological changes its analogue quercetin. The effect of isoquercitin on pancreatic cancer progression was proliferation inhibition, promoted apoptosis and induced cell cycle arrest in those pancreatic cancer cells that were in G1 phase [37].

Hyptis Fasciculata

The *Hyptisfasciculata* of the family Lamiaceae, whose aerial parts serve as a valuable source of isoquercitin, is well known for its capacity to interrupt the glioblastoma cell growth. Though the exact mechanism through which isoquercitin reduces glioblastoma cell growth is not nonebut it is thought that it does by reducing cyclin D1 levels and increasing p27 levels [38].Artificially stressed cells when treated with *Hyptis fasciculate* extract exhibit the free radical scavenger properties of the plant. In addition to its scavenging properties, the extract has also shown to increase the tolerance of cells to H_2O_2 stress thus amplifying the anti-oxidant properties [39].

Curcuma zedoaria

Curcuma zedoaria possesses a valuable essential oil with cytotoxic effects which are particularly efficient against non small lung carcinoma cells and mediates its therapeutic effect through the induction of apoptosis. The notable effects of the isolated essential oil are an increase in the population of sub-G1 cells along with an increased annexin-V binding levels, subsequent cleavage and caspase -3, -8, and -9 activation. In addition to these changes, an increase in the poly (ADP ribose) polymerase has also been observed [40].The principle physiologically active anti-tumor therapeutic agent of *Curcuma zedoaria* is α-Curcumene. However, the anti-tumor effect is proposed to be a synergistic effect of multiple anti-tumor agents and a reliance on a single agent effect has not been reported. An inhibition in growth of sarcoma 180 is mediated by protein-bound polysaccharides and single entity polysaccharides of this specie. In addition, it is evident from recent research that an anti-proliferative effect is brought about particularly on MCF-7, ovcar-3 cells as well as on HL-60 cells. Nonetheless, it is proposed that the principle anti-tumor

effect of *Curcuma zedoaria* is through the induction of apoptosis [41].

Intraperitonial administration of *Curcuma Zedoaria* crude extract produces direct cancer inhibiting actions including anti- angiogenesis effect and a suppressive effect on B16 melanoma cells in pulmonary metastasis. In experimental animals, curcumin isolated from *Curcuma Zedoaria* extract provides highly protective effects from chemically induced liver damage [42].

Aloe vera

The extract of *Aloe vera*follows a dose dependent and time manner to induce cytotoxicity against hepatocellular carcinoma cells. The induction of apoptosis is mediated through an increased expression of TP53 gene and a decrease in the expression of BCL-2 gene [43]. The hydroxy-anthraquinone of *Aloe vera*, Aloe Emodinpossesses a strong anti- neural ectodermal tumor activity both in-vitro and in-vivo. In mice models, this biologically active agent exhibits an inhibition of neuro-ectodermal tumor growth coupled witha combined and severe immunodeficiency without the mediation of any appreciable lethal effects. Moreover, the compound does not cause an inhibition inhemo-poieticprimogenitor cellproliferation nor does it mediates an inhibition in the proliferation of normal fibro-blasts [44].

Among other biologically active compounds isolated from Aloe-vera extracts are feruloyl, cinnamoyl, caffeoyl aloe-sin and p-coumaroyl. The ability of Caffeoyl aloe-sin toproduce a preventive effect on immune suppression induced by UV-B is shown through the utilization of contact-hypersensitivity reaction technique. In addition to thispreventive action, the enzymatic activities of tyrosine-hydroxylase and Dopa oxidase induced activities of monophenol mono-oxygenase is inhibited by aloe-sin in lysates of human melanocyte cells [45]. Another anthra-quinone isolated from aloe vera leaves is barbaloin which alone plays a major role in life span prolongation of animals that have undergone tumor transplantation procedure [46].

Helianthus annuus

Sunflower plants' multifaceted actions have gained it a tremendous popularity in traditional and western medicines alike. Phyto-esterol isan active principle which is rich in the seeds of Helianthus annuus and provides a strong preventive action against the development of breast cancer. In vivo, it has been demonstrated that the most abundant phyto-sterol, betasitosterol, not only causes a growth inhibition in tumor cells of specific types but also mediates a reduction in tumor size as well as extent of metastasis. Evidence from a recent study highlights the positive correlation between reduced risks of premenopausal breast cancer and associated high consumption of sunflower seeds. In skin tumor mouse models, helianthus annuus oil exhibits a chemo preventive potential by providing 40% protection against tumor development. In addition to chemo preventive characteristics, helianthus annuus also possesses significant anti inflammatory capacities [47]. Sunflower seeds are a source of a pharmacologically active bioflavonoid; nevadensin, which possesses an array of significant biological actions including tumor suppression and growth inhibition. The extract of striped sunflower seed cotyledons show a significant oxygen radicals scavenging capacity. Due to the strong antioxidant capacity of sunflower seeds they can mediate a significant preventive action against the development of cancer and other oxidative stress related diseases if consumed daily [12].

One of the most prominent aims of research efforts in the field of natural products is the search for anti-neoplastic agents which show a characteristically high affinity for the inhibition of signaling pathways in tumor cells without having a significant effect on the normal signaling pathways in non-cancerous cells. The polyphenols isolated from sunflower seed extract including chlorogenic and ferulic acid and caffeic acid demonstrate a strong antioxidant potential as well as a high anti-mutagenic actions. The observed characteristically high anti-mutagenic potential of sunflower polyphenols is due to their ability of mutagenic metabolic activation blockage and free radical scavenging and active screening. The trypsin inhibitor isolated from sunflower possesses a protein ring which acts differently in accordance with its form; when it is utilized in its natural form it acts by producing a chemo preventive action against breast cancer through the blockage of breast cancer specific enzymes; the utilization of the modified form, it acts by blocking enzymes involved in the genesis and proliferation of other types of cancer [48].

Euphorbia tirucalli

The succulent shrub of *Euphorbia tirucalli*, African continent native small tree, is cultivated throughout the world due to its immense popularity owing to its vast use in traditional remedies and herbal medicines. Recent identification of bioactive principles, isolated from the plant latex, has led to the identification of their therapeutic properties including anti-tumorigenic properties. An array of bi- and tri-terpenoids and gallic acid are amongst the bioactive principles isolated from the plant latex. Potent anti-oxidant abilities and oxidative stress combating capacity is observed with the extract of leaf and stems of *Euphorbia tirucalli*. A paradox surroundinganti-cancer biological activity of the specie is; interaction with anti-oxidant enzymatic activities through anti-oxidant enzyme geneup regulationis observed with aqueous extracts of the whole plant thus; highlighting the need for the practice of caution during dose calibrations and administration which should be limited to latex extracts till further evidence is demonstrated by prospective studies [49]. The speculated mechanism of action of latex active bio principles in mediating tumor growth inhibition is through granulocyte and macrophage production regulation and functional action expression regulation. The suppressed action of plant latex is mediated on CD4+ and CD8+ T lymphocytes; an inhibition is also induced upon interleukin II and also on the production of interferon-gama and the associated subsequent immunomodulation [50]. Euphol isolated from latex extract is biologically a triterpenealcohol belonging to euphane group, bears a striking structural similarity to cholesterol, possesses a spectrum of therapeutic activities such as, anti-tumorigenic and inflammation combating properties [51]. A characteristic property of euphol is that it specifically targets CS-12 human gastric cancer cells with a greater affinity and exhibits negligible effects on non-cancerous cells [52].

Curcuma longa

Curcuma longa or turmeric, is a rich source of diferuloyl-methane (curcumin), a polyphenol, which has since centuries been extensively utilized in Traditional medicines

particularly Ayurvedic medicines due to its vast spectrum of therapeutic properties such as anti-flammatory and oxidative stress scavenging. Recent studies have revealed additional potential of curcumin including anti-cancer actions through the induction of a variety of pathways. The mutagenesis biological pathways targeted by curcumin are expression of oncogenes, regulation of cell cycle, induction of apoptosis, tumor genesis and inhibits matastasis. A number of receptors of growth factors and molecules pertaining to cell adhesion involved in cancerous cell growth are affected by curcumin. In addition, anti-proliferative effect on a variety of cancer types is mediated by curcumin [53]. A disturbing issue associated with thyroid cancer is metastasis. The natural polyphenoliccompound, curcumin, demonstrates an inhibition in proliferation and mediates an induction of apoptosis [54]. In animal models, curcumin demonstrates an inhibition in tumor development [55].

Beta Vulgaris

The extract of beet root, *in vitro & in vivo*, demonstrates an inhibitory effect on tumor cells. The consumption of beet root mediates a chemo preventive effect [56]. The plant pigments isolated from beet root, betalains, are water soluble and in addition to characteristic properties such as anti-inflammatory, hepatoprotection, radical scavenging, also possess anti-cancer actions. The antioxidant potential is positively correlated with concomitant presence of total phenolic compounds and betalains. The association is thought to be the presence of a synergistic effect of phenolic compounds on the activity of betalains [20].

Phaseolus vulgaris

Phaseolus vulgari, also known as kidney beans, is an annual herbaceous specie, demonstrates a specifically high toxicity human liver carcinoma cells coupled with a negligible activity against normal liver cells. The activity is associated with the presence of a polygalacturonic acid lectin isolated from the specie. In addition to anti-tumor genesis effects, the lectinis also involved in the mediating dose dependent increase in the synthesis of mRNAs coding for the production of pro inflammatory cytokines [21].

Camellia sinensis (Green tea)

Green tea is scientifically referred to as *Camellia sinensis*. The anti cancer potential of *Camellia sinensis*, is attributed to the presence of a moderate concentration of polyphenolic compounds. The specie contains a small amount of Epigallocatechin, a polyphenol attributed to mediating a protective effect on DNA by scavenging harmful oxygen radicals. Green tea, in addition to its chemoproventive effect, also produces an anti tumor genesis and inhibits mutagenic activities. Catechins isolated form green tea; demonstrate an inhibitory effect on angiogenesis and metastatic events. Furthermore, green tea is associated with decreasing the overall risk of development of cancer of stomach and colon [22]. The components of green tea mediate an overall positive effect on the health of an individual, not only through the reduction cancer risk, but also a protective effect against the development of diabetes and hepatitis [57]. The beneficial effects of gallic acid esterified catechins are exerted through a modulation of mitochondrial activity byan impact on the biogenesis of mitochondria, control of bioenergetism, cell cycle alterations and apoptosis regulation [58]. A strong anti proliferative and metastatic properties is demonstrated against human breast carcinoma cells [59]. The inflammatory responses mediated through the MAPK pathways are also inhibited by green tea water [34]. The gallic acid esterified catechins modulate a number of functions of susceptible cells by binding to cell specific protein sites [60].

Prunella Vulgaris

The herbaceous plant, *Prunella Vulgaris*, is associated with producing an anti-cancer effect through an array of targets and pathways. The mechanisms that are possibly involved are calcium ion regulation to maintain a steady state concentration, regulation of cell cycle, and producing an inhibitory effect on proliferation of tumor cells and metastasis [24].

Conclusion

The emergence of modern innovative society is plagued with increased incidence of debilitating diseases which not only cripple the economic backbone of a country but also deplete scarce medicinal resources. In such a scenario, the need for focusing attention and increasing reliancetowards plants as a source of therapeutic principles has been heightened. In such an era, where the drug development process and its subsequent marketing and surveillance often take decades, the emergent evidence of the beneficial anti-tumor genesis properties of plants have proved to be a mercy.

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REVIEW PAPER OPEN ACCESS

A comprehensive review on racecadotril drug

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Abstract

Around the globe, diarrhea is a continuing health problem and also a leading cause of sickness and death in both children and adults. It is one of the major causes of morbidity and mortality in developing countries and can be occurred in any age irrespective of the geological location. The chief reason of the deaths is because of electrolytes loss and dehydration by increased intestinal secretions and poor absorption. For this study, previously published papers were reviewed and key words for the search of literature, included: Racecadotril, enkephalinase inhibitor, diarrhea, oral rehydrating solutions, diarrhea treatment, infectious diarrhea, and epidemiology of diarrhea. Oral rehydrating solutions are used to recover water and electrolytes and these are considered as a mainstay of the anti-diarrheal therapy. Inhibition of fluid secretion and stimulation of fluid absorption from the intestinal mucosa is necessary in acute diarrhea, so that the loss of water and electrolytes can be prevented. Racecadotril (acetorphan) belongs to the pharmacological class of enkephalinase inhibitor. Its mechanism of action involves the minimizing of the intestinal secretions by protecting the endogenous enkephalins, which are secreted by the gastrointestinal tract. It is taken orally and proved to be safe and effective for the treatment of diarrhea in both adults and children. Racecadotril has a rapid onset of action and shows greater tolerability than loperamide in patients with acute diarrhea. Racecadotril gives better results in children and infants when taken as an adjuvant to oral rehydrate solutions (ORS) and also cut the overall cost of treatment with better outcomes.

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Introduction

Though diarrhea is a symptom and it has been roughly estimated that per year 25% of US population go through acute diarrheal episodes. While per annum 5% of said population suffers from chronic diarrhea (Schiller *et al.*, 2014). Diarrhea is defined as the abnormal movements of the intestine with increase production of the stool (Fine, 1993). It can be occurred in any age irrespective of the geological location (Mehta, 2012) and worldwide it puts a major health economic burden (Thiagarajah *et al.,* 2015). The self-limiting nature of acute diarrhea usually does not require any pharmacological intervention. However, if patients desire only then necessary symptomatic treatment may be given through OTC medications (Salazar-Lindo, 2011).

In acute diarrhea the only population, which is a matter of concern is pediatric patients. In developing countries, the number of mortalities induced by acute diarrhea has increased since last few years and in developed countries, mortality rate has increased in adult population (particularly older patients) due to visceral failure secondary to dehydration and delaying in start of anti-diarrheal therapy (Archbald-Pannone, 2014). Contaminated food or water with microorganisms cause infection of the gastrointestinal tract and represented as acute diarrhoea. Acute diarrhea remains usually stay self-limiting and can be resolved (Thielman and Guerrant, 2004). Apart from the infection, a very rare genetic atrophic condition of the intestinal epithelial cells in the gut is known as Microvillus Inclusion Disease (MVID) which causes secretory diarrhea that may lead to life threatening dehydration and electrolyte imbalance (Späth *et al.,* 2016). Individuals suffering from chronic diarrhea should seek medical attention from their physician (Schiller *et al.*, 2014). The use of traditional drugs for the treatment of diarrhea has limited scope due to their side effects. Taking an example of the opiate drugs which are agonist of opiate receptors, produce action by increasing the transit times of the colon and caecal part of the gut (Heel *et al.,* 1978; Shook *et al.,* 1989; Sykes, 1996; Turvill and Farthing, 1997). The increase in transit time may also increase the risk of adverse effects of these drugs on the gastrointestinal tract, like fluid accumulation in the distended lumen of the bowel and also enhance the bacterial colonization (DuPont and Hornick, 1973; Brown, 1979; Ruppin, 1987). The use of oral Zinc preparations is recommended by the World Health Organization (WHO) in addition to Oral Rehydration Salts (ORS). In 2008, a joint working group of the European Society for Pediatric Gastroenterology, Hepatolgy and Nutrition (ESPGHAN) and the European Society for Pediatric Infection Diseases (ESPID) had published proved guidelines about use of anti-diarrheal drugs adjuvant to ORS in the treatment of acute diarrhea (Tormo *et al.,* 2008; Gordon *et al.,* 2016). Prior diagnosis to reduce the worsening of sickness (Pessi *et al.,* 2014), new pharmacological therapies and implementation of current interventions is still required to reduce the health burden and with better results (Kotloff *et al.,* 2013; Ashiq *et al.,* 2017). For the present study, previously published papers were reviewed and key words for the search of literature were included: Racecadotril, Enkephalinase inhibitor, diarrhoea, Oral rehydrating solutions, diarrhea treatment, infectious diarrhea, and epidemiology of diarrhea. Databases of the literature search, included: Google Scholar, PubMed, Scopus and MEDLINE (Kanwal *et al.,* 2018; Tanveer *et al.,* 2019).

Clinical properties of an ideal anti-diarrheal agent

American Journal of Medicine published a paper in 1985 which mentioned the ideal characteristics of a drug (Table 1) used for the infectious diarrhoea treatment (Edelman, 1985).

Racecadotril as drug of choice

According to the several guidelines, concomitant use of Racecadotril with oral rehydration solution may be recommended for the treatment of acute diarrhea in children (Eberlin *et al.,* 2012). Racecadotril has a greater tolerability than loperamide in patients with acute diarrhea (Fischbach *et al.,* 2016). Racecadotril, (±)-benzyl2-(2-(acetylthiomethyl)-2-methyl-3 phenylpropanamido) acetate (Fig. 1) is a new anti-diarrheal drug (Matheson and Noble, 2000).

Enkephalinase discovered in 1975 and showed a major role in gastrointestinal secretions (Schwartz, 2000). Racecadotril is a potent, orally active drug (Prado, 2002) that inhibits the enkephalinase enzyme activity and preventing the degradation of enkephalins which are abundant in the intestinal villi (Pollard *et al.,* 1991; Vishwakarma, 2018). Enkephalins have an antisecretory effect (Vetel *et al.,* 1999) by inhibiting cyclic adenosine monophosphate (cAMP) (Huijghebaert *et al.,* 2003; Wang *et al.,* 2005). Inhibition of enzyme enkephalinase takes place when parent drug (Racecadotril) is converted to its metabolite thiorphan, in peripheral tissue membranes. The concentration level of Enkephalin is increased due to opioid receptors activation which results in cAMP level reduction. Ultimately, electrolytes and water secretion reduced into the intestinal lumen (Matheson and Noble, 2000; Kozuch and Hanauer, 2008; Basniwal *et al.,* 2008). Maximum absorption occurs when the drug is administered orally at different doses and C_{max} is achieved within 1 hour. According to the BCS,

Racecadotril belongs to Class-II drug (high permeability, low solubility). Class-II drugs (BCS) are further classified on the basis of pKa as a Class IIa (pKa<5), Class IIb (pKa>6.5) and Class IIc (Neutral Drug).

Table 1. Clinical properties of ideal drug for infectious diarrhea treatment.

i	Inhibition fluid secretion and stimulation of liquid absorption through intestinal mucosa
ii	Short onset of action
iii	Constipating effects must be limited to avoid fluid pooling in bloated intestinal lumen
iv	Enhancement of bacterial colonization of the upper bowel Invasion by Shigella
v	Must not obstruct the local function of bowel recovery
vi	Effects on central nervous system should be less with greater therapeutic index.
vii	Abuse potential must be low.

The pKa of Racecadotril is 12.6 which mean that drug falls in BCS Class IIb and can be predicted to have high solubility and dissolution rates at acidic pH in the stomach. Racecadotril bioavailability is not affected by food and rapidly converted to its active metabolite. Thiorphan inhibit the enkephainase enzyme activity and decreases the production of secretions. In addition, oral administration of Racecadotril does not cross blood–brain barrier (Eberlin *et al.,* 2012). Racecadotril and its active metabolite, thiorphan can be analyzed by liquid chromatography and detected by UV in human plasma after extraction of solid-phase.

Preclinical studies interprets that in experimental models, the drug (Racecadotril) is active in hypersecretory diarrhea (Marcais-Collado *et al.,* 1987; Primi *et al.,* 1999). These studies proved that in the small intestine, gastrointestinal transit time of Racecadotril does not increase or effect bacterial over growth (Duval-Iflah *et al.,* 1999).

Racecadotril prevents intestinal fluid secretion

Acute diarrhea is a major cause of hyper-secretion that results in water and electrolyte loss in the body (Edelman, 1985). To treat the diarrhea, inhibition of fluid secretion and stimulation of fluid absorption is necessary by the mucosa of the intestine (Wingate, 2001). Racecadotril secretions prevention action in experimental animal models has been verified in a research (Marcais-Collado *et al.,* 1987; Duval-Iflah *et al.,* 1999). In a study, six healthy volunteers were examined to study the influence of cholera-induced hyper secretion and Racecadotril in the jejunum. A small section of the jejunum (approximately 30cm) was perfused in an electrolyte solution with the same concentration as plasma and cholera toxin effect (a 6.25 mg intra-jejunal bolus) was measured with and without oral administration of the drug (3× 100 mg capsules). Cholera toxin caused the net secretion of water. However, Cholera toxin effect was inhibited significantly (PB 0.05) by Racecadotril administration, that altered the net effect of

absorption of water. Transport of electrolyte in the intestine was also changed significantly with respect to absorption (Wang *et al.,* 2005). Another study was conducted on the healthy volunteers and diarrhea was induced by the castor oil and the action of Racecadotril was measured, it is also known as a model of hypersecretory diarrhea. Six healthy volunteers were pretreated with and without oral administration of Racecadotril (10 mg/kg) before 45 min of taking castor oil (30 g). Both treatments were given to all the subjects. The cumulative weight of stool was reduced significantly (PB0.001) with administration of Racecadotril as compared to the placebo. Further, a delayed onset of diarrhoea was seen by the effect of the drug (Baumer *et al.,* 1992).

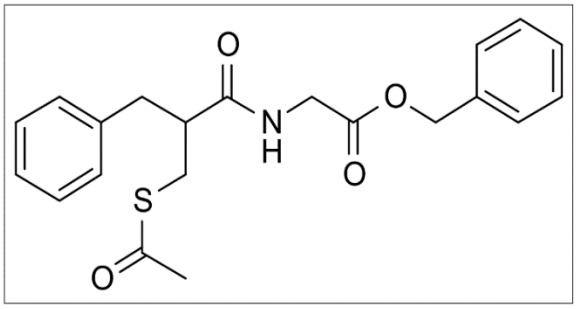

Fig. 1. Chemical structure of Racecadotril.

Racecadotril shows fast onset of action

Onset of action must be rapid for those drugs used for the treatment of diarrhea (Prado, 2002). The studies showed that Racecadotril has rapid onset of action in healthy subjects as well as on the patients that were suffering from diarrhea (Lecomte, 2000; Matheson and Noble, 2000). Effect of plasma enkephalin enzyme was determined in eight healthy volunteers after oral administration of a single dose of Racecadotril (100 mg). Significant inhibition of plasma enkephalin enzyme (PB0.01) was demonstrated after first 30 min of drug administration and maximum inhibition was produced after 1 hour. A double-blind, randomized and parallel-group study shows the rapid onset of action of drug. Racecadotril (100 mg) three times daily was given to adult patients (32 patients, 32 placebo) of acute diarrhea for 7 days. Stool weight was measured to demonstrate the anti-secretory effect of drug, Racecadotril showed a significant, 28.9% reduction (P=0.025) in weight of stool after first 24 hours of treatment, as compared with placebo drug. Significantly less diarrheic stools was associated with Racecadotril than placebo drug (P=0.027) (Hamza *et al.,* 1999).

Racecadotril does not produced adverse gastrointestinal effects

Racecadotril absorbed the fluid from the gastrointestinal tract without causing any harmful effects (Schwartz, 2000). It was proved in a randomized, crossover, double-blind, placebo-controlled study. An investigation was conducted on 12 healthy volunteers to demonstrate the action of Racecadotril on transit time of GIT. Biotransformation of sulphasalazine to active metabolite and sulphapyridine was used to access oro-caecal transit time. Racecadotril (100 mg) or placebo drug was given daily (3 times) to the patients for 7 days. On 7th day, each subject received sulphasalazine (2g) with a standardized breakfast and samples of blood were taken after every thirty minutes over a period of eight hours. The presence of sulphapyridine in the plasma shows the oro-caecal transit time. No substantial effect was seen on mean (9SEM) oro-caecal transit time by the administration of Racecadotril. The transit time of colon was also measured by oral ingestion of radio-opaque markers in first 5 days after starting the treatment of the drug. In colon the number of markers, was counted by X-ray on the 6thday of drug administration. No significant effect of Racecadotril was determined at mean (9SEM) colonic transit time (Racecadotril 31.395.6 h vs. placebo 25.895.8 h). Racecadotril has no effect on transit time of GIT have been confirmed in patients that suffering from acute diarrhoea (Bergmann *et al.,* 1992). Clinical research has been conducted for comparison of Racecadotril and placebo drug to show the occurrence of constipation during the treatment treated 193 patients who had acute diarrhea with Racecadotril (n=95) or placebo (n=98) for a maximum of 10 days. The occurrence of constipation was low in both groups; only four patients receiving Racecadotril, suffered from constipation and two on placebo. The frequency of both abdominal distension and abdominal pain was

considerably (PB 0.05) lesser than the Racecadotril; at the end of investigation out of 18 (20.5%) patients on placebo eight patients (9.6%) had abdominal pain, and 13 (18.3%) had abdominal distension at the end of the analysis compared with 26 (34.7%) on placebo (Baumer *et al.,* 1992). In a double blind trial, two groups of adult patients with acute diarrhea were compared to observe the effects of placebo and Racecadotril. It was reported that there is no significance variance in weight of stool when diarrhea had resolved. The study also showed the lack of constipation with Racecadotril. At the consultation on a second patient on day four the frequency of distension in the abdomen was reported to be 18.2% with placebo as compared to 5.6% with Racecadotril (Hamza *et al.,* 1999). In a double-blind study, which was carried out on patients with acute diarrhea has compared the effects of loperamide (n=32 with a dose of 1.33mg) with Racecadotril (n=37, with a dose of 100mg) at a frequency of 3 times daily for 7 days continuous treatment. When the diarrhea got cured, 31.3% patients treated with loperamide and 8.1% patients who received Racecadotril complained recurrence of constipation (PB 0.02). While abdominal distension was also reported by 50% and 27% of the treated patients with loperamide and Racecadotril, respectively (PB 0.05), in addition to this, 40.5% of patients on Racecadotril reported abdominal pain more than 1 day during the period of treatment as compared 59.4% to patients treated with loperamide reported the same (Roge *et al.,* 1993). A study carried out also endorsed that the frequency of recurrence constipation is lower with Racecadotril than loperamide (Vetel *et al.,* 1999) and showed better tolerability than loperamide in children and adults with diarrhea (Metheson and Noble, 2000).

Racecadotril is drug of high therapeutic index

The medicines used for the cure and management of diarrhea must have a high therapeutic index (Singh and Narayan, 2008). The safety profile of a medication depends upon the therapeutic index (Lecomate, 2000). Pharmacological studies of Racecadotril showed that no toxic effects were observed when it is administered in primates, up to 100 times of the therapeutic dose for the period of 12 months. In human beings, a single dose of two grams that is equivalent to more than 20 times of its therapeutic dose was orally given to healthy volunteers that cause no adverse effects. In a study, clinical trials have been conducted on 1883 patients, treated with Racecadotril, 100 patients was given the drug for at least 90 days. A clinical trial has shown that the safety profile and tolerability of Racecadotril is similar to the placebo drug and highly favorable than loperamide (opiate receptor agonist). Baumer and co-authors, in their research on 193 patients with acute diarrhea, interpreted the occurrence, nature, and severity of adverse effects was same for Racecadotril as well as placebo drug. Global analysis by both physician and patient confirmed the safety and fair tolerability of Racecadotril (Baumer *et al.,* 1992). A study evaluated that 3.1% of patients receiving Racecadotril described adverse events at the second physician consultation on the 4th day when compared with 5.3% of those taking placebo drug (Hamza *et al.,* 1999). The two double-blind relative studies also confirmed that Racecadotril is safe and well tolerated as compared to the loperamide (Roge *et al.,* 1993; Vetel *et al.,* 1999).

Racecadotril has no side effects on the central nervous system

The drugs used for the treatment of diarrhea must have minimal effects on central nervous system and misuse potential should be low (Duval-Iflah *et al.,* 1999). The ability of drug to cross the blood brain barrier was determined by relating the enkephalin enzyme activity in plasma and cerebrospinal fluid when given orally. Two patients undergo myelography had been hospitalized and to them Racecadotril (dose 20 mg/kg) was given orally. Enkephalin enzyme activity in the plasma had reduced to minimum level within 30 minutes that showed maximum inhibition of enzyme by Racecadotril. In contrast, effect of the enzyme in cerebrospinal fluid did not alter, which indicated that Racecadotril has no ability to cross the blood–brain barrier. A double-blind, crossover and randomized study conducted on 12 healthy volunteers confirmed

that Racecadotril has no effect on the central nervous system. Racecadotril placebo (300 mg/day) was given to each subject for 3 days, and a psychometric tests battery was conducted to evaluate the vigilance before and after treatment. Both treatments were given to all subjects and the results demonstrated that vigilance was not impaired by Racecadotril.

The studies conducted in monkeys and rats also revealed a lack of potential for abuse with Racecadotril (Kachel *et al.,* 1986).

Conclusion

Diarrhea is a common symptom which is associated with many pathological conditions. It causes increased mortality and morbidity among children and adults, especially in lower income countries and put a high cost burden of the treatment on health budgets. Racecadotril is a new drug of choice for the treatment of diarrhea with proven clinical efficacy.

It shows a rapid onset of action and has a high therapeutic index combined with the lack of side effects on the gastrointestinal tract and central nervous system. It is concluded from the current study that Racecadotril offers a new approach for the treatment of diarrhea by inhibiting the enzyme enkephalinase and by reducing the GIT secretions. However, there is a need to carry out further research so that reliable conclusions can be measured for the treatment of diarrhea with Racecadotril.

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REVIEW PAPER OPEN ACCESS

Common herbal plants and their role in control of obesity

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Abstract

Obesity is quite common around the globe and linked with the increased prevalence of various other diseases including: immune dysfunction, diabetes, depression, cancer and cardiovascular disorders. Obesity is induced by the diet is usually due to disproportionate intake of calorie enriched diet, lack of physical activity and reduced energy consumption. Worldwide, it was estimated that an average of 603.7 million adults and 107.7 million children were found to be obese in 2015. It was also observed that the prevalence of obesity is quite greater in females than males. The incidence rate of obesity was 12.0% among adults and 5% among children. In 2015, approximately 4 million deaths were reported around the world due to increased BMI. The current review is aimed to study common herbal plants which have proven anti-obesity effect and could be used in the routine diet to reduce weight and to improve the quality of life. The databases used for this review were included Google Scholar, PubMed, Scopus and Medline. There are many common herbal plants and spices which are used in daily routine that could be helpful in reducing weight. Black Chinese tea, *Nigella Sativa*, Green Tea and *Camellia synensis* has exhibited promising anti-obesity activity. To reduce the prevalence of obesity and to improve the quality of life better strategies should be considered. Physicians and other health care professionals with pharmacological interventions should recommend change in daily routine life to patients for better outcomes

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Introduction

Obesity is quite common around the globe and linked with the increased prevalence of various other diseases including: immune dysfunction, diabetes, depression, cancer and cardiovascular disorders. So, right approach should be taken into account to loss the weight and other resultant abnormalities (Vanamala *et al.,* 2012).Worldwide, it was estimated that an average of 603.7 million adults and 107.7 million children were found to be obese in 2015. It was also observed that the prevalence of obesity is quite greater in females than males. Obesity is also associated with polycystic ovary syndrome which is characterized by ovarian dysfunction, hirsutism and acne (Mahmood *et al.,* 2011). The incidence rate of obesity was 12.0% among adults and 5% among children. In 2015, approximately 4 million deaths were reported around the world due to increased BMI. Further, increased BMI was resulted to 120 million disability-adjusted life-years. As link to the BMI, about 39% of the mortalities and 37% of the disability-adjusted life-years were found in people having BMI <30 (Collaborators, 2017). Overall, global economic burden of the obesity was predicted to be 2 trillion US dollars in 2014 (Tremmel *et al.,* 2017).The major reason behind the increased incidence of obesity is probably surplus ease to access and affordability of energy-dense foods. The marketing of such food products and utilization may the key cause of weight gain (Swinburn *et al.,* 2011).Obesity is quite common in both developed and developing countries. Pakistan is an emerging country and ranked on 9th highest position regarding obesity monetary burden (Ahmad *et al.,* 2015). Pakistan is facing many challenges like lack of health resources, malnutrition, trend shifting towards the fast food, occurrence of non-communicable including obesity and economic burden. Due to lack of the regulatory control, the fast food industry is expanded abruptly in Pakistan which resulted into the weight gain and its comorbidities (Sajjad and Qureshi, 2018). Better strategies should be considered to reduce the prevalence of obesity and improve the quality of life (Kanwal *et al.,* 2015; Tanveer *et al.,* 2019). Physicians and other health care professionals with pharmacological interventions should recommend change in daily routine life to patients for better outcomes (Howard, 1981). Obesity is induced by the diet is usually due to disproportionate intake of calorie enriched diet, lack of physical activity and reduced energy consumption. Due to imbalance between the energy intake and utilization either fat cells are increased in size or number (He *et al.,* 2009). Complementary and alternative medicine (CAM) including change in dietary habits and herbal supplements are proven to be effective in the treatment of weight loss (Barnes *et al.,* 2002).In 2002, World Health Organization (WHO) has recommended the Asian countries to reduce the BMI cut-off values (Aziz and Sohail, 2016). Many therapeutically useful compounds are being isolated from herbs and used in treatment of various ailments (Tanveer *et al.,* 2019). There are many common herbal plants and spices which are used in daily routine that could be helpful in reducing weight. Black Chinese tea, *Nigella sativa*, Green Tea and *Camellia synensis*has exhibited promising anti-obesity activity. It is recommended that dose of the medicinal herbs should be determined for effective treatment and possible side effects (Hasani-Ranjbar *et al.,* 2013).In an investigation, 53 medicinal plants were studied for their possible anti-obesity effects. Black tea, Glycyrrhizaglabra, licorice, Saturejakhuzestanica, Fenugreek, cherry, garlic powder (Allicor) and rhubarb stalk has demonstrated a significant reduction in total cholesterol and LDL cholesterol levels(Hasani-Ranjbar *et al.,* 2010).A research was conducted on processed tomato vinegar beverage TVB to evaluate anti-obesity and anti-insulin effects and outcomes has showed the reduction in insulin resistance and visceral obesity (Seo *et al.,* 2014).Tomatoes not only helpful in weight drop but also reduce the risk for the chronic inflammatory diseases (Hazewindus *et al.,* 2014). The current review is aimed to study common herbal plants which have proven anti-obesity effect and could be used in the routine diet to reduce weight and to improve the quality of life. The databases used for this review were included Google Scholar, PubMed, Scopus and Medline (Abid *et al.,* 2019).

Role of herbal plant in controlling obesity

Orange peel

Orange peel or bitter orange peel (*Citrus aurantium*) belongs to family Rutaceae. Many valuable phytochemicals have been isolated, named: synephrine, hordenine, N-methyl tyramine, octopamine, flavonoids, volatile oil and Vitamin C. The isolated compound namedSynephrinehas significant pharmacological activities such as bronchial muscle relaxation and constrictions of vessels. The fruit extracts of the orange peel is widely used to cure multiple diseases such as infections, obesity and cancer (Suryawanshi, 2011; Arshad *et al.,* 2019). In a research, orange peel has been evaluated for the anti-obesity effects. The extracts of orange peel were given to the female mice in combination with caffeine and black tea. It was observed that the mice which taken such combination of diet have exhibited reduction in abdominal fat and in brown adipose tissue (Huang *et al.,* 2009).Another study has also proven the weight loss effects of orange peel by using in vitro model. The outcomes of the study have confirmed that the citrus polyphenols cause lesseningof the cell lipid contents along adipocyte differentiation (Nakajima *et al.,* 2014).

Licorice

Glycyrrhizaglabra is famous as a "licorice". The herb has remarkable properties to reduce obesity. An investigation has done on the plant to prove its anti-obesity effect and for this herb supercritical fluid extract enriched with glabridin was used. For study fat diet was given to rats and anti-obesity effect was observed for about eight weeks. This chemical reduces the obesity by interfere the process of adipose cells generation (Ahn *et al.,* 2013). In Korea, about eight hundred species of the plant was tested to investigate the anti-obesity effect. A chemical known aslicochalcone was proved to be effective and it is separated from the *Glycyrrhizauralensis*root extract. This research has also proved thatlicochalconeimpede the formation of oleic acid by pancreatic lipase (Won *et al.,* 2007).A placebo-controlled study were conducted which was double blinded. For this study slightly obese subjects were chosen, included 56 males and 28 females and they were divide into 4 groups. Daily a placebo dose was given to the participants and sample of the bloods were monitored for the BMI for eight weeks. The study has exhibited that total body fat mass declined in three LFO groups (Tominaga *et al.,* 2009). A double blind placebo controlled investigation was conducted to evaluate the dried licorice extract with a calorie restricted diet on anthropometric indices and insulin resistance with nutrigenetic approach. For this study, subjects (n=2) were randomly assigned to placebo or licorice group. It was concluded that in overweight participants, the Pro/Pro polymorphism of the PPAR-γ2 gene seems to encouragepromising effects on control of obesity. However Further research is still required to verify that PPAR-γ2 gene polymorphisms or another obesity genes can affect responses to obesity cure and management (Namazi *et al.,* 2017).

Cardamom

Elettariacardamomum is known as cardamom and belongs to familyzingeberaceae. A research was done the on Sprague-Dawley rats to check the hypoglycemic and anti-obesityeffect which was instigated by alloxan. This study was performed on 45 rats which were equally divided into three groups of the rats. Samples were taken at three intervals daily for about 14 days to monitor the theblood glucose and cholesterol. The outcomes of the study have shown a marked reduction in glucose and cholesterol level hence proved effective for obesity and hypoglycemic effects (Winarsi *et al.,* 2014). Another study was conducted on animals also proved herb beneficial effect to reduce obesity (Daneshi-Maskooni *et al.,* 2017). An investigation was carried on albino rats to compare the hyperglycemic and anti-obesity activity of cardamom with pioglitazone and dexamethasone. In this study 24 rats were uses and split into 4 groups. One group received dexamethasone and second group received cardamom suspension along with and before consuming dexamethasone for 6 days. The third group received pioglitazone and last group did not receive any medication. Both cardamom and pioglitazone reduced the hepatomegaly and cause weight loss and reduce the blood sugar level (Bhat *et*

al., 2015).

Gurmar

The botanical name of the Gurmar is *Gymnemasylvestre* and belongs to Asclepiadaceae family. The most significant active constituents of Gurmar is Gymnemic acid and it has hypoglycemic, anti-inflammatory and anti-helmentic activity (Saneja *et al.,* 2010).The usual recommended dose of leaves is 75-150 mg to reduce the obesity (George and Nimmi, 2011). The chief phytochemicals of Gurmar are includinggymnemicacids, gymnemasaponins, and a polypeptide, gurmarin.Its herbal extract used to reduce the blood cholesterol and also reduce body weight (Tiwari *et al.,* 2014).

Black cumin

Nigella sativa is a common herb and used widely to treat many disorders. It was used by Unani physicians of customary medicine (*Hakims* or *Tabibs)* and ayurvedic practitioners (*Vaids*) for the cure of many pathologies i.e. dyslipidemia, hypertension and obesity (Qidwai *et al.,* 2009).A study has conducted to provide an explanation of herb extracts effects on adipocytes and PPARγ.

The findings of the study have revealed the plant extract act as an agonist of PPARγ. The outcomes of the research data have suggested that *N. sativa*seed oil has potential to cure obesity and to reduce increased blood sugar (Benhaddou-Andaloussi *et al.,* 2010).Many studies have indicated that the plant has anti-cancer, cardio-protective, anti-diabetic andimmune-modulatory properties. Black cumin also exhibit marked anti-oxidant properties by preventing generation of reactive oxygen species (Tanveer *et al.,* 2014).Herb active phytoconstituent called hymoquinone hasrevealed bioactivity in a variety of disease models and still the mechanisms of action is not known. Further growing interest in and the use of functional foods and nutraceuticals, as well as the rise in obesity and chronic diseases globally, more investigations are needed to verifyuseful effects of the plant (Vanamala *et al.,* 2012).

Tea

Tea or *Camellia sinensis* is belongs to family Theaceae. Polyphenols have been isolated from the tea plant and studied for their potential role to treat chronic disorders with special reference to obesity. Various scientific studies have exposed the impendingeffectiveness of both black and green tea to reduce the weight. However, exact mechanism is still unknown and is needed to be explored (Grove and Lambert, 2010). It has been shown that green tea, when consumed on a daily basis, supports health. Many of the beneficial effects of green tea are related to its catechin, particularly (−)-epigallocatechin-3-gallate (EGCG), content. There is conclusive evidence from *in vitro* and animal studies which provide the concepts for underlying functional mechanisms of green tea catechins and their biological actions (Thielecke and Boschmann, 2009).

Garlic

Till then many studies have conducted on garlic to validate the wisdom behind its use to reduce weight and hyperlipidemia. A research was performed on obese rats to discover the effects of garlic oil and onion oil on serum lipid levels. For study, ninety six male Sprague-Dawley rats were used and divided into 8 random groups on basis of their blood levels of triglycerides, cholesterol and body weight. For about 60 days, they were given extracted volatile from the plant orally and then different obesity measuring parameters were examined. The results of study have implied that garlic oil and onion oil are effective in controlling the obesity (Yang *et al.,* 2018).

Onion

Weight reducing potential of the onion (*Allium cepa*) extract was evaluated in both obese and diabetic Zucker diabetic fatty rats. The efficacy of the results was determined by assessing the relevant obesity and diabetes markers. The findings of the study have confirmed that the onion is quite effective in minimizing the serum glucose level and lipid profile. Onion contains many useful constituents like cycloalliin, *S*-propyl-l-cysteine sulfoxide, *S*-methyl-l-cysteine, dimethyl trisulfide and *S*-methyl-l-cysteine

sulfoxide were reported to be effective in inhibiting formation of oil drop in the cells, suggesting that these compounds may be involved in the anti-obesity effect of the onion extract (Yoshinari *et al.,* 2012).Male 8 week old mice were purchased (n=60) and they were kept under standardize conditions and divided into 5 groups and they were fed on HFD and normal saline 2g/kg /day for 10 weeks and control group was fed only normal saline the body weight of mice fed the high fat diet was higher than that of mice fed the normal diet by approximately 32.5%. In the orlistat treated group as positive control the body weight was significantly decreased by approximately 16.5% (Sung *et al.,* 2014). A research has also proved that the administration of onion reduced the size of adipocyte and serum hyperlipidemia in obese rats. Moreover, the antihypertensive effects of onion were also noticed. It is suggested by the study that onion reduces the serum lipid components and improves hypertension in obese rat (Kanf*et al.,* 2010).

Tomato

Tomato or *Solanumlycopersicum*is widely used across the word and embraced with many valuable chemicals which are effective for the treatment of many ailments. A study was conducted to evaluate the tomato and broccoli extracts for control of obesity and to regulate glucose homeostasis through the modulation of resistin levels. There is an association between the resistin and obesity. For study 48 male albino rats were used and investigated for about 1 month. By using the ELISA and spectroscopic techniques, levels of leptin, resistin, adiponectin, insulin and glucose were determined. The outcomes have shown that tomato and broccoli extract treatment regulates glucose homeostasis via reduction of serum resistin and may be a useful non-pharmacological therapy for obesity (Aborehab *et al.,* 2016).Intake of vegetable is more beneficial against many diseases also including obesity which is a major health problem now a day. Tomato is a beneficial vegetable that could help in weight reduction. A study was performed on zebra fish because we can feed every type of vegetables to zebra fish. After giving tomato's to the zebra fish a marked reduction in weight was observed (Tainaka *et al.,* 2011).Tomato andvinegar also inhibit the deposition of different types of fats in body and decreased the cholesterol level in liver and plasma (Lee *et al.,* 2013).Now great consideration is given to use of herbs, vegetables and fruits for the control of weight as these dietary approaches are safe and effective.Tomatoes contain caretenoidsin abundance which play a key role in humanto reduce the free radicals and hence act as the anti-oxidant (Pinela *et al.,* 2016).It also contain the vitamin C called ascorbic acid and vitamin E called tocopherolwhich also play a significant role in reduction of weight (Davey *et al.,* 2000; Baiano and Del Nobile, 2016)as these chemicals also have a function of antioxidant (Lee *et al.,* 2004) andintake of tomato can maintain balance of the such vitamins in body (Abushita *et al.,* 2000; Singh and Jialal, 2004).

Ginger or *Zingiberofficinale*has both non-volatile and volatile constituents. The extracts of the ginger are commonly used to treat many diseases and by studies many potential roles of the plant has verified (Misawa *et al.,* 2015).The plant contains the many valuable active compounds that lower the blood cholesterol, improve digestion and reduce the weight (Srinivasan, 2017). At a dose of 800mg/dl, the plant volatile components remarkably reduce the body glucose and fat. Hence it can be used to treat obesity and diabetes (Andallu *et al.,* 2003; jewole, 2006).

Conclusion

Obesity is quite common around the globe and linked with the increased prevalence of various other diseases including: immune dysfunction, diabetes, depression, cancer and cardiovascular disorders. The major reason behind the increased incidence of obesity is probably surplus ease to access and affordability of energy-dense foods.

The marketing of such food products and utilization may the key cause of weight gain. There are many common herbal plants and spices which are used in daily routine that could be helpful in reducing weight. Black Chinese tea, *Nigella sativa*, Green Tea and *Camellia synensis* has exhibited promising anti-obesity

activity. To reduce the prevalence of obesity and to improve the quality of life better strategies should be considered. Physicians and other health care professionals with pharmacological interventions should recommend change in daily routine life to patients for better outcomes.

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Review Article

PHYTOCHEMICAL AND PHARMACOLOGICAL PROFILE OF THE MEDICINAL HERB: *BRYOPHYLLUM PINNATUM*

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ABSTRACT

Worldwide, *Bryophyllum pinnatum* is extensively used to treat the various ailments in folk medicine. The plant is enriched with a diverse range of active therapeutic constituents which are responsible for various significant pharmacological effects. The objective of current study is to highlight the latest evidence-based information regarding pharmacognostical, phytochemical and pharmacological profile of the medicinal plant. Data for the present study was taken from previously published work and to ensure the credibility only indexed research and review articles were used. The databases were included: Scopus, Google Scholar, PubMed, Science Direct, and MEDLINE. *Bryophyllum pinnatum* contains valuable phytochemicals such as polyphenols, tannins, glycosaponins, flavonoids, steroidal glycosides and many other important chemical constituents that are responsible for its anti-oxidant, anti-pyretic, anti-inflammatory, anti-arthritic, anti-allergic, analgesic, anti-septic, sedative, anti-depression, wound healing, hepatoprotective, nephroprotective, tocolysis, urolithic, anti-psychotic, muscle relaxant, anti-protozoal, anti-microbial and anti-diabetic effects. Bufadienolides have been isolated from the leaves of plant which could be the potential chemotherapeutic agents and hence plant has anti-tumor activity as well. Although, many aspects of the herb have been explored still there is need to carry out a more comprehensive investigation in order to confirm its therapeutic efficacy and to appraise rationale behind its use in folk medicines.

Key words: *Bryophyllum pinnatum*, *Kalanchoe pinnatum*, pharmacognostical, phytochemical, pharmacological, bufadienolides.

INTRODUCTION

Globally, medicinal plants are extensively used for the treatment of various diseases (Gover *et al.,* 2002). According to the World Health Organization (WHO), medicinal plants are the great source to offer a diverse range of potential therapeutic drugs and these drugs can be relatively safe and economical as compared to the synthetic medicines (Mekuria *et al.,* 2017; Ekor, 2014; Bahmani *et al.,* 2014). Since the last many years, herbal drugs are increasingly focused by the researchers and several plants are being monitored for their prospective therapeutic effects (Uprety *et al.,* 2010). Based on the therapeutic value of medicinal plants the current study provides an updated insight of *Bryophyllum pinnatum* which is extensively used in folk therapeutics.

Bryophyllum pinnatum (family: Crassulaceae) is also known as *Kalanchoe pinnatum* or *Bryophyllum calycinum* (Sadhana *et al.,* 2017). It is 3 to 5 meters high perennial herb and has opposed glabrous leaves (Afzal *et al.,* 2012; Kamoj and Saluja, 2017). It has a sour taste, hot strength and sugary post digestive effect. The herb contains a wide range of valuable chemicals that could be responsible for its various pharmacological effects (Jaiswal and Sawhney, 2006).

Vernacular names
English: Air plant
Hindi: Zakhmhaiyat, Patharchur
Bengali: Koppatha, Patharkuchi
Sanskrit: Parnabeeja, Asthibhaksha

Other common names include: Miracle leaf, Mexican Love plant, Panfutti, Divine herb, Wonder of the World (Pattewar, 2012), Canterbury bells, life plant, air plant and Cathedral bells (Plangger *et al.,* 2006; Naz *et al.,* 2009; Kamoj and Saluja, 2017). In Pakistan, it is famous as Pathar Chat and Zakham-e-Hayat (Mahmood *et al.,* 2011; Gilani *et al.,* 2014).

Taxonomy
Kingdom: Plantae
Vascular plants Division: Spermatophyta
Order: Rosales
Family: Crassulaceae – stonecrop
Genus: Bryophyllum
Species: *Bryophyllum pinnatum* (Lam.) Kurz

Distribution: *Bryophyllum pinnatum* is indigenous to Madagascar. It grows naturally and found in the temperate regions of Asia, Galapagos, West Indies, New Zealand, Macaronesia, Mascarenes, Caribbean and

Pacific, Melanesia, Polynesia, Hawaii and Australia (Zamora *et al.,* 1998).

Ethnophramacological relevance: Around the globe, it is consuming for the treatment and management of various pathologies such as conjunctivitis, edema, piles, cuts, eczema, constipation, epilepsy, cholera, asthma, chest colds, menstrual disorders, chicken pox and fever (Quazi *et al.,* 2011). The plant parts are frequently applied for the cure of burns, rheumatoid arthritis, anti-septic, blisters, cough suppression, insect bites, psychiatric disorders and abdominal discomforts (Sadhana *et al.,* 2017). It is well-known for its anti-inflammatory, wound healing, analgesic and hemostatic qualities (Ferreira *et al.,* 2014). Leaves extracts are useful for the remedy of jaundice, hypertension, renal stones and diabetes. Slightly heated leaves are applied on superficial skin infections and also used for the dropping of placenta in Southeast Nigeria, hence it act as a tocolytic agent to prevent the premature labor (Gupta *et al.,* 2016; Mouhssin *et al.,* 2015). The plant is also used for the cure of leg edema, fever, gout, abscesses, otitis and palpitations (Afzal *et al.,* 2012). *Bryophyllum pinnatum* is widely utilized in ayurvedic medicines for the treatment of numerous conditions such as menorrhagia, hemorrhoids, vomiting, corns, ophthalmia and hematemesis. Root extract is being used for its hepatoprotective, laxative, diuretic and anti-psychotic effects (Afzal *et al.,* 2013). Paste of the crushed leaves is applied on skin for the treatment of boils and abscess (Saikia *et al.,* 2006). In Germany, anthroposophic physicians prescribed *Bryophyllum pinnatum* preparations for tocolysis and behavioral disorders (Simões *et al*., 2012).

MATERIALS AND METHODS

Data for the current study was taken from previously published work and to ensure the credibility only indexed research and review articles were used. The databases were included: Scopus, Google Scholar, PubMed, Science Direct, and MEDLINE.

RESULTS AND DISCUSSION

PHYTOCHEMICAL CONSTITUENTS: Numerous important chemical constituents and secondary metabolites of the plant have been documented in which the most significant are bufadienolides and flavonoids (Fürer *et al.,* 2016). From leaves, bryophyllin B and A have been isolated which are major bufadienolides (Potterat *et al.,* 2013). In leaves and their extracts various flavonoids are separated, included: quercitrin, kapinnatoside, 8-methoxyquercetin-3, 7-di- O-rhamnopyranoside and 3', 4'-dimethoxy quercetin. Other flavonoid compounds i.e. Afzelin and α-rhamnoisorobin were also found. In ethanol extract of the plant, fatty acids such as stearic acid, palmitic acid and traces of the arachidic and behenic acid were also spotted (Milad *et al.,* 2014). The presence of alkaloids, saponins, glycosides and tannins has been confirmed in the plant (Telefo *et al.,* 2011). Moreover, phytochemical screening of root chloroform extract has shown the occurrence of different flavonoids and steroids however a thorough research is still required (Majaz *et al.,* 2011). It has also found that the presence of different flavonoids, polyphenols, triterpenoids and other chemical constituents in the plant are responsible for its various therapeutic activities such as anti-nociceptive, anti-inflammatory, anti-bacterial and anti-diabetic effects (Ferreira *et al.,* 2014). The herb is an excellent reserve of vitamins such as ascorbic acid, niacin and thiamine and also has minerals i.e. Ca, Mg, Na, Fe, P, K and Zn (Milad *et al.,* 2014). It contains essential oils and about twenty four compounds were isolated out of which nonanal and (E)-geranylacetone are the most abundant (Adeyinka *et al.,* 2017). *Bryophyllum pinnatum* is enriched with a diverse variety of the pharmacological active chemicals (Kamoj and Saluja, 2017) and therefore it is necessitate carrying out further scientific research in order to confirm the justification behind its use in folk therapeutics (Hamburger *et al.,* 2017).

BIOLOGICAL AND PHARMACOLOGICAL EFFECTS

Anti-inflammatory and Analgesic activity: Customarily, *Bryophyllum pinnatum* leaves and its flowers are used for the anti-inflammatory and analgesic effects. It contains flavonoids which have ability to inhibit the cyclooxygenase enzyme and minimize the activity of α- tissue necrosis factor (Ferreira *et al.,* 2014). From leaves, a novel steroidal derivative has been separated and now its structure is also elucidated. In aqueous extract this new steroidal compound was found to be active in reducing inflammation when tested by carrageenan induced rat paw edema and compared with diclofenac. Furthermore, it has revealed 75.72% protection in analgesic activity when tested by mice acetic acid induced writhing test (Afzal *et al*., 2012) hence it has proven that aqueous extract of the plant has potent analgesic activity (Igwe and Akunyili, 2005). Leaves ethanolic extract was proved to be effective against the topical acute and chronic inflammation which is due to cramming of the arachidonic acid pathway (Chibli *et al.,* 2014).

Anti-allergy activity: An *in vitro* study has shown that the plant is helpful in reducing allergy. Its anti-allergic effect is due to the halting of antigen induced mast cell degranulation and also by minimizing the secretion of histamine (Cruz *et al.,* 2008).

Anti-cancer activity: The plant chloroform extract and its fractions have exhibited a concentration dependent inhibition of human cervical cancer cell growth. The fraction was more potent than the extract and strong activity was observed against human papillomavirus (HPV) which performs a vital job in the growth of cervical cancer (Mahata *et al.,* 2012). In leaves, five bufadienolides have been separated and investigated for their inhibitory effects on Epstein-Barr virus early antigen. From all the bufadienolides, an obvious inhibition was exhibited by bryophyllin A. Study outcomes have strongly recommended that the *Bryophyllum pinnatum* bufadienolides could be the potential chemotherapeutic candidates to treat the cancer (Afzal *et al.,* 2012).

Anti-diabetic activity: For many years, the plant has been utilized for its anti-hyperglycemic effects. The aqueous extract of leaves, after postprandial and streptozotocin induced diabetes in rats has exhibited striking hypoglycemic effects. Moreover, an advance investigation has confirmed its effectiveness in heart diseases and in diabetes (Ojewole, 2005).

Antihypertensive activity: Medicinal herb is used to treat various cardiovascular related disorders in folklore therapeutics (Tedge *et al.,* 2005). Now it is confirmed that aqueous extract of the leaves has an antihypertensive effect on rats which justify its use in folk medicines. It has been demonstrated that the extract has potent anti-oxidant effect on aorta thus plays a significant role in the lessening of blood pressure (Bopda *et al.,* 2014).

Anti leishmanial activity: Flavonoids present in the herb are responsible for its anti leishmanial effects. In the aqueous extract of leaves, it has been proven by testing three flavonoids separately against the *Leishmania amazonenis* amastigotes in comparison with quercitrin, quercetin and afzelin. The quercetin aglycone type structure and a rhamnosyl unit linked at C-3 were found to be essential for anti leishmanial activity (Muzitano *et al.,* 2006).

Antimicrobial and Antifungal activity: The plant different crude extracts were analyzed for their anti-microbial effect and it was determined that the extracts have broad spectrum anti-bacterial activity (Aqil and Ahmad, 2003). Considerable antibacterial activity was confirmed against gram positive and gram negative bacteria by the ethanolic extract of the plant (Biswas *et al.,* 2011). A methanolic extract of the roots was found to be effective against *S. aureus, P.* aeruginosa and *E. coli* but not effective against *C. albicans* (Majaz *et al.,* 2011).

Urolithic activity: The medicinal herb is used for the treatment of renal stones in traditional medicines (Tedge *et al.,* 2005). Leaves aqueous extract markedly decreases the level of urine oxalate and consequently it can be helpful in the cure of urolithiasis (Shukla *et al.,* 2014). In Pakistan, this medicinal herb is being used for the cure of kidney stones in customary treatment. *Bryophyllum pinnatum* has been proven beneficial in the reduction of renal stones because it enhances the excretion of oxalate crystals by reducing the size of crystals and by converting them from dehydrate crystals to calcium oxalate monohydrate form (Yasir and Waqar, 2011). Investigations have confirmed that the plant extracts protect the kidney cell from calcium oxalate crystals, oxidative stress and also lessened the formation of renal stones by increasing the solubility and excretion of these stones through the urine (Tiwari *et al.,* 2012).

Gastroprotective/ Anti-ulcer activity: *Bryophyllum pinnatum* possess gastroprotective effects and it has been verified by its striking dose dependent defensive effect on ethanol induced gastric injury. However, further studies should be carried out to validate its use in gastric ulcers (Sharma *et al.,* 2014).

Effect on hematological parameters: *Bryophyllum pinnatum* methanolic extract of the leaves has exhibited a marked effect on various hematological parameters i.e. it improves the hemoglobin level, packed cell volume and total white blood cell count (Aprioku and Igbe, 2017).

Hepatoprotective activity: The plant has been monitored for its hepatoprotective activity. In rats, carbon tetrachloride stimulated hepatic injury was induced and found that the ethanolic extract of the leaves reduces the levels of liver enzymes, serum bilirubin, serum cholesterol and serum total protein. Results have illustrated that the herb has an obvious hepatoprotective activity. Increased regeneration of hepatocytes and microsomal enzymes inhibition also defend the liver from damage (Yadav and Dixit, 2003).

Anti-oxidant activity: The medicinal plant is tested for its anti-oxidant activity by metal chelating assay, 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay and 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay. Study outcomes have indicated that the ethanolic extract has marked anti-oxidant activity (Sindhu and Manorama, 2015). Roots extracts have also exhibited the anti-oxidant effects when analyzed by DPPH assay (Gupta and Banerjee, 2011).

Nephroprotective effects: *Bryophyllum pinnatum* is widely used for its nephroprotective activity in folklore and the rationale behind its use has been proven by the studies. Results of an investigation have shown that this effect is dose dependent. The nephroprotective activity against the genatmicin induced nephrotoxicity on the Wistar rat kidney was tested and it is anticipated that this effect is due to the plant anti-oxidant and radical scavenging properties (Harlalka *et al.,* 2007). It is

suggested that the juice of leaves is more effective in the cure of hyperactive bladder and has fewer side effects than anti-cholinergic drugs (Schuler *et al.,* 2012).

Wound healing activity: The plant is used topically for the healing of wounds in traditional therapeutics. It is proposed that the plant has saponins in huge amounts which promote wound healing by aggregating the erythrocytes. Moreover, tannins present in the plant also enhance the process of wound healing because of their astringent effect (Pattewar, 2012).

Neurosedative and muscle relaxant activity: *Bryophyllum pinnatum* has marked effect on the CNS and it has been proven that the methanolic extract produced a significant change in behavior pattern. A study results have demonstrated that the herb caused the CNS depression and dose-dependent stimulation of pentobarbitone sleeping time (Ojewole, 2005). Another study has also suggested that it is useful in treating the sleep troubles during pregnancy (Afzal *et al.,* 2013). The medicinal plant is helpful for the treatment and management of seizures and that was confirmed by testing on mice. It showed a dose dependent increase onset and duration of pentobarbitone-induced sleep and decline of exploratory activities in the head-dip and evasion tests. A dose-dependent muscle incoordination has been verified in the inclined screen, traction and climbing tests. In both strychnine and picrotoxin induced seizures it caused a late onset of convulsions (Yemitan and Salahdeen, 2005).

Figure 1. The plant of *Bryophyllum pinnatum*

Uterine relaxant activity: In traditional therapeutics, the plant is used for tocolysis and the rationale behind its use has proven by *in vitro* studies and further research is still required (Gwehenberger *et al.,* 2004). The effect of leaf press juice and its chemical fractions were studied on human myometrial strips and were found to be useful in relaxing the myometrial strips (Wächter *et al.,* 2011).

Warning: *Bryophyllum pinnatum* contains the cardiac bufadienolide glycosides which may cause cardiac poisoning, especially in grazing animals. So, it should be used with the caution in impaired digestive system and also avoid for long period as it subsides the immune system (Pattewar, 2012).

Products available in market: *Bryophyllum pinnatum* present in the Amantol cream as an active ingredient which is used to treat upper respiratory disorders (Quazi *et al.,* 2011).

Conclusion: The current study focuses on the latest evidence base information regarding pharmacognostical, phytochemical and pharmacological profile of the *Bryophyllum pinnatum*. It is concluded that the divine herb contains many valuable active pharmacological constituents that are responsible for plant various therapeutic effects. Different studies have explained and verified the wisdom behind its use in traditional medicines. More exploratory studies are still required to confirm and justify use of the herb in folk medicine and also to prove its safety and efficacy.

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PREVALENCE AND ROLE OF DIFFERENT RISK FACTORS WITH EMPHASIS ON GENETICS IN DEVELOPMENT OF PATHOPHYSIOLOGY OF CORONARY ARTERY DISEASE (CAD)

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SA designed the study and wrote the manuscript. KA reviewed the paper, S, SUS and MQ edited and formatted the paper. HS checked the plagiarism. All authors contributed equally to the submitted manuscript.

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ABSTRACT

To focus on the prevalence and role of different risk factors contributing in pathophysiology of coronary artery disease (CAD). Relevant articles published between 2006 and 2018 were studied with the help of various data bases including Google scholar, PubMed, Medline, Springer link, and Science direct. Articles published only in indexed journals were taken in account to ensure the credibility of data. Coronary artery disease (CAD) is a silently progressive chronic disorder which generally establishes overtime to an advance stage till the symptoms appear. In high income countries, the mortality rate has declined since 1980 whereas, middle and low income countries bear three quarters of the global CAD burden. South Asians are at a greater risk and the prevalence is 50% to 300% higher than the rest of the world. It is a multifactorial disorder and arises from an interaction between environmental and genetic factors. The conventional CAD risk factors (CRFs) include age, gender, blood lipids, smoking, blood pressure and diabetes. Most of the CAD risk factors are modifiable by targeting lifestyle changes, drug intervention and prior identification of those who are at high risk of developing disease. The variability in disease susceptibility in individuals exposed to similar environmental factors and having almost same CRFs can be attributed to the genetic variations. Genetic testing may improve discrimination over and above the CRFs.

Key Words: Coronary artery disease (CAD), Risk factors, genetic testing, Oxidative and inflammatory pathways, Diabetes, Hypertension, Obesity.

INTRODUCTION

The word cardio relates to heart and vascular, so cardiovascular diseases (CVDs) refer to a group of disorders related to heart and blood circulation. Among CVDs, coronary artery disease (CAD) is most common in the developing nations where it is a major threat and leading cause of mortality.[1] Coronary artery disease is also known as coronary heart disease (CHD) or Ischemic Heart Disease (IHD), in which constriction of blood vessels leads to the poor oxygen supply to the heart and subsequently results an imbalance state between oxygen demand and supply.[2] Regulation of blood flow to coronary arteries occurs through two major blood vessels (i) Resistance vessels and (ii) Epicardial conduit vessels. Resistance vessels oppose the blood flow as its diameter decreases less than 300 µm. Epicardial conduit vessels show little resistance to blood flow and driving pressure along this vessel is maintained in such a way that only a little blood pressure falls in distal epicardial vessels. This driving pressure is a key regulator of myocardial blood flow.[3] In coronary artery disease, atherosclerosis plays a key role in which obstruction of blood flow occurs due to some systemic disorder including lipid metabolism and inflammatory procedure. This can be subclinical disease in which plaque remains asymptomatic while in some cases it may be vulnerable due to thrombosis.[4] Atherosclerosis in the blood vessels leads toward the development of three major clinical presentation of disease: Stable angina which develops due to stenosis, Unstable angina that occurs due to the disruption in blood circulation by aggravation of thrombosis and Myocardial infarction which is the most serious condition that involves permanent obstruction of the blood circulation.[5] The CAD may manifest as acute (e.g., myocardial infarction) or chronic condition (e.g., stable symptoms due to ischemia).[6] The spotting of disease depends on clinical symptoms like difficult breathing, chest pain and sudden rise and fall in the blood troponin (cTns) level with variation in electrocardiography (ECG).[7] Furthermore psychological and different social factors such as work pressure, poor lifestyle, financial stress may also increase the chances of the onset of the disease.[8]

The main objective of current review is to put main emphasis on the prevalence and role of different risk factors contributing in pathophysiology of coronary artery disease (CAD). The study was carried out by reviewing the relevant articles published between 2006 and 2018 were considered with the help of various databases including Google scholar, PubMed, Medline, Springer link, and Science direct. To ensure the credibility of data the articles which wereonly publishedin indexed journalswere considered.

PREVALENCE AND MORTALITY RATE

According to the data presented by World Health Organization (WHO), the global burden of coronary artery disease in year 2002 was 7.1 million which was predicted to be raised to 11.1 million by year 2020. Worldwide, so far the most affected region where this disease is the major cause of death is the Indo-Pakistan subcontinent.[9] The likeliness of the occurrence of CAD In this region is four times high (40% higher mortality rate) as compared to the other European countries.[10] As mentioned earlier adoption of modern life style and increasing rate of metabolic disorders are the main grounds for high prevalence of disease. The metabolic disorder rate area is about 40% in the elderly population of south Indian urban region. One of the main predisposing factors of CAD is Obesity as in 2001 Obesity National Health survey has reported that the prevalence of obesity in Pakistan is about 13% in males and 23% in females.[12] As far as mortality of Coronary artery disease is concerned, a great variation is found among Asian continents i.e. low mortality rate in east and high mortality rate in south Asian countries.[13] The report of World Health Organization (WHO) states it to be the third most highest prevailing fatal disease on the globe.[14]

The most effected country by CVS diseases worldwide according to American Heart Association and World Health Organization, where it serves to be the first cause of mortality is United States.[15] Ischemic heart disease put a serious economic burden on public health systems. Due to mortality from congenital heart diseases, diabetes and stroke, WHO reported that India has lost 8.7 billion US dollars from national income.[16] Worldwide, the annual mortality rate due to non-communicable diseases (NCD) is about 38 million whereas the low and middle income countries account approximately 70-80% of this number. World health organization has reported in country profile (2014) of non-communicable diseases (NCD), that in Pakistan the communicable diseases account for about 38% while non-communicable disease contribute about 50% of the overall disease burden. Among all NCDs, cardiovascular disease contributes almost 19%, furthermore 1 in every 4 adults are presented with coronary artery disease.[17,18]

During 1960 to 2002, the Asian countries have displayed increase rate of about six fold in coronary artery disease in the urban areas while two fold rise in rural areas.19South Asian countries (India, Pakistan and Bangladesh) have about 22% of world population (among the top ten most populated countries in world) and incidence of coronary artery disease appeared 10 year earlier as compared to the rest of the world.[20] Over past 30 years downward trend in the progression of CAD is seen in various developed countries like United States, Canada, France, Australia. The major cause behind this decrease rate was awareness among people about risk factors related to this disease.[21]

RISK FACTORS

Both environmental and genetic factors have played a key role in advancement of coronary artery disease.There are two broad categories of conventional risk factors (CRFs):

1. Modifiable risk factors
2. Non –modifiable risk factors.

The prevalence of the conventional risk factors also differed among different countries.[22]

The modifiable risk factors include following

a) Smoking
b) Obesity
c) Diabetes mellitus
d) Hypertension
e) Dyslipidemia
f) Stress and depression

g) Sedentary life style

Non-modifiable risk factors are like

a) Male gender

b) Family history of premature coronary artery disease

c) Age > 40 years

d) A third category which is known as partly modifiable includes risk factors include menopause and personality type.

e) Other non-traditional risk factors are serum Apo lipoprotein-a, interleukin-6, highly sensitized c-reactive protein (hsCRP), myeloperoxidases, homocysteine and fibrinogen levels.[23]

MODIFIABLE RISK FACTORS ROLE IN CORONARY ARTERY DISEASE

Smoking and tobacco consumption

Overall there is 70% increase in the risk of death due to cardiovascular diseases in smokers as compared to non-smokers. In 1999, occurrence of about four million deaths was seen and the main cause behind these deaths was the use of tobacco.[24]

Smoking induces coronary artery disease by triggering of the following mechanisms:

a) By starting endothelial damage and impairing its function.

b) It reduces the level of high density lipoprotein (HDL).

c) In combination it also increases the intensity of proatherogenic lipids and also causes initiation of oxidation of these lipids.

d) It causes initiation of inflammation which cause development of procoagulation in circulation.[25]

Obesity and dyslipidemia

One of the main independent factor that contributes to the cause of coronary heart disease is Obesity. It is considered as a major cause of death particularly among south Asian population.[26] Obesity is responsible for about 23% of global burden of coronary heart diseases. Moreover the high levels of low density lipoprotein (LDL) with low levels of high density lipoprotein (HDL) are considered as a major risk factor for causing cardiovascular diseases. Obesity can be defined as when body mass index (BMI) is more than 30.[27] Obesity promotes the coronary artery disease by exacerbating factors: hypertension, plasma lipids and inflammation which puts a burden on heart and effecting both heart function and structure.[28]

Diabetes mellitus

Worldwide, diabetes mellitus prevalence increased around 177 million in 2000 and will increase to approximately 360 million cases by year 2030. According to EDIC (Epidemiology of Diabetes Interventions CAD) patient who have aggressive glucose control have less chance of developing cardiovascular diseases.[29] Diabetes is defined as more than 126 mg/dl of plasma glucose level in fasting. In type 2 diabetes mellitus, insulin sensitivity impairs due to release of free fatty acids (FFAs) from adipose tissue. Free fatty acids initiate production of reactive oxygen species which cause defect in activation of Phosphatidylinositol-3-Kinase and Protein Kinase B (PI3K-Akt) signaling and insulin receptor substrate (IRS-1), which ultimately leads toward the down regulation of insulin responsive glucose transporter 4 (GLUT-4).This results defect in phosphorylation of endothelial nitric oxide synthase (eNOS) causing endothelial dysfunction and increased vascular thickness which is an important predictor of cardiovascular disease.[30]

Hypertension

Hypertension or high blood pressure is a condition in which when cardiac muscles of heart pumps the blood there is increased force of blood against the wall of blood vessel. The major risk factors which lead towards the hypertension are kidney dysfunction, obesity, high triglycerides and high sodium to low potassium levels.[31] Arterial hypertension is stated as diastolic blood pressure which exceeds more than 90 mmHg or when systolic blood pressure is more than 140 mmHg. Hypertension is considered as a leading risk factor for cardiovascular diseases as it causes the disruption of two major pathways: hyperactivation of renin-angiotensin aldosterone system (RAAS) and increase in vascular tone.[32] Two major effectors molecules are renin and aldosterone. Active form of renin is produced by proteolytic and non- proteolytic cleavage of pro-renin. Then angiotensinogen is cleaved by renin into angiotensin I. This is cleaved by angiotensin-converting enzyme into angiotensin II, Then neutral endopeptidases or angiotensin converting enzymes 2 (ACE2) also cleave this angiotensin I into angiotensin-(1-7) which opposes angiotensin II thus favors the vasodilation of cardiac tissue.[33] Hypertension causes no symptoms thus also known as silent killer. Renin-angiotensin aldosterone system is an essential regulator of hemodynamic stability as it controls electrolyte balance and circulating volume in human body. The most important therapeutic target is based on RAAS inhibitors such as AT1 receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors causes the vasodilatation by lowering the degradation of bradykinin hence contribute towards the release of nitric oxide and prostaglandins while both inhibitors block angiotensin II.[34]

Sedentary life style

Coronary artery disease is also influenced by the adaptation of modern life style factors. Smoking is among the most notorious environmental risk factor for disease. Obese or overweight adult persons and high Body mass index (BMI) in late childhood is a major cause of disease. Moderate physical activity also proves beneficial in reducing the risk for development of disease.[35]

NON-MODIFIABLE RISK FACTORS ROLE IN CORONARY ARTERY DISEASE

Age and gender

Age is an another independent risk factor for developing coronary artery disease and advance aging accelerate the global burden of acquiring the cardiovascular diseases.[36] Reduced physical exertion and activity among older age groups is also considered as prime cause of developing heart diseases. Physical inactivity is reported by American Heart Association as a most contributing factor in the development of heart diseases.[27] The prognosis of cardiovascular diseases in female is late as compared to males i.e. about seven to ten years.[37] This gender differences is due to the variation in hormonal status as estrogen hormone in women

have protective antioxidant effect.[1] Estrogen mediates the vasodilation of endothelial blood vessels. This hormone has several regulating factors on metabolic disorders like inflammatory process, coagulant system and also plays an important role during lipid metabolism. But after menopause there is a decline in these estrogen levels and due to this hormonal fall there is a susceptibility of an increased risk of developing metabolic syndrome alongside cardiovascular diseases. This is because the disturbance in lipid metabolism occurs and central obesity with increase visceral fat also develops after menopause.[37]

Genetic basis of coronary artery disease

Atherosclerosis which is one of the key processes behind CAD is caused by both genetic and environmental factors. Atherosclerosis is characterized by inflammation of large arteries in which inflammatory, lipid molecules and fibrous element slowly start depositing in vessels walls. There is a transformation of macrophage into foam cells that happened as a result of binding of Oxidized LDL to macrophage along with release of interleukins which ultimately leads toward the development of fatty streaks. This could be characterized as atherosclerotic lesion in which there is deposition of foam cells in sub endothelial cells.Genetic factors are responsible for causing disease by two major mechanisms either by its direct intervention or by exerting their effects through cardiovascular risk factors.[38] During each stage of atherosclerosis cytokines plays a very important role and also mediate survival and proliferation of the cells which are involved in plaque formation (Table 1). Like IL1-1β is a pro-atherogenic it causes atherosclerosis due to causing oxidative stress and arterial inflammation.[39] The endothelial and smooth muscle cells apart from cytokine also proliferate due to inflammatory and biochemical modifications which ultimately progress toward the formation of plaque. The formation of plaque is then preceded by the rupturing of plaque which initiates the process of thrombosis i.e. facilitated due to the interaction between platelets, coagulation proteins and procoagulant material within the core of plaque.[5]

Table 1: Major Inflammatory Genes Involved in Pathogenesis of CAD

GENE	CYTOKINE
IL1A, IL1B, IL1RN	IL-1 system
IL-10	IL-10
IL-6	IL-6
TNF	TNF α
LTA	TNF α
TGFB1	TNF α1
TGFB2	TNF α2
SELE	E-Selection
SELP	P-Selection

There are several metabolic pathways which worksin an unorganized and improper manner during this disease and contributes in the disease advancement. The major pathways by which these genes presents their involvement in causing coronary artery disease are by regulating the lipid metabolism, oxidative stress, folate metabolism, DNA damage, Renin-angiotensin pathway and various other such inflammatory process.[40] Genes that involved in pathogenesis of CAD are presented in table 2,3,4 and 5.[5]

Table 2: Major Inflammatory Genes Involved in Pathogenesis of CAD

Metabolic pathway	Gene symbol	Gene name	Chromosomal location
Lipid metabolism	LPL	Lipoprotein Lipase	8p22
	APOE	Apolipoprotein E	19q13.2
	APOB	Apolipoprotein B	2p24 -p23
	APOA1	Apolipoprotein A -I	11q23 -q24
	APOA5	Apolipoprotein A -V	11q23
	APOC3	Apolipoprotein C -III	11q23.1 -11q23.2
	ABCA1	ATP -binding cassette A -I	9q31.1
	CETP	Cholesteryl transfer protein	16q21
	LIPC	Lipase	15q21 -q23
	LPA	Lipoprotein -a	6q26
	LDLR	Low density lipoprotein receptor	19p13.3

Table 3: Gene Involved in Endothelial Integrity

Metabolic pathway	Gene symbol	Gene name	Chromosomal location
Endothelial integrity	NOS3	Nitric oxide synthase 3	7q36

Table 4: Genes Involved in Renin Angiotensin Pathway

Metabolic pathway	Gene symbol	Gene name	Chromosomal location
Renin angiotensin pathway	ACE	Angiotensin converting enzyme	17q23.3
	AGT	Angiotensinogen	1q42-q23

Table 5:Gene Involved in Hormonal Pathway

Metabolic pathway	Gene symbol	Gene name	Chromosomal location
Hormonal	ESR1	Estrogen receptor 1	6q25.1

Other metabolic pathway involved in CAD

Gene involved in oxidation reduction pathway

Paraoxonases gene (PON) gene:

Paraoxonasesas the name indicates are group of enzymes which like most other enzymesare substrate specific. These are basically lactonases (acyl-homoserinelactonase). There are three types of paraoxonases which are PON1, PON2, and PON3. All these three enzymes metabolize compounds which are derived from arachidonic acid. Its lactonases activity enabled it to degrade and breakdown lipophilic lactones and thus it has ability to breakdown oxidized lipids in lipoproteins and cells. This gene property has enabled it to provide protection against cardiovascular diseases. The location of PON2 is intracellular while PON1 and PON3 are extracellular and associated with high density lipoproteins (HDL) which are present in many tissues as well as in circulation.[41]

PON1 gene:

The identification of this gene was first done by Abraham Mazur's in early 1950's and it was named after its ability to hydrolyzed paraoxon which is a toxic metabolite of insecticide parathion.[42] PON1 is responsible for provision of protection against atherosclerosis by preventing lipid per oxidation and this serves as one of its key role. It is a calcium dependent glycoprotein which is basically synthesized in liver and then secreted into plasma where it is associated with high density lipoproteins (HDL).[43] These enzymes are important in elimination of carcinogenic lipid soluble radicals by inhibiting the oxidation of low density lipoproteins and high density lipoproteins. Thus it blocks the formation of oxidized LDL and LDL derived oxidized phospholipids and also prevents oxidation of phospholipids of HDL.[44] PON1 have two major activities which may differ from each other in their mechanisms: one is the esterolytic and other is hydroxyperoxide activity. Its hydrolytic activity facilitates the degradation of esterified lipid. Basically the paraoxonases 1 avert the two key major pathways in atherosclerosis one is plaque formation and other one is foam cell formation. MCP-1 and M-CSF, the two major chemo attractant enables the process of foam cell formation when MCP-1 and M-CSF helps in the passage of monocytes through artery wall where they get converted into macrophage. LDL gets oxidized by reactive oxygen species (ROS) as they enter the blood vessels. Then macrophage has

scavenger receptors for this oxidized low density lipoprotein which leads to its transformation into the foam cells. PON 1 resists all these process by the following routes:

1. PON1 decreases the level of oxidized low density lipoproteins by inhibiting LDL oxygenation by ROS.

2. It also inhibits foam cell formation by stopping the release of chemo attractant.

3. It facilitates and helps in increase efflux of cholesterol from macrophages.[45]

PON1 structure:

The enzyme commission of the International Union of Biochemistry and Molecular Biology classified as an aryldialkylphosphatase. It is a glycoprotein which has 43KDa molecular mass and composed of 354 amino acids. Along its association with HDL it is also related to apo A1 and clusterin. X-ray crystallography revealed its structure which is a six bladed propeller which has a lid covering the active site passage along with it contains 2 calcium ions. One connected calcium ion is used for its stabilization of the whole structure while other is important for its activity.[46]

PON1 gene structure:

PON 1 is located on q arm of chromosome at position 21.3-22.1(49) where as PON2 and PON3 are also located on the same arm of chromosome adjacent to PON.[43] It is 26KB in size. There are total nine exons which are located in coding regions along with splice donor and accepter site. Polyadenylation signal sequence is absent in this gene. It has eight introns (non-coding) region while no canonical TATA box is present at 5 UTR. Sterol regulatory binding protein 2 (SREBP2) and specificity protein 1 (Sp-1) has binding sites on the promoter which up-regulate the level of PON1 in the presence of statins.[46]

Single nucleotide polymorphisms (SNPs) in PON1 gene

A total of two hundred single nucleotide polymorphisms have been reported in this PON1 gene.[47] (Table 6)

Single nucleotide polymorphism (Q192R) in coding region of PON1 gene

Table 6: SNP's Present in Different Regions of PON1 Gene.

Gene region	SNPs reported
Exonic region	5 SNPs
Intronic region	171 SNPs
Promoter region	7 SNPs
3´-untranslated regions	15 SNPs

Polymorphisms both in coding and promoter region of gene paraoxonases1 are functional SNPs.[48] PON1 gene coding region has two major polymorphisms in its coding region, one happens to be L55M where at position 55 methionine replacement occur instead of leucine.[49] The other polymorphism is present on exon 6 which is a Q192R where a glutamine (Q) to arginine (R) substitution occurs at position 192 or A G nucleotide substitution of Q192 (CAA) or R192 (CGA).[50] The catalytic activity of gene paraoxonases 1 is effected by single nucleotide polymorphism.[51] This polymorphism effect on activity is substrate dependent.[46] The glutamine variant has higher hydrolytic activity of substrate paraoxon as compare to arginine variant.[52] The R192 isoform is less stable in preventing oxidation of low density lipoprotein as compare to Q192. Thus R allele carriers are more vulnerable to cardiovascular diseases.[51] This gene polymorphism is also a risk factor and presents a major concern for developing other diseases like type 2 diabetes and inflammatory bowel disease, Parkinson's disease.[53] Though there is a difference among different ethnic group populations as north American Caucasians revealed R-allele as a risk allele for CAD while opposite results are obtained from Spanish, Korean and British Caucasians.[43]

Inflammatory pathways

Atherosclerosis is characterized by the chronic inflammation of coronary artery wall. The primary reason is accumulation of oxidized lipid in inner walls of arteries.[54] Inflammatory processes currently serves as a key cause for developing atherosclerotic plaque. A large number of inflammatory cells and proinflammatory cytokines (IL-1, IL-6and TNF) are present in the plaque that regulate inflammatory processes along with it involvement in cardiovascular diseases by changing the plaque stability.[55] Inflammatory cells which are important for the progression of atherosclerotic plaque produce cytokines like interleukin-1; interferon gamma and tumor necrosis factor.Various interleukins are related to arterial wall inflammatory process including Interlekin-6 which manages the expression of adhesion molecules and endothelial cell proliferation on arterial wall.[54]

Interleukin-1 gene cluster

Immune processes are regulated by cytokines which are short and small acting. The inflammatory process though is most importantly regulated by the interleukin-1 (IL-1), tissue repair and cell growth. IL-1 has three major members in this group: Interleukin-1 A (IL-1A), Interleukin- 1 B (IL-1B) and IL-1 RN (IL1RN). These three genes are present on q-arm of chromosome two (2q13-21) located within a 430 kb region. IL-1A and IL-1B encode the two agonists IL-1α and IL-1β respectively while IL-1 RN encodes one antagonist (IL-1Ra).[56] Both interleukin-1A and B bind to IL-1 receptor and are proinflammatory cytokines while an inhibitor of binding of this interleukin to receptors are IL-1 receptor antagonist. IL-1RN gene has 86bp variable numbers of tandem repeats (VNTR) which causes length variation within intron 2. IL-1 receptor antagonist expression depends upon the IL-1RN gene.[57] This interleukin 1 family has various roles in coronary artery disease development by regulating mitogenesis of smooth muscle cells, lipoprotein metabolism, and thrombogeneic response of endothelial cells, extracellular matrix production and

leukocyte adherence. This gene family have specific pathway for developing and rupturing of atherosclerotic plaque: (i) favor thrombosis by modifying endothelium, (ii) smooth muscles present in coronary artery are stimulated by the IL-1 gene through transforming growth factor-β (TGF-β) and (iii) it increases endothelial expression of adhesion molecules thus favoring atherosclerotic plaque progression.[56]

Interleukin-1B gene structure and SNP (-511) T>C

Interleukin gene 1 family is present on long arm of chromosome 2 present within 430-kb section of DNA. Interleukin 1 family contains nine genes including IL-1A, IL-1B, and IL-1RN.58IL-1β SNPC/T has a significant role in regulation of gene expression. The high levels of IL-1β expression is may be due to T (thymine) allele which replaced the cytosine in this single nucleotide polymorphism. Disease progression and severity depends upon the balance between IL-1 and IL-1Ra. There may occur an alteration in the Expression of IL-1receptor antagonist due to this single nucleotide polymorphism in the promoter region of IL-1β. Thus individuals carrying this polymorphism may changes susceptibility to diseases which includes interleukin 1 gene family such as myocardial infarction.[59] This also illustrates the variance in some ethnic region such as Caucasian have higher C allele frequency in control group as compared to cases while its opposite results are seen in African-Brazilians.[54] In Pakistan there is no available data related to this SNP so it is advantageous to study this polymorphism in this territory.

CONCLUSION

In conclusion, the complex diseases like CAD are difficult to dissect at the molecular level, however, advances in the understanding of the physiological pathways and the genes controlling the different biochemical pathways is helping to identify the risk factors unique to particular ethnic groups. In this regards, the role of common polymorphisms with low-modest effect sizes acting quantitatively can be crucial.

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Review on phytochemical evaluation and extraction of *Nigella sativa* (Kalongi) with pharmacological and traditional applications

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Key words: Medicinal plant, *Nigella sativa*, Kalongi, Phtyomedicine, Traditional medicine.

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Abstract

Nigella sativa is an annual flowering plant and belonging to family Ranunculaceae. The plant is commonly grown and nurtured in India and Pakistan. In addition, Mediterranean countries have also been reported to cultivate the plant. The height of the herb is about 45 cm and length of the leaves is from 2.5 to 5.0 cm. The shape of the leaves is lanceolate and linear. The color of petals of the flower is pale blue and its seeds are externally black in color and internally white. The plant has been utilized conventionally as well as pharmacologically for treatment of various diseases, i.e. chest congestion, hypertension, obesity, piles, bacterial infections, fever, jaundice, fungal infections, cancers, inflammation, oxidative stress, paralysis, fatigue etc. Seeds are consumed in a variety of ways interchangeably i.e. as condiment and spice. *Nigella sativa* is enriched with various significant phytochemicals, including: glycoscides, carbohydrates, alkaloids, tannins, alkaloids, volatile oil, terpenoids, and flavonoids, steroids resinous and phenolic compounds. The other most important chemical constituents are thymol, carvone, thymoquinone, nigellicimine, nigellicine, dithymoquinone and thymohydroquinone. The medicinal herb contains relatively good amounts of copper (Cu), iron (Fe), potassium (K), phosphorous (P), calcium (Ca) and zinc (Zn). Natural products have been used as a major source of treatment and diet for the provision of essential nutrition and health for both animal and humans. All these aspects catch the attention of researchers to approach the utility, efficiency and potency of *Nigella sativa*.

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Introduction

Nigella sativa which is commonly known as Kalongi is an annual flowering plant. It is responsible for causing the stimulation of energy in the body and it alleviates fatigue and dispiritedness (Abbas *et al.,* 2012). It has been widely used in Unani Tibb system of medicine as a cure for many diseases. According to different researches in medicine it has been approved to be used as astringent, bitter stimulant, diuretic, emmenagogue, anthelminitic. Moreover, it has also been directed for treating piles, paralysis, intermittent fever, jaundice, dyspepsia and skin diseases Javed and Shahid, 2010). World Health Organization (WHO) has estimated that almost 80% of the people globally treat their ailments with medicinal plants. *Nigella sativa* as a whole plant could be utilized for the purpose of phytomedicine. Plants main activity and therapeutic profile is due to the presence and formation of secondary metabolites which are biosynthesized within the plant from primary metabolites. Information of occurrence of these metabolites within the *Nigella Sativa* has been obtained from various analytical and pharmacological procedures (Malika *et al.,* 2004). The characterization of these phytochemical constituents could be done as glycoscides, carbohydrates, alkaloids, tannins, alkaloids, volatile oil, terpenoids, and flavonoids, steroids resinous and phenolic compounds. The chemical nature of these constituents is entirely diverse due to which their pharmacological action also differs (Khan, 1999). These phyto constituents are formed through different metabolic pathways and this is the reason for their diversification and different pharmacological uses as well as other roles such as veterinary sciences, agriculture, forestry and human therapy. Besides these usages have been experimentally tested and corroborated scientifically. *Nigella sativa* is native herbaceous *plant*. It is grown is different countries and is named in a different languages depending on the region where it is grown e.g. kalajira (Bangali), shonaiz (Persian), kalonji (Urdu), habba-tusawda (Arabic) and black cumin (English). *Nigella sativa* is commonly grown and nurtured in India and Pakistan. In addition Mediterranean countries have also been reported to cultivate the plant well (Sofowora, 1993). Religiously black seeds have been in use by various communities. For instance Muslims has a strong acceptance of its use for curing every disease excluding death. Hence the seeds have a popular use as nutritional, folk, natural and medicinal plant. Its use has an ancient history which has been thoroughly verified by modern day scientific researches. For this reason and because of the presence of several active constituents *Nigella sativa* is utilized for the treatment and healing of different diseases (Shafi *et al.,* 2009). This study is aimed to provide comprehensive review about the plant *Nigella sativa* and its pharmacological activities.

Nigella sativa

Botanical description

In English *Nigella sativa* is also commonly known as Black caraway and Black seed. Though whole part of the plant could be utilized as medicine but the main part of the plant that constitutes main phyto-constituents is seeds. It is the member of family Ranunculaceae. It is found in southwest and South Asia. The height of the herb is about 45 cm and length of the leaves is from 2.5-5.0 cm. The shape of the leaves is lanceolate and linear. The color of petals of the flower is pale blue and its seeds are externally black in color and internally white also seeds are dicotyledonous and are angular. *Nigella Sativa* has a characteristic aromatic odor and bitter in taste (Chopra *et al.,* 1958; Atta-ur-Rahman *et al.,* 1995). The plant has divided but not thread like leaves with overall height of the plant is 20-30cm or is 7.9-11.8 inches tall. The petals are five to ten in number (Daba and Abdel Rahman, 1998; Saleem and Hossain, 2000). The arrangement of flower is delicate. The plant usually follows sexual reproduction and is required to cultivate from seeds. Seeds are developed indoor four- six weeks prior to the initiation of last average frost date. This is to avoid any sort of damage to young seedlings by extreme weather conditions. Then the seeds are sown and grown outdoor in mixture of clay. The seed cultivation requires specific sort of sandy or heavy clays and soil requires moist conditions for its appropriate cultivation and growth.

Furthermore, water and fertilizers play essential role in the proper growth of the plant. The fruit of the plant constitutes united follicles which are three to seven in number each comprising various seeds. The size of fruit is quite large and inflated and is in capsule form. The plant bears flowers and fruits from January to April. Generally, the appropriate time for the cultivation of plant is from November to April and the germination of seed occurs within 10-15 days. It could be grown asexually in vitro from the callus culture from roots, leaf and stem plants from special seedlings. Seeds besides being small aretrigonus, angular, tubercular, dicotyledonous, trigonus, and are regulose-tubercular (Rifat-uz-Zaman and Khan, 2004; Bamosa *et al.,* 2010). The seeds when cut into transverse section show a single epidermal layer comprising of oval cells which have dense walls and has an external covering of papillose cuticle consisting filling of dark brown contents. Epidermal layer is then followed by parenchymatous cells which are comprised of 2-4 dense walled layers elongated tangentially, followed by a reddish brown pigmented layer composed of thick walled, rectangular, elongated cells (Rifat-uz-Zaman and Khan, 2004). Seeds are consumed in a variety of ways interchangeably i.e. as condiment and spice (El-Dakhakhny, 1963; Agrawal *et al.,* 1979; Beckstrom and Duke, 1994; El-Dakhakhny *et al.,* 2000).

Ethnopharmacology of Nigella sativa

In Northern Africa, the plant has been used traditionally used for the treatment of skin diseases (eczema), upper respiratory tract diseases (bronchitis, cough, influenza) and for other ailments like fever, headache and rheumatic diseases. However, In Indian traditional medicine system black cumin seeds are utilized in variety of ways such as anti-paralytic, antipyretic, anti-flatulent, anti-carminative, bitter stimulating agent, diuretic, anthelmintic, as astringent, anti-hepatic, as emmenagogue, for treatment of jaundice, piles, dyslipidemia, hypertension and dermatological problems. Also, it has been used as tonic, analgesic, as liver tonic and for other GIT diseases. Moreover, Gulf region of Arabia has been using black seeds for the management of hypertension, paralysis, obesity, heart diseases and chest congestion as well as for the treatment of infection, inflammation, GIT diseases, rheumatoid ailments, diabetes, dysmenorrhea, chronic headache, migraine, dizziness, hemiplegia, back pain and for treating flatulence (Gilani *et al.,* 2004; Ahmad *et al.,* 2013). Additionally, it has also been utilized as spice and preservative. Besides there are few more applications which are included relieving toothache, preventing radiation damage and post- surgical adhesions along with lethargy (Randhawa *et al.,* 2002).

General collection and extraction methods for experiments

The dry seeds of *Nigella sativa* are grounded in a mortar and pestle to convert it into the powder form. Then, the powder was passed through the sieve to get rid of any unwanted particle or enities. Different solvents are used for the extraction of *Nigella sativa* through different methods such as, chloroform, methanol hydro-alcoholic solution (20% DM water in methanol). Powder is loaded in the extraction equipment which is run by solvent with (no. of cycles required). Collect the extract, filter it and evaporate it (El-Kadi and Kandil, 1987; El-Tahir *et al.,* 1993; El-Daly, 1998).

Extraction by speed extractor: The crushed powder is placed in the extractors together with purified sand. The solvent containing principle is in its purified form. This is then preceded by automatic extraction which is continued till three cycles are completed and the colour of the extract begins to change and becomes potent. The procedure remains sustained till potent dark colored extract is obtained. Same procedure is followed with four different polar and non- polar solvents. Then the resultant extract is kept in dried and clean container (Saleem and Hossain, 2000; El-Dakhakhny *et al.,* 2000).

Extraction by speed extractor: Similarly active constituents could be obtained through extraction by soxhlet extractor which is also a hot continuous extraction. The extraction is continued and repeated

with different solvents of varied polarity till the desired extract is obtained. For prevention of impurities dried and clean extractor is used (Beckstrom and Duke, 1994; El-Daly, 1998).

Extraction by aspirator: Furthermore extraction could be carried out with aspirator as well. Powdered form is obtained after drying and crushing the seeds. Solvents of diverse polarity are used and decanted. The solvent is then subjected to undisturbed overnight placement preceded by its collection and storage the next day. These resultant stored extracts are then concentrated and dried by using Rota evaporator equipment till concentrated oil or sticky solid is obtained. Then the division of hydro-alcoholic portion is done against chloroform and ethyl-acetate. The remainder portion which is organic in nature is collected and dried till all the oil droplets are collected. They are mixed with parent extract. Then, it is stored in cool and dry place. The left part is only dried to form solid (El Tahir *et al.,* 1993; Hailat *et al.,* 1995; El-Daly, 1998 ;).

Phytochemistry

There are various chemical constituents which are isolated from the black cumin. The main chemical constituents are thymol, carvone, thymoquinone, nigellicimine, nigellicine, dithymoquinone and thymohydroquinone as shown in figure 1.

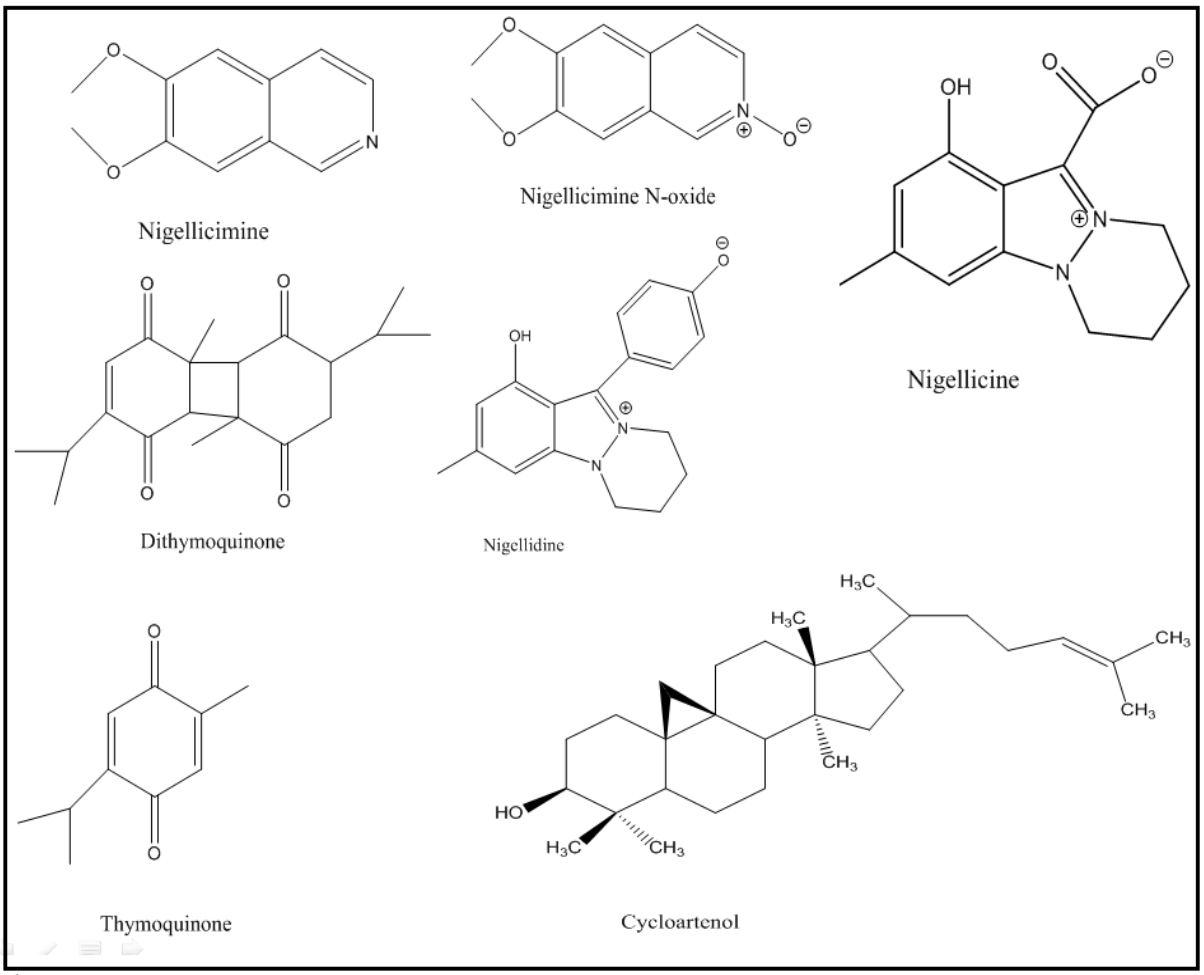

Fig. 1. Various important phytochemicals of *Nigella sativa*.

Extensive studies were done to evaluate the constitution of black cumin seeds. *Nigella sativa* seeds have the composition of saponins, essential oils, alkaloids, fixed oils, and proteins **(**Staphylakis and Gegiou, 1986; Khan, 1999; Goreja, 2003). The unsaturated fatty acids comprises of myristic acid, linoleic acid, palmitic acid, arachidonic acid, oleic acid, eicosadienoic acid, palmitoleic acid and stearic

acid. However fixed oils constitutes 32-40% apart from other constituents such as sterol glycosides, beta-sitosterol, sterolesters, cycloartenol and cycloeucalenol. (Tembhurne *et al.,* 2014). The saturated fatty acids are also present alongside volatile oils (0.4-0.45%) which are carvacrol, *p*-cymene, d-limonene, α and β-pinene, d-citronellol and nigellone which serves as the only constituent with the carbonyl content. Seeds of *Nigella sativa* have volatile oils which contains t-anethole, 4-terpineol and longifoline (Enomoto *et al.,* 2001; Ahmad *et al.,* 2013); Black seed also have few traces of pentacyclictriterpene (Hosseinzadeh *et al*., 2005). Also there are two different forms of alkaloids in the black cumin seed: Isoquinoline alkaloids that comprises of the constituents mentioned earlier as nigellicimine, nigelliciminen-oxide and Pyrazol alkaloids that includes: nigellidine and nigellicine. Besides this *Nigella sativa* is also composed of nutritional content such as proteins involving nearly nine essential amino acids, fats, mineral elements, carbohydrates and vitamins (Haq *et al.,* 1999). Sodium dodecyl sulfate poly acryl amide gel electrophoresis (SDS-PAGE) was used for the fractionation of the plant seed) which showed bands that ranged from 94 to 100kDa molecular mass. There are some more contents present in black seeds such as alpha hederine, citronellol and limonene as well as have relatively good amounts of Copper(Cu), Iron (Fe), Potassium (K) , Phosphorous (P), Calcium (Ca) and Zinc (Zn). In N. sativa, the therapeutic actions are generally due to the occurance of quinine which in turn has high content of thymoquinone (TQ). TQ is responsible for treating convulsions (Hosseinzadeh *et al.,* 2004; Parvardeh *et al.,* 2005, Hosseinzadeh *et al.,* 2005), reduces oxidative stress levels (Hosseinzadeh *et al.,* 2012), reduces inflammation (El Gazzar *et al.,* 2006), used as anti-carcinogenic (Gali-Muhtasib *et al.,* 2008), antifungal activity (Abdel Azeiz *et al.,* 2013) and antibacterial activity (Halawani, 2009).

Physicochemical analysis

Nigella sativa oil has been investigated for the free fatty acid extinction coefficients (K232andK270), relative density (Ph.Eur.8.0/2.2.5), iodine value (Ph.Eur.8.0/2.5.4) (%Oleicacid) (Ph.Eur.8.0/2.5.1), saponification value (Ph.Eur.8.0/2.5.6), un-saponification matter(Ph.Eur.8.0/2.5.7), peroxide value (Ph.Eur.8.0/2.5.5) refractive index (Ph.Eur.8.0/2.2.6), (Satyavati *et al.,* 1987; Aitzetmüller *et al.,* 1997; Cheikh-Rouhou *et al.,* 2007), iodine value and refractive index were determined according to AOCS recommended practices Ca5a-40,Cd8b-90,Ch5-91,Cc7-25,Cd1c-85; Free fatty acid content, peroxide value (PV), respectively (AOCS,1998). Free fatty acid content was expressed as percent to oleicacid, extinction coefficient (K 232andK 270) was expressed as the specific extinction of a 1%(w/v) solution of oil in cyclohexanein 1cm cellpathlength PV was stated as milli equivalent of active oxygen per kilogram of oil (MeqO2/kg oil), and, a CARY100 Variant UV spectrometer was used (Aitzetmüller *et al.,* 1997).

Oxidative stability of seed oils

Determination of oxidative stability of each sample was done as per the AOCS (American Oil Chemical Society) recommendations Cd12b-92 (AOCS,1998) such as the documentation of the induction period (IP,h) was done by a 743 Rancimat (Metrohm,Switzerland) apparatus using 3 go foil sample was done. Samples were poured in standard tubes of Rancimat and tested by placed in Rancimat standard tubes were investigated by warming at 110°C with an adjustment of an air flow of 20L/h (Cheikh-Rouhou *et al.,* 2007).The values have been determined and compared statistically (Aitzetmüller *et al.,* 1997; Cheikh-Rouhou *et al.,* 2007).

Nigella sativa pharmacological actions

Extensive *in vitro* and *in vivo* research has been done in order to confirm plant various pharmacological and toxicological effects.

Anti-cancer properties: The plant is a valuable source of thymoquinone which has significant potential to cure cancer. It inhibits the different signaling pathways that are involved in abnormal cell division and production hence proved to be useful for the cure

of different malignant tumors (Chaieb *et al.,* 2011; Kouidhi *et al.,* 2011).

Anti-obesity: Previous studies have confirmed its beneficial effect in reduction of the body weight. The plant has an ability to lessen the body mass index (BMI) especially in diabetic patients. This effect is may be due to the peroxidation of the lipids which then resulted into the overall decrease in the body weight (Qidwai *et al.,* 2009; Razavi and Hosseinzadeh, 2014).

Reproductive system: Many investigations have proven that the black seed oil could impede the involuntary actions of uterine smooth muscle and also effect the oxytocin induced contractions (Parhizkar *et al.,* 2016).

Bronchodilator effect: *Nigella sativa* has potential to inhibit the histamine H1 and can be used as the bronchodilator. Further, it also stimulates the inhibitory non-adrenergic, non-cholinergic nervous system (NANC) or inhibition of stimulatory NANC. The opening of potassium channels and inhibition of phosphodiesterase may be the alternative methods for the bronchodilator effect (VanAmsterdam *et al.,* 1989; Buckle *et al.*, 1993) and most significantly calcium blockage (Miyaharaetal. 1993), due to the calcium inhibitory effect it also relaxes the bronchial muscles (Boskabady *et al.,* 2010).

Antioxidant effect; the plant isolated phytochemicals by the thin layer chromatography have demonstrated the compounds radical scavenging abilities and shown the potent anti-oxidant activity (Burits and Bucar, 2000).

Anti-inflammatory and analgesic actions: By applying the three different nociceptive experiments on the rats and mice i.e. hot plate method, tail-pinched method and acetic acid-induced writhing test it was concluded that the plant has ability to reduce the pain stimulus. The findings have confirmed that the plant black seeds fixed oil has potential anti-nociceptive actions that are may be due to an opioid part in the oil. This portion is act as naloxoneis i.e. an inhibitory effect for the pain. Moreover, the plant oil has considerable CNS depressing activities (Al-Ghamdi MS, 2001).

Anti-carcinogenic and mutagenic activity: Various studies have been conducted to evaluate the anti-cancer effects of the plant. The crude methanol seed extract has showed a significant cytotoxicity activity on tumors i.e. Erlich ascites carcinoma, Dalton's ascites lymphoma and sarcoma. The researchers have verified the cytotoxic ability of the black seeds *in vivo* by deterring the growth of Erlich ascites carcinoma (Salem, 2005; Randhawa and Alghamdi, 2011).

Hepatic and nephrotoxicity protection: Around the globe, this herb is used to treat various liver related disorders in traditional medicine. Its hepatic protective role has been confirmed on rats. The findings of the study have verified that the plant phyto constituent named thymoquinone has an ability to reduce the hepatic toxicity which was induced by the tert-butyl hydro peroxide (TBHP). A study has illustrated the thymoquinone effect as kidney protection when administered cisplatin. Further, it also increases the antitumor activity of the medicine (Mahmoud *et al.,* 2002).

Respiratory actions: It has been investigated that the intravenous administration of the seeds volatile oils increase the intra tracheal pressure and respiratory rate and this effect is dose dependant (El-Tahir *et al.,* 1993a). However, TQ has little or no effect on rate of respiration but increased the intra tracheal pressure (Mathur *et al.,* 2011).

Antidiabetic action: Traditionally the plant has been used to treat the diabetes and this anti-diabetic activity of the herb was evaluated in rabbits. The findings of a study has described that after 4-6 hour of intra-peritoneal administration of the plant oil at dose 50mg/kg significantly decreased (about15%–23%) the fasting blood glucose concentration in both normal and hyper glycemic rabbits. Insulin concentration was not affected which highlighted that

the hypoglycemic effect was moderated by an unknown mechanism (Bamosa *et al.,* 2010).

Cardiovascular activities: The plant is proved to be quite beneficial to treat various cardiovascular disorders. Many studies were carried on the rats and results have demonstrated that the herb oil is effective to treat hypertension. It is also helpful in reducing the heart rate and could be possibly use to treat arrhythmia. The methanol soluble portion of seeds oil showed inhibitory effects on arachidonic acid induced platelet aggregation and blood coagulation. Several compounds having anticoagulation effect were isolated and some of them are more potent than aspirin (Houghton *et al.,* 1995).

Antiulcer action: An investigation on rats has demonstrated that the aqueous extract of the herb seeds was effective in reducing the ulcer index that was induced by aspirin. The treatment decreased peptic activity and production of the acid and it did not alter the mucin activity. Hence, these studies have proven the gastric protective effect of the plant (Hanafy and Hatem, 1991).

Anti-microbial and anti-parasitic properties: The oil and the extract have been investigated to have a broad spectrum of activity against microbes. For example, in *in vitro* studies have shown that the essential oils have marked antibacterial effects even in 1:100 dilutions against number of organisms, included: *Staphylococcus albus*, *Salmonella typhi*, *Escherichia coli*, *Shigella niger* and *Vibrio cholera*. A study has demonstrated the effectiveness in reducing the number of *Schistosoma mansoni* worms in the liver and total number of ova in both the liver and intestine pointed when volatile oil was administered orally to dose of 2.5 and 5.0mL/kg for two weeks (Hanafy and Hatem, 1991).

Nigella sativa toxicological effects

The plant seed extract and its isolated phtyoconstituents have demonstrated the minimum level of the toxicity i.e. the TQ value of LD_{50} was determined to be 2.4g/kg (range1.52–3.77). The acute administration of the high doses resulted into the liver, kidney and heart toxicity. Introduction of TQ in the drinking water of mice with concentrations of upto 0.03% for 3 months resulted in no sign of toxicity, except for a significant reduction in concentration of fasting plasma glucose. Oil of the plant is used topically to treat various skin infections and to reduce the inflammation. Despite the fact that it is quite useful, two case of contact dermatitis was reported after application of the pure seed oil. Furthermore, it also enhances the concentrations of the certain enzymes i.e. creatine phosphokinase, lactate dehydrogenase, alanine amino transferase and creatinine concentrations. In clinical trials which were conducted on recruited patients it was concluded that the plant has potential to reduce the appetite and overall decrease in the body weight (Ali and Blunden, 2003; Khader *et al.,* 2009).

Conclusion

Nigella sativa is enriched with valuable phytochemicals which are responsible for its various therapeutic activities. Detailed studies are required to ensure its safety and efficacy and possible use of phytochemicals as drug candidate.

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REVIEW ARTICLE

CANCER EPIGENETICS AND THE ROLE OF DIETARY ELEMENTS

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ABSTRACT

Cancer has been a fatal disease since many decades. Over the time, it is presented in multiple ways and is a matter of consideration as accounts for the high rate of mortality. The aim of the current review was to focus on the genetics, epigenetics factors and role of medicinal plants for the cure of this inimical disease. Related articles available in English language (2002-2018) were reviewed with help of different database, including PubMed, Springer Link, Medline, Google Scholar and ScienceDirect. In order to ensure credibility and accuracy of data only those articles were considered which are published in indexed journals i.e. Web of Science and Scopus. This project was conducted at the Department of Pharmacy, Government College University, Faisalabad, Pakistan from 02-01-2019 to 28-02-2019. The genetic machinery is vibrantly involved in the interpretation of the signals and is observed to be affected by various dietary factors. A sequence of modified activities is observed with use of these dietary elements. However, the modification is reviewed through the histone acetyltransferase (HAT), histone deacetylase (HDAC) and DNA methyl transferase (DNMTs), effecting the expression of gene. These modified genes, in turn then express the signals in multiple reformed ways. Different dietary elements that are used such as polyphenol, alkaloid and flavonoids are effective against cancer. The progression of disease involves genetics and epigenetics due to amplification, translocation and mutation during gene expression. Though, many studies have been conducted elaborating the role of plants and their ingredients which play a part in inhibition of cancerous cells by blockade of cell cycle and apoptosis; more in-depth investigations are still required to identify the new drug target and novel therapeutic modalities.

KEY WORDS: Cancer; Epigenetics; Histone Acetyltransferase; Histone Deacetylase; Medicinal Plants.

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INTRODUCTION

From the beginning of time, cancer has been presented in a variety of ways. Right from the time of Hippocrates, cancer was named following evidence of thick blood vessels feeding the tumor, acquiring a shape resembling the claw of a crab that grabs the tumor. Later in the era of Laennec, cancer was considered as a disease that is predisposed at the different stages of cell proliferation.[1] Last decade has shown up with the development of the genetic model of cancer. Boveri et al. was the first to link cancer with genetics due to the displacement of abnormal chromosome in cancer cells.[2]

Now a great deal of development has been done in the identification of the genes that are marked for the progression of cancer in different organs, like, mutations in ERBB2 and EGFR for the disposition of lung cancer, HER2/NEU mutations in breast cancer, BCR-ABL predisposition in chronic myelocytic leukemia. The studies have revealed the prevalence of disease on the basis of methylation in the DNA, whether it is hyper- or hypomethylation.[3] Methylation occurs on carbon no. 5 of cytosine. Also, summing up of different functional groups on the histone tails

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is observed. This is a common phenomenon in health and disease to express codes in genomes that vary in population .[4] This involves acetylation and deacetylation of histones. Histones are present as core entrapped in octamers of DNA chains made of 146 base pairs. Among these chains, one is a tetramer (H3-H4) and two chains are dimers (H2A and H2B). Each core is separated from other by almost 60 base-pairs in between. Histone acetylation in chromatin governs activation of genes for expression called as euchromatin while inactivated or closed chromatin doesnot express and is called heterochromatin. The base pairs of DNA are bound to the histone through epsilon-amino acid of lysine. This binding is aided by the enzyme called histone acetyltransferase (HAT). It helps to initiate the modification by acetylation of lysine residue in histones. Another enzyme involved is HDAC, histone de acetylase, meant for deacetylation of the lysine on histones.[5]

As the scenario predicts, epigenetics is concerned with the transfer of the heritable memory in genetics through meiosis and mitosis. The translational mechanistic of DNA is actually involved in the development of the human tissues and organs. The pluripotent cells are destined according to the memory they retain during the translation of DNA. In this process of transfer of heritage through genes: methylation of DNA, chromatin material reassembling and alterations and replacement of histone tails and histones, respectively, is involved. Irregularities in any of these stages may cause cancer lesions.[6]

Now, epigenetics is one of the primary cause in progression of malignancy. Epigenetic disease variations can be influenced by environmental and dietary factors. Animal studies have revealed that environment-induced epigenetic changes can be facilitated by diet. Different dietary elements that are used such as polyphenol and alkaloid are effective against cancer by acting on HDAC.[7]

In DNA methylation, variant other enzymes are involved such as DNMTs which cause DNA silencing and non-coding genomic regions. DNMT1 act as conservative methylating agent while DNMT3a and DNMT3b act to initiate de novo pathway. These are molecular targets in epigenetics for available anti cancer drugs that are approved by FDA.[8]

RNA silencing can occur in two ways: tracriptional and post-transcriptional. Post transcription silencing of genes occurs to produce hetrochromatin thereby wrapping up the chromatin material and the transcription sites. Connection of RNA silencing in different organisms has been studied in detail. For example, in the yeast (*Schizoaccharomyces pombe*) silencing of different components of the RNA machinery results in the inhibition of methylation of H3k9 along with disruption of centromere function.[9]

Epigenetics and Dietary components

Curcumin

Curcumin obtained from the rhizome of the *Curcuma longa*, and commonly called as turmeric. It's been used as a traditional drug in Chinese ayurveda medicine. It is under investigation for its beneficial properties.[10] It contains curcuminoid complex (80%), demethoxycurcumin (17%) and bisdemethoxycurcumin (3%). In cell culture of tumors, curcumin has shown to have potent inhibitory effects on profliferation of tumors. It also inhibits the tumor development in various xeno-transplant and ortho-transplant mouse models. It has shown anticancer activity with chemopreventive and chemotherapeutic effect with no observable side effects.[11]

HDAC inhibition

Curcumin is involved in modifying the various protein expressions. It inhibits the cell proliferation, angiogenesis and metastasis of different form of cancer. Curcumin has activity against HDAC. It stimulates apoptotic induced brain cell death through PRAP and caspase 3 by histone deacetylation.[12]

HAT inhibition

P300/CBP HAT activity is inhibited by curcumin, both, *in vivo* and *in vitro*. Curcumin strongly inhibits the H3 and H4 acetylation by p300/CBP. These findings are very important in cancer because HAT activity has a significant role in cancer.[13] Curcumin also reported as epigenetic modulator of TREM-1 gene expression, and this epigenetic modulation in TREM 1 promoter region done by inhibiting p300 activity, which causes hypoacetylation of histone 3 and 4.[14] HAT, p300 and acetylated CBP/p300 gene expression are down regulated by curcumin. Following reduction in gene expressions used to minimize various diabetic problems by inhibiting high glucose induced proinflammatory cytokines. Curcumin is very effective against the diabetes induced by streptozotacin in male Sprague dawley rats.[15]

Resveratrol

Red grapes, peanuts and pines are great sources for resveratrol. Dimethyl ether derivative of resveratrol is pterostilbene (3, 5-dimethoxy-4-hydroxystilbene). It is an ayurvedic medicine. These polyphenols have activity against the DNA methyltransferases (DNMTs) enzyme.[16]

HDAC Inhibition

It was found that when these two compounds are given in combination they inhibit the activity of

SIRT1, a type III histone deacetylase (HDAC).[17] Resveratrol causes inhibition of MTA1/NurD complex that is involved in the prostate cancer. This complex over expression in prostate cancer results in tumor aggressiveness. Resveratrol causes suppression of MTA1 protein and causes acetylation of P53.[18] Resveratrol regulates transcriptional activation and suppression of various genes including p53 and activation of SIRT1. SIRT1 has HDAC activity and thus it is effective against cancer.[19] Now efforts are being focused to increase bioavailability of resveratrol as it is very effective against cancer.[20]

DNMT Inhibition

Resveratrol has less DNMT inhibiting activity. However, it prevents epigenetic silencing of BRCA1 which is a tumor suppressor protein.[21] Another study revealed that resveratrol activating SIRT1 and p300, which are HDAC inhibitors. SIRT1 encoded protein are very important for the treatment of cancer and its chemo preventive action is meditated by resveratrol.[22]

Green tea

Epigallocatechin (EGCG) found in green tea is a polyphenol that could inhibit DNA methylation. EGCG produces a decrease in an enzyme activity which is called DNMT1. EGCG have anti-neoplastic, anti-inflammatory and antitumor effect.[23] EGCG may induce apoptosis and cell cycle arrest. EGCG has also been involved in regulation of many signal transduction pathways. The transduction pathway includes JAK/STAT, MAPK, NF-□B, and AP-1. Additionally, green tea has been involved in induction of tumor suppressor genes p53, p21 and p16.[24] EGCG induces apoptosis by over expression of TFPI-2. So it is an effective agent for the cure of renal cell carcinoma.[25] It is also involved in the reduction of expression of hTERT, a major catalytic unit of telomerase.[26,27]

DNMT AND HDAC Inhibition

Epigenetic regulation by EGCG is important in chemoprevention because of its DNA methyltransferases (DNMTs) and histone acetyltransferases (HATs) inhibition activities.[28] EGCG activity by inhibition of DNMTs has been shown to lead to global and local hypo methylation of a number of gene promoters.[29]

Genistein

Genistein (GE) isoflavones, are found in various plants including soya beans. It has anticancer and antiangiogenic activity. Genistein is involved in gene transcription and gene silencing activity by modifying epigenetic events.[30]

Genistein epigenetic modification involves not only in reactivation of tumor suppressor genes but also inhibits the expression of a tumor promoter gene such as hTERT. In human breast cancer cells it involves in transcriptional repression of hTERT expression. It was found that in low concentration, genistein moderately demethylated the GSTP1 tumor suppressor gene promoter and reactivated ts expression in MDA-MB-468 human breast cancer cells.[31]

Apoptosis mechanism

A study has reported that Genistein (GE) is involved in induction of apoptosis and reduction in proliferation in human prostate cancer. HT-29 and colo320 are suppressed by GE isoflavones. Additionally, other investigation showed that GE inhibits the growth of HCT 116 cells with a dose-dependent manner. Genistein inhibits the augmentation of breast cancer cell lines ADA/MB231, MCF-7 and HBL-100. Peterson and Barnes stated that GE (50 or 100 μM) inhibits ER-positive breast cancer cell growth in the human.[32] Numerous investigations have shown that GE causes apoptosis at 50-100 μM concentrations.[33]

Cell cycle arrest

GE causes cell cycle arrest at G2/M in ovarian cancer. In ovarian cancer, GE causes supression of cell cycle arrest at the G2/M phase. Some researchers have reported the relationship between GE and Bcl-2 family.[34]

Inhibition of Metastasis of cancer cells

Lee et al. investigated that GE can inhibit metastasis of cancer cells.[35] Another study showed by Zhang et al. and Chen et al. that use of foods rich in soy can decrease the frequency of ovarian cancer. With a high intake of genistein in the women leads to a lowering in the rate of cancer.[36]

Sulforaphane

Isothiocyanate is found mainly in cruciferous vegetables like cabbage sprouts. It has shown significant activity against the cancer.[37] Different studies have reported that increase utilization of cruciferous vegetables, expressively decreases cancer risk.[38] It has shown anticancer effect through various mechanisms, including cell cycle arrest, apoptosis and phase 2 detoxification enzyme.[39] Sulforaphane (SFN) involved in supression of HDAC activity, and this inhibition involves in epigenetic mechanism. SFN showed an irreversible cell arrest which causes inhibition of cellular growth. In LNCap prostate cancer cells an increase in the G2/M cell cycle arrest was observed after SFN incubation in a concentration and time dependent manner.[40] SFN induced cell death in different tumor cell lines by increased p53, activated caspase -3 proteins and decrease hypoxia inducible factor -1 alpha activation.[41] Apoptosis in human breast cancer MDA-MB-231 cells by SFN was initiated by induction of Fas ligand, which triggered the pathway caspase-8, caspase -3and PRAP.[37]

Lycophene

Lycopene is found in tomatoes, and other red fruits. It regulates the expression of various genes pertinent to cell cycle control. It also regulates DNA repair apoptosis in MCF-7 and MDA-MA-231 breast cancer cells.[42] Lycopene has antioxidant activity. A number of studies showed that it has activity against prostate adenocarcinoma (PCa).[43] Clinical investigation showed that treatment with lycopene supplementation in men with PCa, decreased DNA damage and serum prostate specific antigen concentrations.[44] Another study found that Lycopene demethylate is a promoter of the GSTP1 in a breast cancer cell line.[31]

Quercetin

Quercetin is a natural antioxidant flavonol, present in citrus fruits, onions, parsley, leaves and grains. Quercetin showed anti-cancer activity by regulating mitogenic signaling, cell cycle regulation, apoptotic signaling and metastatic steps in cancer.[45] It showed a concentration dependent effect on hyper methylation of $p16^{INK4a}$, a tumor suppressor gene, in human colon cancer cell lines (RKO). After 120 h of treatment with quercetin, it resulted in reversal of hypermethylation.[46] Quercetin is involved in stimulation of HAT and inactivation or supression of HDAC, both of which are involved in acetylation of H3 histone in leukemia HL60 cells and induces FasL dependent apoptosis. Several studies showed that *in vitro* anti-cancer activity of quercetin is linked to histone hyperacetylation. Quercetin can inhibit the DNMTs and thus DNA methylation indirectly by changing the concentration of SAM and SAH (S-adenosyl-L-homocysteine) intracellularly.[47] Quercetin has an effect on histone acetylation. Another study demonstrated that Quercetin decreases the level of COX-2 (cyclooxygenase-2) protein by hindering the binding of various transcription activators such as CREB2, NF-□B, p300, and c-Jun to the promoter of proinflammatory gene *COX2*, which results in its anti-neoplastic activity.[48]

Garcinol

Garcinol, a polyisoprenylated benzophenone is derived from Garcinia indica fruit rind. Garcinol strongly inhibits the histone acetyltransferases p300 and PCAF both in vivo and vitro. The kinetic investigation showed that it is a mixed type of inhibition with an augmented affinity for PCAF compared with p300. Garcinol intensely inhibited the HAT activity-dependent chromatin transcription. Additionally, it has been investigated that garcinol is a potent inducer of apoptosis, and it down regulates the global gene expression of HeLa cell lines.[49]

Lunasin

Lunasin is a 43 amino acid soy peptide. It has been investigated that it showed chemo preventive activity in mammalian cells and in a skin cancer mouse model against oncogenes and chemical carcinogens. As lunasin involved in inhibition of core histone acetylation, this activity of lunasin led to proposal of epigenetic mechanism. Soy lunasin and synthetic lunasin both are involved in inhibition of core histone acetylation in a dose-dependent manner.[50]

Parthenolide

Parthenolide (PN) is a sesquiterpene lactone obtained from *Tanacetumparthenium*. It has been investigated that parthenolide involved in induction of apoptosis and cell cycle arrest.[51] PN was shown to precisely deplete HDAC1. HDAC1 depletion was occurred through proteasomal degradation. PN led to depletion of HDAC1 which causes the ubiquitination of MDM2 result in activation of P53 and sustained DNA damage response.[52]

Anacardic acid

Anacardic acid 6 pentadecyl salicylic acid is an effective inhibitor of HAT. It inhibits p300 and p300/CBP-linked HAT activities.[53]

Garlic, Onions

They are members of the *allium* family that consist of a complex range of water-soluble and fat-soluble organ sulfur compounds. These organosulphur have activity against cancer and employed in cancer treatment.[54]

Garlic constitutes allyl derivatives which are amongst the first compounds having an impact on histone acetylation. Allyl mercaptan (AM), diallyl disulfide (DADS), *S*-allylcysteine (SAC), *S*-allylmercaptocysteine (SAMC) and allicin showed increased acetylation of histone (H3/H4) in human cancer cells.[55] AM responsible for causing H3 hyperacetylation and facilitated Sp3 and p53 binding on the *P21WAF1* promoter in human colon cancer cells.[56] Preclinical studies *in vitro* and *in vivo* showed the importance of garlic-derived organosulfur compounds in prostate cancer prevention.[57] DAD caused increase in histone acetylation and apoptosis in cancer like prostate cancer.[54] AM on human colon cancer cells causes rapid histone acetylation along with HDAC inhibition.[56]

Selenium

Selenium is an important trace element found generally in inorganic forms. While in its organic forms, it is found in Brazil within nuts and seafood. Selenium have an anticarcinogenic effect coming from its selenoprotein and importantly organoselenium metabolites.[58] It is a broad spectrum anticancer agent, found in lungs, ovarian, liver bladder and colon. Many of its forms are involved in epigenetic effect via histone modification.It decreases the HDAC activity and increases histone acetylation while many of its forms are involved in epigenetic changes. Some of the forms include sodium selenite, keto-methylselenobutyrate (KMSB), methyl selenocysteine (MSC), and methyl selenopyruvate (MSP).[59,54]

Silymarin (silibinin)

The flavonolignansilibinin is an active component of the milk thistle plant (*Silybummarianum)* that has been reported to increase acetylation of histones in hepatic cancer. Silibinin has exhibited increased acetylation of histone H3 and H4 *in vitro* in HuH7 cells[60] and *in vivo* in HuH7 xenografts in nude mice.[61] It also causes inhibition of HDAC activity and decreased HDAC levels and found to reduce DNMT activity in SW480 and SW620 cell lines following 72h of treatment. [62]

Rosmarinic Acid

Rosmarinic Acid is an ester of caffeic acid and naturally occurring phenolic compound. It has been reported that rosmarinic acid has a number of potential biological activities like anti-viral, antibacterial, anti-inflammatory and anticancer activities.[63] Rosmarinic acid has an inhibitory effect on DNA methyltrasnferase. In human breast cancer cell line MCF7 has shown decreased activity of methytransferase. [64] In cancer, DNA methylation undergoes aberrant changes resulting in variety of tumor suppressor genes undergoing promoter hypermethylation and becoming transcriptionally silent leading to tumor formation. Inhibition of DNA methyltransferase reverses the effect with rosmarinic acid having potential therapeutic effect against cancer. It has been investigated that rosmarinic acid may inhibit the bone metastasis from breast carcinoma by the NF kappaB ligand RANKL)/ RANK/osteoprotegerin (OPG with suppression of expression of interleukin 8. OPG factor is proangiogenic and through its inhibition, inhibition of metastasis of cancer cells can be achieved.[65]

Plumbagin

Plumbagin is a natural compound isolated from plants of the family Plumbaginaceae as well as from plants belonging to the family of Droseraceae. In India and China, plants extracts from these families have been traditionally employed in the treatment of an array of microbial and allergic diseases. The anti-cancer, anti-hyperlipidemic and anti-artherosclerotic actions of 5-hydroxy-2-methyl-1, 4-naphthaquinone (Plumbagin) is revealed by many research studies in the past. PL mediates an anti-tumorigenesis effect through the utilization of various molecular mechanisms including NF-□b and Bcl-2 inactivation, network of microtubule disruption and DNA breakage. In addition to these mechanisms, arresting of the cell cycle and reactive oxygen specie generation is also invovled.[66] The H460 lung cancer cell lines are more sensitive to plumbagin than A549 cells. The mechanism of action through which plumbagin targets H460 cells is the modulation of EGFR mediated AKt signaling pathway. Furthermore, the compound induces apoptosis through the arrest of G_2/M. The cell viability is also inhibited through the actions of PL.[67] In human breast cancer MCF-7 cell lines, PL induces potent cytotoxicity in a manner which is ROS dependent because a crucial role is played by ROS in the induction of cell dealth. [68] Plumbagin mediates its anti-cancer potential in a dose and time dependent manner. Human GC cells are also susceptible to the anti-cancer capacities of plumbagin. The human GC cells in response to therapy with the biologically active principle demonstrated growth inhibition, apotosis and an increase in chemosensitivity. [69]

Pomiferin

The osage orange fruit is the source of prenylated isoflavone known as Pomiferin which demonstrates, a remarkably potent free radical scavenging capacity. The photochemi-luminescence assay system of pomiferin exhibits a strong anti-oxidant activity against the superoxide anion. A selective anti-tumor growth against human breast cancer MCF-7 cell lines is observed *in vitro* with pomiferin[70] also showing a cytokeratin downregulation, in a proteomics approach. *In Vitro* studies involving Human-Dermal-Fibroblasts, it reveals its potent protein stimulant capabilities in the extracellular matrix. [71]

Sanguinarine

Sanguinarine demonstrates potent anti-proliferative activity against various types of cancer i.e. oral squamous cell **carcinoma.** It is an alkaloid belonging to the class of benzophenanthridine, demonstrating a selective action against prostate cancer cells through inhibition of survivin with negligible effects on normal prostate cells. The expression of survivin protein is inhibited through the degradation of proteins through the utilization of ubiquitin-proteasome system.[72] In addition to anti-invasive and anti-tumorigenisis effects, sanginarine also mediates anchorage independent cell growth inhibition.[73] The progression of prostrate cancer, which is castration resistant, is promoted by altered expression of survivin. The bioactive principle is also known to cause blockade of the cell cycle as well as apoptosis in human prostate cancer cells through the modulation of machinery of cell cycle and apoptosis. [72]

CONCLUSION

Cancer date backs to the era of Hippocrates, always known fatal to human life. It has shown up in multiple ways affecting almost all organs of the body. Its association to the genes has been thoroughly studied and evaluated for any possible counter. Genetics have contributed to cancer mortalities via signals and shown direct linked to diet related factors. Modified activities of genes are observed in association to these factors including histone acetyltransferase (HAT), histone deacetylase (HDAC), DNA methyl transferase (DNMTs) etc. effecting the expression in totality. Numerous studies have been conducted elaborating the role of plants and their ingredients play a part in inhibition of cancerous

cells by blockade of cell cycle and apoptosis or as the case may be.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	FA, MS
Acquisition, Analysis or Interpretation of Data:	FA, MS, SY, SQ, KA, SA, SA
Manuscript Writing & Approval:	FA, MS, MAB, ST, MQ, KA, SA, SA

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Original article:

Knowledge, attitude and practices among the inhabitants of Lahore, Pakistan towards the COVID-19 pandemic: an immediate online based cross-sectional survey while people are under the lockdown.

Kanwal Ashiq[1], Sana Ashiq[2], Mayyda Asif Bajwa[3], Samreen Tanveer[4], Mehwish Qayyum[5]

Abstract:

Background: COVID-19 is an emerging infectious disease and has reached a status of global health emergency. It is widespread in Pakistan causing morbidity and mortality amongst masses. ***Objectives:*** Undertaken study aims at investigating knowledge, attitude and practices of the people residing in Lahore, Pakistan whilst the global crisis with sparse data available previously. ***Methodology:*** Following lockdown announcement, an immediate online cross sectional study was conducted from the 31st March to 6 April 2020. Data was analyzed by using SPSS IBM version 22. 00. ***Results:*** A total of 316 responses were received. Our study has shown that people 95.80% were well familiar with COVID-19, informed via news channels 46.2%. 91.7% believed the virus is contagious, 95.8% reported that the virus is spread by the respiratory droplets, 89.2% believed that all ages are at risk while 62.3% believed it risky for geriatrics only. 60.4% believed in its prevention with 91.7% respondents agreeably quarantined themselves while 6.6% didn't. 99.7% participants were aware of social/physical distancing and 75.6% found it affecting mental health i.e. cause anxiety, depression etc. 59.2% of respondents were optimistic expecting it to end soon while 32.3% were uncertain. 49.1% said they have diagnostic facility and 89.6% acknowledged efforts of researchers/healthcare providers (doctors, pharmacist, nurses, allied health professionals and paramedical staff) for the society. 94.3% believed that there is need of awareness regarding COVID-19. ***Conclusion:*** An ever increasing need of awareness amongst the local population regarding COVID-19 is needed. It will lend hands in preventing spread of COVID-19 with minimal secondary transmission. It is recommended that extensive survey studies are required that can provide supportive data in developing and implementing public health policies regarding COVID-19 pandemic. It would further control and arrest the spread of COVID-19 in country.

Keywords: Coronavirus, COVID-19, Pakistan, Pandemic, Quarantine

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Introduction

A walk down through history, brings to our notice a gigantic number of outbreak of diseases, affecting masses all around the globe. Epidemic or pandemic, has tremendously affected people in terms of morbidity and mortality, overall affecting the lives, economy and lifestyles in the worst possible way. The history of pandemic has been well known to the public, with its first ever encounter through a viral outbreak reported in 1918. This was renowned as Spanish flu with H1N1 influenza virus being the causative agent. The viral outbreak affected as many as 500 million people across the world with a massive rise in death toll shooting from 17 to 50 million. A similar situation was faced on the face of the globe in 2009 by the spread H1N1 Swine flu during the time frame of 2009-2010. This contributed to an enormous feat rate inflicting around 6.8 billion people while killing nearly 5 million people of the world population[1]. In recent times,

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COVID-19 outbreak is accounted as a global issue with a health emergency like situation. This has been closely associated with unprecedented outburst of pneumonia with an etiology previously not known well. The viral outbreak was first reported in Wuhan City, lying within Hubei province in the last month of year 2019. Following the findings of this disease, a novel virus that is corona virus was identified as the sole agent. Later named by the WHO (World Health Organization) as COVID-19. This has shown close association with previous outbreaks reported under, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[2-3]. Structurally, coronaviruses are described as enveloped, single-stranded positive large RNA virus that is known for its zoonotic feature. Morphologically, it appears as spherical virions composed of a core shell fitted with surface projections akin to a solar corona. This is how the name was established from Latin word corona, meaning crown. Apparently, SARS-CoV-2 transferred from animals to humans via its oral consumption as food, finding its display in the Huanan sea food market in Wuhan, China[4]. The symptoms seen in patients infected with COVID-19 indicated a higher leukocyte count with high levels of plasma pro-inflammatory cytokines followed with abnormal respiratory findings. To understand better, a case with COVID-19 was reported with the 5 days of recurring fever with body's temperature affixed at 39.0 °C. Patient also had a cough presenting sounds of coarse breathing. Through clinical investigations, the sputum of the subject revealed positive real-time polymerase chain reaction (PCR) confirming COVID-19 infection[5]. In order to better understand the transmission and risk factors, a consistent data of epidemiological information must be obtained. This would rather explain, course and magnitude of geographic spread, infection related risks, transmission routes and to better plan to reduce this global burden via epidemiological models enabling prioritized surveillance post collection of real time data[6]. The current healthcare system of Pakistan does not promise a thorough service to the entire population. Thus, the only option feasible in times remains restriction of spreads, in turn less active cases. The number may decrease with timely testing of masses, quarantining active patients, imparting isolation and social distancing practices amongst public to break the chain of spread. Also passive counseling of public with communication between designated health authorities is the need of hour[7]. In addition to this, with rising threat of COVID-19 improving the technical skills and knowledge of healthcare workers is also of paramount importance. Improvement in knowledge and global updates is a must to combat this pandemic disease[8]. The spread of this disease has taken the entire world alike, people's knowledge, adherence to control measures, precautions and overall attitude is important to be learnt in best interest of public health[9, 10]. The underlying study aims at investigating the knowledge, attitude and practices of the people residing in Lahore, Pakistan on this global crisis, as previously no such study was found through extensive literature review.

Materials and Methods

Duration

Following the lockdown announcement of towns/ cities, immediately a week study was conducted from the 31st March to 6th April, 2020. An online cross sectional study was done in order to obtain the data since physical interaction for questionnaire distribution and filling was not possible to have the community based survey.

Participants

For the purpose of sample collection, a form of two pages was generated by consulting the recent published studies[9, 11]. Further, sample collection proforma was uploaded on the Google forms and links were shared on different platforms (WhatsApp, FaceBook, LinkedIn, Twitter etc). Authors have also sought help from their reliable connections to spread this sample collection form in order to get maximum response from the volunteers. Participants who were sixteen years of age or above were allocated for the data collection based on their understanding. No area was confined to allow maximum data collection throughout the region. Respondents had to respond either in no or yes in order to confirm their participation voluntarily. Once approval of voluntary participation was confirmed participants were navigated to the sample collection instrument.

Sample collection instrument and statistical analysis

The sample collection form was divided into the two parts. First section dealt with demographic information including: Name, age, gender, marital status, education and residence city/town. Second area broadly covered knowledge, attitude and practice analysis which included various questions provided with yes, no and may be options. Knowledge was analyzed through question 1 to 17 while questions from 18 to 25 assessed population attitude. However, questions from 25 to 29 were constructed to know the practices followed by the population in the current scenario. Following this, collected data was

analyzed by using SPSS IBM version 22. 00. Option codes 0, 1, and 3 were assigned to maybe, yes and no respectively while entering the data in SPSS. Frequencies, percentages, standard deviation (SD), independent t-test and ANOVA were calculated to evaluate the received data. The value of p (statistical significance level) was kept less than 0.05 which considered significant for this study.

Results

A total of 316 responses were obtained. The socio demographic information (table 1) showed that the majority of the population belonged to an age group of 21-25. Among 316 respondents 169 (53.48%) were females while 147 (46.52%) were males and most of them had a graduation degree 120 (37.97%).

Table 1. Demographic characteristics of the participants

	n (%)	±SD
Age		0.58
16-20	83(26.27%)	
21-25	168(53.16%)	
26-30	27(8.54%)	
31-35	18(5.70%)	
36-40	13(4.11%)	
above 40	7(2.22%)	
Gender		0.5
Male	147(46.52%)	
Female	169(53.48%)	
Marital Status		0.32
Married	51(16.14%)	
Unmarried	265(83.86%)	
Education		0.55
Matric or below	21(6.65%)	
Intermediate	67(21.20%)	
Undergraduation	76(24.05%)	
Graduation	120(37.97%)	
Post-graduation	32(10.13%)	

Results regarding knowledge, attitude and practices were summarized in Table, 2, 3 and Figure 1. Our study has revealed that 303 people (95.80%) were familiar with COVID-19 and most of them heard about this disease through news channels 146 (46.2%) as compared to the social media 147 (46.5%), family 10 (3.2%) and other sources 13 (4.11%). 218 (69.1%) knew the cause of this pandemic while 93 (29.4%) were unaware of the exact cause of this pandemic, demonstrating the need to educate people about the disease. 290 (91.7%) participants revealed their knowledge of contagiousness of virus and 303 (95.88%) reported that virus spreads by the respiratory droplets. 283 (89.2%) respondents answered that the virus affects people of all age groups. 197 (62.3%) claimed that elderly people were more prone to the infection while 21(6.64%) respondents were uncertain about this and 98 (31.0%) participants answered in negation. In terms of treatment of the COVID-19, 265 (83.9%) said that it was not available while 51 (16.1%) believed that treatment is available for COVID-19 infection.

191 (60.4%) of the current study candidates believed that COVID-19 infection is preventable while 115 (36.4%) were uncertain about this. 290 (91.7%) respondent quarantined themselves including their family members. 315 (99.7%) participants were well aware that social/physical distancing is helpful in avoiding the infection and breaking the chain of spread of disease. Regarding the COVID-19 diagnostic facility 155 (49.1%) respondents were found to have diagnostic facility as compared to the 81 (25.6%) who lied on the other extreme while 80 (25.3%) were unsure about this question. 297 (94%) of the participants responded in affirmation to the knowledge of COVID-19 symptoms which included dry cough, fever, fatigue and difficulty in breathing while 19 (6%) were unconvinced about the symptoms of COVID-19 infection. 238 (75.3%) participants thought that early supportive and symptomatic treatment could be helpful in cure of COVID-19 infection. 295 (93.4%) of the respondents said that isolation from the people who are infected with the COVID-19 virus is an effective way to reduce the spread of the virus as compared to 17 (5.4%), who were unsure about it.

295 (93.4%) of participants were well informed that people having interaction with someone having this infection should be immediately isolated for 14 days as an observational period. 308 (97.5%) of this survey candidates said that COVID-19 pandemic badly affected the world economy and 272 (86.1%) of the participants answered that in the prevailing scenario, people are faced with trouble in getting basic necessities (food/rations etc.). 239 (75.6%) of participants said that this pandemic affects people's mental health i.e. causing anxiety, depression etc. 187 (59.2%) of the respondents were optimistic and said that COVID-19 infection will end soon as compared to the 102 (32.3%) who were uncertain while 27 (8.5%) replied in negative. 193 (61.1%) of this survey candidates were satisfied by the government initiatives and practices to prevent infection as compared to the 65 (20.6%) and 58 (18.4%), who were not sure about it. 91 (28.8%) respondents said that herbal plants could be beneficial in treatment of infection as compared to the 190 (60.1%) who were

indeterminate. Only 174 (55.1%) respondents claimed that people took this as a health emergency and followed preventive measures. 283 (89.6%) survey participants acknowledged the efforts of researchers/ healthcare providers (doctors, pharmacists, nurses, allied health professionals and paramedical staff) for their society. 298 (94.3%) participants responded that there is a dire need to spread general awareness regarding COVID-19 and the same number of participants revealed that they wash hands for 20 seconds and follow recommended procedure for washing hands. To prevent infection, participants practiced measures including social/physical distancing 219 (69.3%), wear mask 27(8.54%) etc. To improve mental health, participants replied that they adopted healthy activities which included exercise, yoga and walk 133(42.1%), maintain personal hygiene 62(19.6%), avoid junk food, eat fruits and take good sleep 55(17.4%), reading 23(7.3%) etc.

Table 2. Knowledge, attitude and practices assessment of the respondents

Items	Yes n (%)	No n (%)	May be n (%)	±SD
You know about COVID-19	303 (95.80%)	3 (0.9%)	10(3.3%)	0.138
You know the cause of this COVID-19 pandemic	218 (69.1%)	93 (29.4%)	5(1.5%)	0.478
COVID-19 virus is highly contagious	290 (91.7%)	10 (3.16%)	16 (5.0%)	0.232
Virus spread by respiratory droplets	303 (95.88%)	11 (3.48%)	2(0.06%)	210
COVID-19 affect all age groups	283 (89.2%)	16 (5.0%)	17(5.3%)	0.49
Only elderly people affected severely	197 (62.3%)	98 (31.0%)	21(6.64%)	0.516
Treatment is available for COVID-19 virus infection	51 (16.1%)	265 (83.9%)	0	0.445
COVID-19 infection is preventable	191 (60.4%)	10 9 (3.2%)	115 (36.4%)	0.535
You and your family members have quarantined in order to avoid infection	290 (91.7%)	21 (6.6%)	5(1.5/%)	0.249
Do you think social/physical distance is helpful in preventing the spread of disease?	315 (99.7%)	01 (0.3%)	0	0.056
Is there any diagnostic testing facility available in your region?	155 (49.1%)	81 (25.6%)	80 (25.3%)	0.715
Dry cough, fever, fatigue and difficulty in breathing are the symptoms of COVID-19 infection.	297 (94%)	0	19 (6%)	0.238
Early supportive and symptomatic treatment can be helpful in cure of COVID-19infection	238 (75.3%)	11 (3.5%)	67 (21.2%)	0.465
Isolation from the people who are infected with the COVID-19 virus is an effective way to reduce the spread of the virus.	295 (93.4%)	4 (1.3%)	17 (5.4%)	0.255
People who have interaction with someone having this infection should be immediately isolated for 14 days as an observational period.	295 (93.4%)	3 (0.9%)	18 (5.7%)	0.254
COVID-19 pandemic affects the world economy badly	308 (97.5%)	1 (0.3%)	7 (2.2%)	0.158
In prevailing scenario people facing trouble in getting basic necessities (food/rations etc)	272 (86.1%)	14 (4.4%)	30 (9.5%)	0.37
COVID-19 pandemic affects mental health (depression, anxiety, loss of interest etc.)	239 (75.6%)	32 (10.1%)	45 (14.2%)	0.493
Do you think this infection can be controlled soon?	187 (59.2%)	27 (8.5%)	102 (32.3%)	0.594
Are you satisfied by current practices and initiatives taken by the government?	193 (61.1%)	65 (20.6%)	58 (18.4%)	0.624
Herbal plants can be used treat this infection	91 (28.8%)	35 (11.1%)	190 (60.1%)	0.688
People taken this health emergency seriously and follow preventive measures	174 (55.1%)	81 (25.6%)	61 (19.3%)	0.668
You acknowledge the efforts of researchers/healthcare providers (doctors, pharmacist, nurses, allied health professionals and paramedical staff) for their society	283 (89.6%)	14(4.4%)	19 (6%)	0.231
There is need of general awareness about COVID-19 pandemic316 responses	298 (94.3%)	7 (2.2%)	11 (3.5%)	0.239
You wash hands for 20 seconds and follow recommended procedure for washing hands	298 (94.3%)	3 (0.9%)	15 (4.7%)	0.236

*All calculated *p* values were less than 0.05 which means these were significant.

Table 3. Answers reported by the respondents

Items	n (%)
From where you heard about this disease?	
News Channels	146 (46.2%)
Social Media	147 (46.5%)
Family	10 (3.2%)
Others	13 (4.11%)
In your opinion, reason of COVID-19 is	
Caused by virus	273(86.3%)
By eating infected food	13(4.11%)
Gathering	14(4.4%)
Poor immunity	16(5.06%)
Preventive measures you have taken to avoid or spread the COVID-19 infection	
Social/physical distancing	219(69.3%)
Wear mask	27(8.54)
Hand wash	70(22.2%)
Healthy activities adopted during quarantine to improve mental health	
Exercise, yoga and walk	133(42.1%)
Reading	23(7.3%)
Cooking	18(5.7%)
Indoor games	25(7.9%)
Avoid junk food, eat fruits and take good sleep	55(17.4%)
Maintain personal hygiene	62(19.6%)

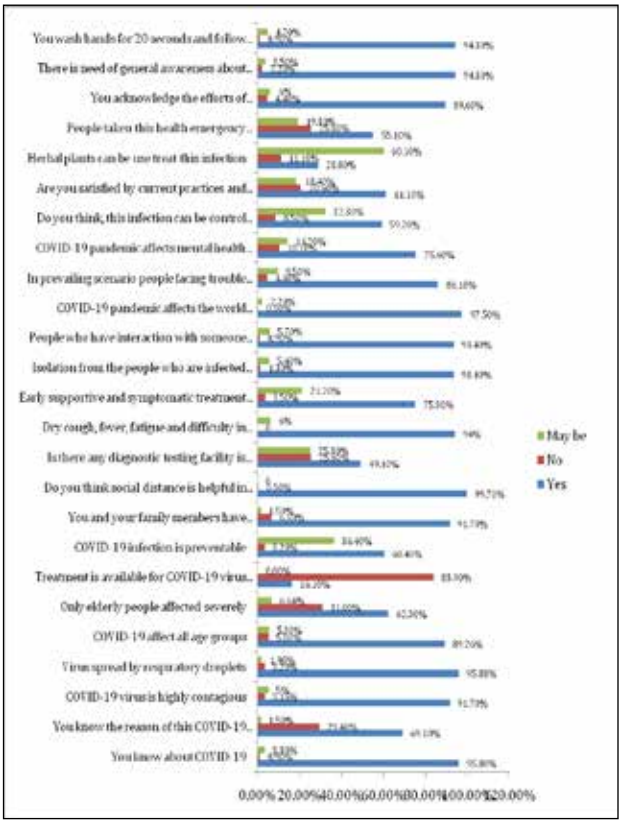

Figure 1. Knowledge, attitude and practices assessment of the respondents

Discussion

To the best of our knowledge it is the first study in Pakistan which is based on knowledge, attitudes and practices of the community towards the COVID-19. Majority of the population in this study is educated and belongs to females. Current study indicates that the community is well informed and has sound knowledge about the COVID-19. News channels and social media have played a significant role in this regard, to make communities familiar with COVID-19 pandemic[9, 12]. However, this study has several limitations i.e. only literate people were accessible through online portals and to fill the form. English language must be understood by the respondents, participants needed to have an account to access the questionnaire and dissemination of the sampling instrument only through an online platform[10]. Majority of the population stated that COVID-19 is transmitted through respiratory droplets, can affect all age groups and elderly people were more prone to develop severe infection which could lead to death[13]. Public was well aware about the signs and symptoms of the COVID-19 infection which included dry cough, fever, fatigue and difficulty in breathing. Many participants of this study were unsure if COVID-19 infection is preventable and early supportive treatment and isolation of the infected patient is helpful in controlling the spread or not. Many studies suggested that COVID-19 infection is preventable at the general population and national level through implementation of proper strategies. For COVID-19 infection there is no treatment available and a large number of the respondents agreed on this point[14]. Quarantine or social distancing is helpful in reducing the number of COVID-19 cases. In the prevailing scenario, the government deemed that lockdown could be a best option which may prove beneficial in controlling the infection and declared countrywide lockdown. Many people respect this decision and keep themselves under the lockdown but still there are people who didn't take this health emergency seriously. These people are at high risk to have infection and become a source of spreading COVID-19 infection which may result into a hindrance in achieving the goal i.e. controlling the infection[15, 16]. This survey indicates that more than fifty percent of the respondents admire government initiatives and practices in order to cope with the current situation while remaining are not satisfied. The present study has also highlighted that the public is facing troubles while getting basic necessities (food/rations etc). Further, Pakistan is

already facing the economic crisis and it is quite difficult to sustain this lockdown for a longer period otherwise it is supposed that people may face issues to have basic necessities[17, 18]. Many people residing in Pakistan also imply herbal medicines to treat various ailments with strong belief but for COVID-19 cure, many people are unconfident. An investigation has suggested that cure of H1NI and SARS through Chinese traditional medicine is well documented, based on human evidence and historical data and such medicine could be an alternative approach to prevent COVID-19 in high risk communities[19]. This study is also focused on the availability of diagnostic facilities to the public. Less than half of participants agreed on its availability while remaining claimed that it is not available or unsure. Earlier, Pakistan lacked the COVID-19 diagnostic facility and now Pakistan has received Primer from Japan and the rapid diagnostic kits from China. Now, Pakistan has the diagnostic facility at major centers and still there is need to establish more testing points to screen maximum population[20]. COVID-19 also poses challenges to the mental well-being and resilience of the societies. This current global health emergency has badly impacted the psychological health (i.e. depression, anxiety, boredom, frustration etc.) of the individuals. To deal with it many people have adopted healthy activities which include exercise, yoga, playing indoor games, reading, writing, cooking etc.[21, 22] further launching of many new free online courses in this duration of crisis is also an effective way to keep people (especially students) busy and has opened new doors of learning[23]. Worldwide frontline heroes including the health care providers (doctors, pharmacists, nurses, allied health care professionals and paramedical staff) and researchers are working tirelessly to fight against the COVID-19 by putting their lives at risk. People not only Pakistan, but globally acknowledge their efforts and struggle[24-26].

Conclusion

Present study concludes that people are well informed about COVID-19 however still there is need of awareness amongst masses regarding COVID-19 to counteract the spread. People should rather quarantine themselves in order to prevent infection, catering this as a health emergency by keenly observing precautionary measures. However, to keep a mental and physical balance of health, people should adopt healthy activities during the lockdown. It is obvious from this study that the community also acknowledges the struggle and determination of the researchers and frontline healthcare providers for the well-being of their society.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

None

Ethical clearance

This cross sectional survey study has been conducted after obtaining suitable informed consent from volunteers. After approval from the participants data were collected and confidentiality of the information was secured.

Authors contribution

Data gathering and idea owner of this study: Kanwal Ashiq

Study design: Kanwal Ashiq, Sana Ashiq

Data gathering: Kanwal Ashiq, Sana Ashiq, Mayyda Asif Bajwa, Samreen Tanveer, Mehwish Qayyum

Writing and submitting manuscript: Kanwal Ashiq, Sana Ashiq

Editing and approval of final draft: Kanwal Ashiq, Sana Ashiq, Mayyda Asif Bajwa, Samreen Tanveer, Mehwish Qayyum

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A Review on Existing Tetracyclines Analogues and Their Pharmacologically Targeted SAR

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REVIEW ARTICLE

A Review on Existing Tetracyclines Analogues and Their Pharmacologically Targeted SAR

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Authors' Contributions
1 Conception & Study design, Data Collection & Processing, Data Analysis and /or interpretation, Drafting of Manuscript, Critical Review.
2 Data Collection & Processing, Drafting of Manuscript, Critical Review.
3 Data Analysis and /or interpretation, Critical Review.
4 Conception & Study design, Data Collection & Processing.
5 Data Analysis and /or interpretation, Critical Review.
6 Data Collection & Processing, Data Analysis and /or interpretation.
7 Data Collection & Processing, Critical Review.
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ABSTRACT

Background: Tetracyclines belong to a class of broad spectrum antibiotics. Around the globe, they are prescribed to treat various gram negative and gram positive bacterial infections. Once in the cell, they reversibly bind to the receptors which are located on 30S subunit of bacterial ribosome. They act by averting the protein synthesis, in turn, halting the bacterial growth.

Aim and Objectives: The aim of current review is to study tetracyclines, identifying potential activity against infections and highlighting the microbial resistance associated with various analogues.

Material and Method: The data for this review is collected from various databases including Scopus, PubMed, Springer Link and Google Scholar. To ensure the credibility only indexed articles were used in current study.

Result: The outcome of the study has suggested that tetracyclines and number of its analogues show selective bioactivity and strength to the biological targets. Through modification at certain positions, activity of drug is changed substantially. This not only affects therapeutic activity and safety profile but also has influence the bacterial resistance.

Conclusion: As antibiotic resistance amongst bacteria is emerging tremendously, demanding more research. It is still needed to synthesize the novel analogues that would be helpful to cure infections caused by the resistant bacteria. Further these analogues can be tagged with radioisotopes that would be helpful for diagnosis and treatment of infectious diseases.

Keywords: Tetracycline, Structure activity relationship, Pharmacological activity, Analogues, Anti-bacterial.

INTRODUCTION

Tetracyclines are broad spectrum antibiotics which inhibit the microbial protein synthesis by interfering aminoacyl tRNA and acceptor sites of ribosomes [1].It exerts its action by binding to 30s ribosomal RNA [2]. It is effective against gram positive and gram negative micro-organisms. Tetracyclines are used widely due to their higher safety profile. It is also used prophylactically against Plasmodium falciparumin

malaria. It is also used against micro-organisms that are resistant to other antibiotics [3].

Structure Activity Relationship

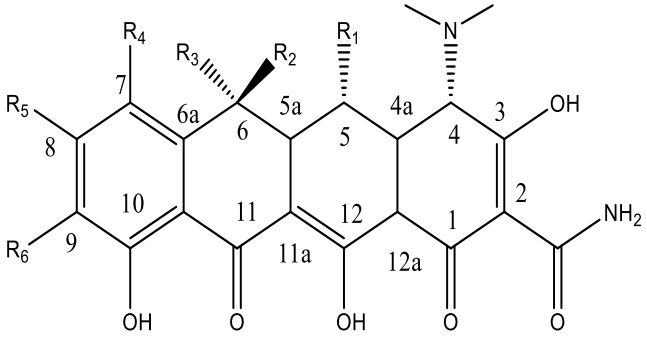


Figure 1. Structure of tetracycline.

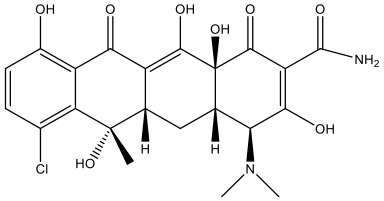
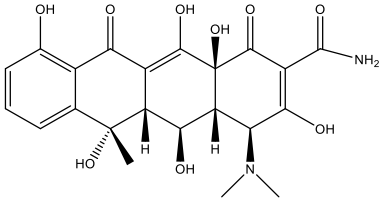
Tetracyclines are linearly fused 6 membered, four carbocyclic ring systems as shown in Figure **1**. Among ring C and ring D, one must be aromatic. Unsaturation at positions 2- 3 and 11- 12 are essential for activity. Presence of keto-enol system at position 1-3 and 11-12 is necessary for activity. Other important structural features in tetracyclines are amino acyl group at position 2 ,tertiary amine at position 4, diethyl group at position 5 and position 6 having hydroxyl and methyl group[4].

Amide functional group at position 2 should remain unsubstituted for activity, if substitutions are necessary then one hydrogen can be replaced with alkyl amino methyl group as in rolitetracycline [5,6].Presence of tertiary amines at position 4 is importantto keepketo-enol system of ring Aintact.Position 4 tertiary amine can bear substituents such as hydrazine, hydroxyl or oxime. Epimerization occur at 5a position [7]. Electrophilic substitution can occur at position 7 & 9 of ring D with nitro group or halogens; halogens probably used mostly because they are less carcinogenic for host [8].

With respect to discovery and development of tetracyclines, chlortetracycline and oxytetracyclines were firstly originated from *Streptomyces aureofaciens* and Streptococcus rimosus in 1940s [9,10].This discovery was followed by synthesis of many semi-synthetic tetracyclines such as minocyclines, methacyclins and doxycyclines[11].

Tetracyclines were first discovered by Dr. Benjamin Dugger of Lederle Laboratories in the mid 1940s as the fermentation product of an unusual golden-colored soil bacterium named as*Streptomyces aureofacians*[12].These tetracyclins and their analogues have wide range of activity against microbes. Tigecyclinewas found to haveantibacterial activity [13].Omadacycline was the first intravenous and orally effective 9-aminomethylcycline in clinical development for use against multiple infectiousdiseases including acute bacterial skin and skin structure infections (ABSSSI), community-acquired bacterial pneumonia(CABP), and urinary tract infections (UTI). The comparative in vitro activity of omadacycline was determined against a wide range of Gram-positive clinical isolates, including methicillin-resistant *Staphylococcus aureus* (MRSA) [14], vancomycin-resistantEnterococcus (VRE), Lancefield groups A and B beta-hemolytic streptococci, penicillin-resistant Streptococcus pneumonia (PRSP), and Haemophilus influenzae (H. influenzae). The omadacycline MIC90s for MRSA, VRE, and beta-hemolytic streptococci [15].

Table 1. Sources, structures, pharmacological activities of natural tetracyclines.

Sources	Structures	Pharmacological Activity	Substitutions
Chlotetracyclines[16]		Antibacterial activity (Primarily act at 30s / tRNA ribosome). Used in conjunctivitus in cats, dogs and horses [47].	Cl group at position 7
Oxytetracycline [17]		Primary target is 30s / tRNA ribosome and exhibit antibacterial activity.	OH at 5th position

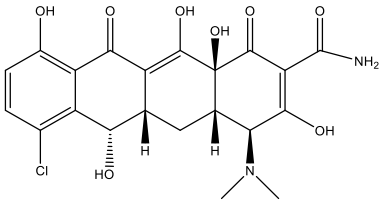
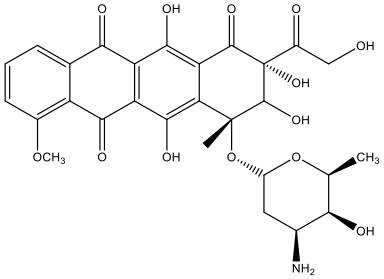
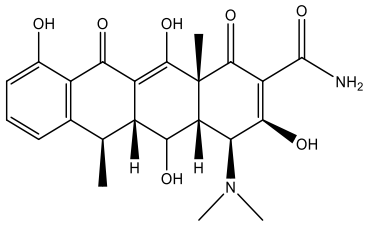
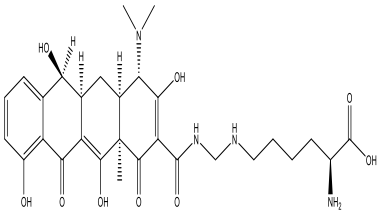
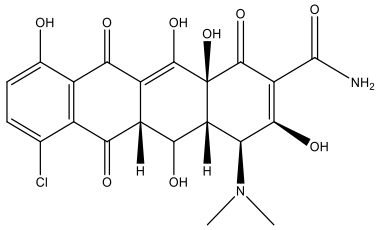
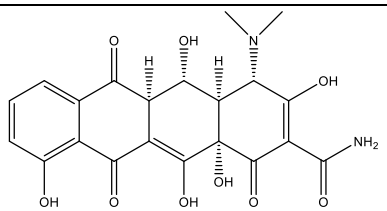
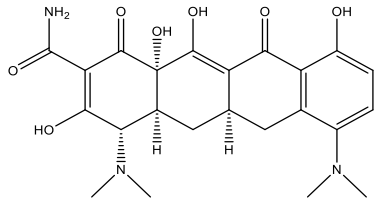
Demeclocycline [18]		Antibacterial (bind to 30s ribosomal RNA)	Cl group at position 7 and removal of CH_3 at position 6.
Doxurubicin [19]		Exerts its anticancer effect by apoptosis and oxidative Stress mechanism.	Substitution at 1 & 9 position.

Table 2. Sources, structures, pharmacological activities of semisynthetictetracyclines.

Sources	Structures	Pharmacological Activity	Substitutions
Doxycycline [20]		Anticancer (apoptosis and oxidative Stress mechanism), veterinary medicine, Respiratory tract and intestinal diseases of poultry [47].	OH group at 5th position and deoxylation at 6th position
Lymecycline [21]		Antifungal (oxidative stress) Lonophore and Chelating Mechanism	Substitution at 2 position.
Meclocycline [22]		Antifungal (Oxidative Stress) Lonophore and Chelating Mechanism	Substitution at 7 position.
Methacyclin [23]		Antifungal (Oxidative Stress) Lonophore and Chelating Mechanism	Methylene group at 6th position & OH at 5th position
Minocycline [24]		Anticancer (apoptosis and oxidative Stress mechanism),veterinary medicine, canine brucellosis [47].	Addition of Dimethylamino at 7th postion & removal of CH3& OH group at position 6th

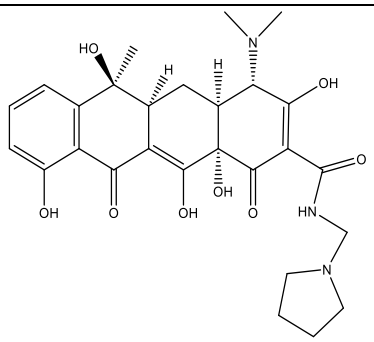
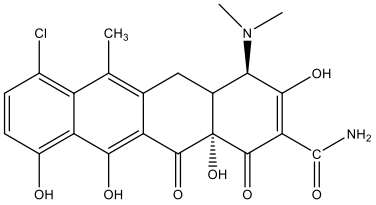
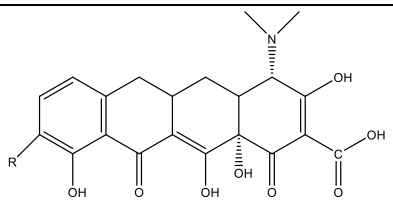
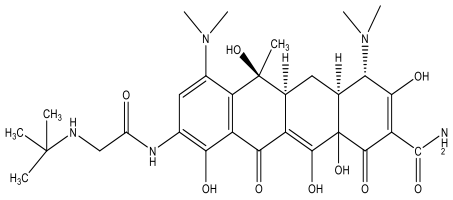
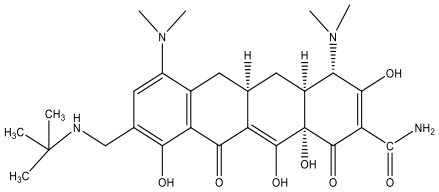
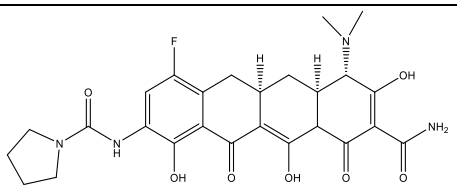
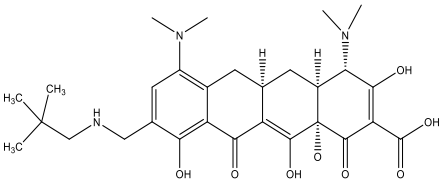
Rolitetracyclin [25]		Antibacterial (bind to 30s ribosomal RNA)	Pyrrolidine ring at 2nd position
Epi-ANhydrochlorotetracycline [26]		Antibacterial (Atypical Mechanism) Primary Target is not Bacterial Ribosomal	Substitution at 7 position.

Table 3. Sources, structures, pharmacological activities of synthetic tetracyclines.

Sources	Structures	Pharmacological Activity	Substitutions
Tigecycline [27]		Antibacterial (bind to 30s ribosomal RNA)	Substitution at 9 position.
Glycylcycline [28]		Antibacterial (bind to 30s ribosomal RNA)	Substitution at 7 & 9 position.
Aminomethylcycline [29]		Antibacterial (Atypical Mechanism) Primary Target is not Bacterial Ribosomal	Substitution at 7 & 9 position.
Fluorocycline [30]		Antibacterial (Atypical Mechanism) Primary Target is not Bacterial Ribosomal	Substitution at 9 position.
Omadacycline [31]		Antibacterial (bind to 30s ribosomal RNA)	Substitution at 9 position.

Medicinal importance of Tetracyclines

Tetracyclines are broad spectrum antibiotics because its activity is being evaluated against wide array of bacterial infections [32].Tetracyclines have been used immensely in the prophylaxis and treatment of bacterial infections as they are inexpensive and broad spectrum antimicrobials [33].Tetracyclines are predominately a low-cost alternative among other antibiotics. Interestingly, certain type of tetracycline has recently been used inprevention of cancer recurrence by inhibiting such enzymes and processes that usually stimulate growth of cancerous cells [34, 6]. These drugs may show potential for long-term management of some types of cancers [11, 35].

Radioprotective activity

Kwanghee and coworkers in 2009 conducted a research to recognize medicinal agents that shield body tissues from detrimental effects of radiation therapy. They tested radioprotective activity of tetracyclines and fluoroquinolones in murine lymphocyte rat model which were subjected to total body irradiation. Results manifested that tetracyclines and fluoroquinolones exhibited marked radioprotective activity owing to their planar ring structure. Tetracyclines also averted injurious affects of radiations on human lymphoid cells by preventing DNA strand breakdown. These findings proved that tetracyclines have tremendous potential in reducing radiotherapy damage on normal tissues [36].

Tumor detection

Radio isotopes of tetracyclines has been developed and used in localized tumor detection.Tetracycline radioisotope 99mTc has been successfully employed in external scanning of tumor lesions in rabbits, mice, rats and humans [37].

Anticancer activity

Leezenberg and Wesseling in 1979 carried out a retrospective research on 218 cancer patients. These patients were stricken by nasopharyngeal cancer. This study was aimed to evaluate effects of tetracyclines therapy on life span of patients. Results revealed that patients who received tetracyclines not only lived longer but tetracyclines also improved the detrimental effects of methotrexate. It is believed tetracyclines exert this action owing to inhibition of mitochondrial protein synthesis [38].

A study revealed that tetracyclines regulated gene delivery system along with radiation therapy employed in prostate cancerous rat model, developed tumor immunity in cancerous rats and augmented immune response [39].

Prevention of corneal ulceration

Tetracyclines are used as prophylactic treatment for corneal ulceration after severe optical damage. They exert their action by inhibiting protein degradation through its suppressive action on neutrophil collagenase, alpha 1 antitrypsin degradation and through its anti-oxidant activity [40].

Antimicrobial activity

Analogues of tetracyclines also show promising antimicrobial activity. 9- substituted analogues of tetracyclines were synthesized by reaction of organotin reagent with salt of C-9 diazonium tetrafluoroborate tetracyclines. These analogues show significant activity against other antibiotic resistant infections [41].

Tetracycline is used in variety of bacterial infections of different body organs such as respiratory pathway, urinary pathway, intestine, reproductive organs, lymph nodes, and skin etc [42].Many sexually transmitted diseases (STDs) including syphilis, gonorrhea, or chlamydia and also acute acne are treated by these analogues [43].

A wide range of gram positive and gram negitive bacteria e.g. Brucella, *Coxiella Burnetii*, Rickettsiae rickettsii, *Chlamydia trachomatis, Mycoplasma pneumoniae*, Chlamydiae species, *Helicobacter pylori* etc are treated by tetracyclines [44].

Treatment for acne

The growth suppression of an anaerobic organism,*Cutibacterium* acnes, demonstrated by the tetracyclines makes this class of drug important for the treatment of moderate and severe acne. Moreover, the anti-inflammatory effect of tetracyclines is an added advantage for the acne lesions [43, 45, 46].

Veterinary use

Several analogues of tetracyclines including minocycline, methacycline and doxycycline were considered harmful for veterinary use. It was found out that minocycline and doxycycline were rather effective in treatment of animal diseases. These tetracyclines have high lipid solubility that explain its better pharmacokinetic profile that is improved absorption and distribution which may results in efficient antimicrobial activity. Doxycycline excretes

through intestine; it is useful in renal impairment situations.Doxycycline is used in intestinal and respiratory tract infections in poultry. Minocycline is used in combination with streptomycin in treatment of canine brucellosis [47].

Miscellaneous uses

Tetracyclines are useful in treatment of number of diseases such as relapsing fever, syphilis, pneumonia, throat irritation; bacterial urinary tract infection, anthrax, Rocky mountain spotted fever, sinus irritation and congestion, chronic slow progressing ulcerative granulomatous disease [48].The infections induced by direct contact with the infected animals and adulterated edibles are also treated with antibiotics. Tetracycline can be served as a substitute for penicillin or other antibiotics in cases of severe infections like Anthrax, Listeria, Clostridium, Actinomyces, and others [49].Tetracyclines are used in treatment of bones and also used for calcification of cartilage [12, 50].

Precautions

The intake of milk, dairy products that contain calcium, iron, antacids, or aluminum salts should be avoided at least 2 hours before or 6 hours after using antacids when using this therapy [51].Dose of tetracyclines should be taken with water and one hour before or two hours after meals [52, 53].

CONCLUSION

Tetracyclines belong to a class of broad spectrum antibiotics. Worldwide, they are recommended to cure various gram negative and gram positive bacterial infections. They exert their action by reversibly binding to 30S subunit of bacterial ribosome.Tetracyclines analogues are commonly used because of their availability and cost effectiveness especially in developing countries. Thestructure-activity-relationship (SAR) studies of tetracyclines shows the selective bioactivity and strength to the biological targets which makes this class of medicinal compounds able to label with radioisotopes and providing outstanding results in detection and treatment of localized tumors. Furthermore, advanced methods of therapy has been introduced against infectious lesions includes radiotherapy by using the radioisotopes of tetracyclines. In time to come, more radiolabeled tetracyclines analogues can be derivatized for diagnosis and treatment of infectious diseases.

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REVIEW ARTICLE

Health Emergency with COVID-19 and Supporting Role of Community Pharmacists in Pakistan

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ABSTRACT

Background: The infection (COVID-19) inflicted via newly discovered strain of the virus was first spotted in Wuhan in December 2019 and established as a worldwide public health emergency on 30th January, 2020 demanding support from all healthcare sectors, on urgent basis.

Objective: The objective of this review is to highlight and appreciate roles of community pharmacists during COVID-19 pandemic.

Methodology: For literature review various databases were used such as Google Scholar, Springer Link, PubMed, MEDLINE and Science Direct.

Results: The proposed provisions such as social distancing and lockdowns to quite an extent aided in restricting the dispersion of the virus. In addition, wearing face mask, washing hands, using sanitizer with periodic disinfection of surrounding was recommended. These measures were registered to provide protection to all and positively influence the life of special population i.e., those suffering from chronic diseases, as they don't approach the healthcare facilities on a regular basis for their everyday care and supervision, in terms of medication. However, the easiest approach to gain access to sophisticated health facilities in such conditions remained and is through retail pharmacy outlets.

Conclusion: The existing healthcare system with surging stress and fear can be profoundly reduced by participation of community pharmacists and their thorough involvement in managing chronic illnesses and strengthening medication adherence.

Keywords: Community Pharmacists; COVID-19; Pandemic; Pharmacy.

INTRODUCTION

The 2019 coronavirus infection (COVID-19), driven by a newly emerging strain of coronavirus was first spotted in Wuhan, a populous city of China in December 2019. It was asserted to be a worldwide public health emergency by the World Health Organization (WHO) on January 30, 2020. In line with the Centers for Disease Control and Prevention (CDC, USA), epidemic refers to a swift growth in morbidities beyond the usual expected occurrence in a certain region or zone. A pandemic is the intensified form of the epidemic, as the disease spreads out to wider geographical zones, across countries and continents. Pandemic strikes a significantly higher number of individuals around the globe [1, 2]. The virus has influenced the economy and affected the

healthcare system of almost every country. The low- and middle-income countries (LMICs) with formerly poor healthcare systems are particularly called into question. This pandemic has severely affected countries, as before the coronavirus outbreak, healthcare systems in LMICs already had to deal with huge challenges in terms of high-quality, affordability and universally accessible care. Conditions normally turn worse with low financial resources, incompetent health professionals and deficiency of medications are similar challenges faced by the supporting staff. The pandemic has greatly incited high morbidity and mortality rates. However, with the objective to counter the threat of COVID-19 some major actions with close monitoring must be taken. WHO has voiced its concern observing the risky circumstances in various countries [3, 4].

Some novel precautionary measures are up taken to cope with this novel virus and put off its transmission. These measures comprise of movement restrictions and the closure of schools, universities, local gatherings, restaurants and retail shops [5].

Across the globe, community pharmacies follow a business model but overall governed by local health laws. Presently, the professional role of pharmacist in hospitals and community pharmacies is shifting from dispensing and mere sale of drugs, to patient centered services including counseling on a global scale. Previously medicine dispensing was practiced in store, unsupervised, pharmacists serving barely as salesmen and failing any contributions to society [6].

Covid-19 and Supporting Role of Community Pharmacists

With the intention to improve the patient care, community and hospital pharmacies are widening their services and working hours for the adequate provision of the same [7]. Several developing nations have streamlined their pharmaceutical services via taking in consideration the importance of community pharmacists and their interaction to the patients [8]. Here in Pakistan, pharmacist are providing medicine, diagnostic tools, helping with their use and tackling and side effects reported, sharing and lowering the burden of hospital [2, 4]. At this time, where hospital is filled with patients and a red zone for any person accompanying the patient. Community pharmacists have played a part in strengthening medicine adherence and overall therapy management. During this need of the hour, inputs from community pharmacists are helpful to regulate the fundamental services. Unlike physician or specialist, pharmacist is in a better position to individually monitor and counsel the patient and provide patient centric treatment [9].

In human settlements, pharmacists are majorly approachable healthcare workers and are first contact points to the patient. Out of multiple health professions, community pharmacy has a vital part to play in addressing this global emergency. The fact that community pharmacists are most easily approachable healthcare professionals and widely located in every community is well established. It is acknowledged that a community pharmacy will be the first port of call for the COVID-19 infected patients or any epidemic outbreak as the patients will rely for the advice and counseling on a licensed health professional. With media and awareness otherwise quacks and dispensers are rarely relied upon, by the people, anymore [10, 11].

A pharmacist is ideally positioned in a community to offer support to compromised individuals. In the recent past, it was accepted that a pharmacist can play four key roles for a disease that include its prevention, preparedness, response and recovery [12]. Currently, the International Pharmaceutical Federation (FIP) published interim guidelines for the pharmacy workforce that provides an overview of core duties that are associated with the pharmacists' professional responsibility during the recent pandemic [13]. Furthermore, these guideline laid down the responsibilities to handle the pandemic for both hospital and community pharmacists. Therefore, during this outbreak it is noteworthy to investigate how the pharmacists are carrying out their conventional rules along with additional and new roles, worldwide [14]. Pharmacists in the community facilities and retail outlets are contributing as an essential part in controlling the viral spread in line with the doctors and allied health care workers, who are battling at the frontline [15].

Community pharmacists are also entrusted with the responsibility of early detection and appropriate referral, besides provision of sustained stock of essential medicines and turning into a support center for information regarding the COVID-19 infection. They are also providing input to execute government arrangements, perform diagnostic tests and initial treatment [16]. Patients are oblivious about major and comprehensive pharmaceutical care services although their insight about general roles of pharmacist is found to be optimistic [17].

In underprivileged areas there is a lack of competent physician, or pharmacist, thus role of quacks prominent with declining health. The role of pharmacist has been supporting in this while and if restrictions are pulled out then pharmacists performing in hospitals, clinics, physician offices, and community settings can broaden their care services as they are skilled enough to treat infectious diseases and provision of initial and basic healthcare. Moreover, there clinical expertise and understanding of medicine in terms of constituent, does and side effects is far more better and reliable than another professional [10].

With the changes observed in patient's needs and disease characteristics during COVID-19, the PC (Pharmaceutical care) services shall come up with varying features and some fruitful variations in future health system. In general, pharmaceutical care is characterized by patient centered pharmacist activity, which aims at enhancing medication handling amongst the diseased individuals [18]. Community pharmacies operate actively in providing patient's medication, precautionary measures and deliver protective equipment. Community pharmacists are and can better be trained and equipped enough to offer proficient and efficacious PC services to the public, leading to improved medication safety and promotion of the overall COVID-19 pandemic control [19].

Regarding COVID-19 vaccination, community pharmacists can be provided with this duty as health care professionals to participate thoroughly in the immunization process. Similarly it can be practiced with patients, at local retail pharmacy setups, already receiving tetanus shots and influenza vaccines. Over the previous few years, pharmacies have become the yet another point of contact for flu vaccination in adults due to convenience and lower costs [20]. Medication review obtained from patients is a step that gradually leads to enhanced and rational drug use. The definitive goal of majority of the medication review programs is to boost patient health outcomes [21,22].

For the provision of pharmaceutical care in the course of COVID-19 outbreak, the emphasis on role of community pharmacists will be on the prevention, identification and/or resolution of drug therapy problems for patients in each facility. The existing stress on the healthcare system can be lightened by the participation of community pharmacists by taking the lead in managing chronic illnesses and strengthening medication adherence. Unlike, in the past when such services were delayed and occasionally provided on hospital visit [9].

Meanwhile, telepharmacy has added importance in patient counseling, medication selection, therapy monitoring and the delivery of clinical services. The rural population observes major benefits of telepharmacy as the health information and pharmaceutical care is timely provided to them. The community pharmacies can aid the triage and refer patients of rural areas that lack competent physicians, to greater levels of care when diagnosis and advanced treatment is essential. Telepharmacy has also extended the capabilities of rural hospitals for the provision of pharmaceutical services 24/7, around the year. According to the anticipated intake of coronavirus cases, telepharmacy could be exercised for medication approval that will eventually decrease the delay time in getting medicines to the infected patients. At the same time, we also know that telepharmacy is based on technology that is not accessible to everyone in the country. Therefore, it becomes a limiting factor for its implementation. For the establishment of telepharmacy service aside from the technological requirements, significant amount of time, money and effort is also required [19, 23].

Collaborative inputs of pharmacists and physicians are desired so that they work with their governments and assure a standardized clinical treatment, focusing exclusively upon infected individuals at local clinics and pharmacies. While COVID-19 has and continues to be a challenge. This can also be the time for physicians and pharmacists to think creatively about new strategies for enhanced collaboration with a major focus on patient care optimization [24-27].

CONCLUSION

The sudden status of Covid19 outbreak, as a world pandemic has reshaped the entire health care system defining new roles and responsibilities of pharmacists. Pharmacists, not only have complemented the frontline workers but have also opened up new horizons for their mates, to polish and deliver services to the ailing community, like never before. Where appreciation is extended to physicians, nurses and other allied health care workers for their role as frontline guards in this crucial split of time, the role of pharmacists in particular the community pharmacist is

also worthwhile, tackling majority of population in their respective communities. Supply of equipments, there use, medicines utilization and due precautions are responsibly, provided by them. It is important to note that by division of labor, sharing the current load and working together as one healthcare team we can fight and end this disease and come out with a strengthened healthcare system, all across the globe.

Conflict of interest

There is no conflict of interest among the authors.

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A comprehensive review on gout: the epidemiological trends

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NARRATIVE REVIEW

A comprehensive review on gout: The epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment

Kanwal Ashiq,[1] Mayyda Asif Bajwa,[2] Samreen Tanveer,[3] Mehwish Qayyum,[4] Sana Ashiq,[5] Rabia Khokhar,[6] Farah Abid[7]

Abstract

The current review was planned to assess updated knowledge about gout and to highlight the various areas which need to be focussed upon for better healthcare. Relevant articles published in English language were reviewed by utilising various databases including Google Scholar, Springer Link, Science Direct and MEDLINE. Data revealed a precipitating number of gout cases from the developed countries, while the developing countries on the other hand were found to be faced with an even higher threat. The risk factors and pathophysiology of gout are immaculate and clearly established. Hence, appropriate measures can be explored and worked on to pinpoint diagnosis, and economical treatment. In order to lessen the elevated global health burden along with revolutionising the patient's quality of life, an immediate action is required in certain aspects, like the adoption of a healthy modified lifestyle, a reduction in exposure to risk factors, robust prophylactic measures, bettering awareness, and an approach to early diagnosis followed by optimal treatment protocols.

Keywords: Gout, Inflammation, Hyperuricemia, Allopurinol, Xanthine oxidase.

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Introduction

Gout is well-known for decades as a chronic inflammatory condition of the joints.[1] In the past, gout was considered one of the benign diseases associated majorly with over-eating and to some extent of alcohol consumption. However, advanced studies and research revealed its roots in metabolic disorder, finding its origin with urate crystals, making deposits in joints, kidney, skin and various other tissues.[2] It is also termed "men's disease" owing to a high rate of incidence amongst males compared to females. The overall prevalence in men is estimated to be four times that of women. Females enjoy a comparative leverage because of the presence of estradiol that exhibits inhibitory action on urate crystal synthesis.[3] Gout finds a major association with a number of co-morbidities, like diabetes,[4] stroke, myocardial infarction (MI) and hypertension (HTN) amongst several others. Altogether, with other co-morbidities, it gives a major rise in the rate of mortality and an overall decline in life expectancy.[5] Gout can be expressed as a raised serum uric acid, i.e., hyperuricaemia, with levels reaching >6.8mg/dl. The rise in the levels of serum uric acid causes the generation of urate crystals, immediately followed by the formation of renal stones and backed with tophi that eventually lead to gouty arthritis.[1,3] The spectra of the disease extend from subclinical hyperuricaemia, mapping its way to acute gouty arthritis and ultimately chronic tophaceous gout. The latter persists for a protracted duration and leads to a nastier stage called chronic arthopathic gout.[6] The prevalence of gout can be traced amongst some of the developed countries, while the rate is considerably high when seen with under-developed countries. Some of the initiating factors of the disease worth mentioning are high sugar intake, alcohol consumption, a high intake of meat and protein-rich diet. Acute pain, subcutaneous tophi, and persistence of low-grade inflammation for longer time cause deformation of joints, restricted mobility and permanent disability that negatively influences a patient's quality of life (QOL).[7] Deposition of the uric acid crystal may often damage kidneys and the condition may even progress to chronic nephritis. An immense increase in the economic burden of the disease has been observed worldwide, contributed majorly by malpractices, including suboptimal disease care, poor diagnosis, lack of communication between patient and healthcare providers, little awareness and understanding of the disease and unavailability of medicines.[8] Consequently, a greater number of the patients are witnessed by hospitals that in turn raise the overall cost of the treatment.[9] Presence of various co-morbidities makes the estimation of the exact economic burden of gout a bit difficult. However, steps can be taken to reduce this

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overall burden over the economy due to gout by promoting maximum awareness, controlling the symptoms, introducing a healthy lifestyle, timely and accurate diagnosis followed by optimised recovery protocols and treatment.[10]

The current narrative review was planned to provide streamlined information regarding gout, the most prevalent type of arthritis.[1,4,8]

Methods and Results

Literature was searched on various databases, including Google Scholar, Springer Link, Science Direct and MEDLINE, without any time limit. Search key words included: 'gout', 'gouty arthritis', 'hyperuricaemia', 'gout economic burden' and 'prevalence, diagnosis and treatment for gout'. The search was narrowed down by referring articles exclusively subjected to human studies and published in the English language. Also, the search was restricted to research papers, literature reviews and systematic reviews.

The articles included focussed on the objectives of the current study and took a critical view on epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment of the gout. Articles excluded were the ones that lacked thorough information and did not comply with the objective of the present study, comprised epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment of the gout.

Of all the articles screened, 52 were shortlisted. After full-text review, 35(67.3%) articles were included.

Epidemiology: All around the globe, the human population is faced with frequently occurring inflammatory arthritis called gout.[1,4,8] Chang-Fu et al. published an epidemiological study revealing that the overall incidence and prevalence of gout has increased immensely over the past few years. The incidence of disease is uneven around the world and the occurrence is greater in the Pacific regions. Genetic factors can play a role as some ethnic groups are more prone to developing gout.[11] The United States of America (USA) and Europe top the chart with the highest number of gout affectees, with manifold increase over the last two decades. In Canada, the prevalence is considerably increased and in 2012, about 3.8% gout cases were reported.[12] The frequency of gout has increased in the USA in the past few years and the terns still continues. Approximately 8.3 million individuals are suffering from gout and the rate of incidence is higher in men (6.1 million) compared to women (2.2 million). The United Kingdom (UK) has reported having more than 700,000 people suffering from gout. The annual number of outdoor gout patients visiting the hospital in the United Kingdom is estimated to be four million.[13] As per another estimate, there are 4 males and 1.4 females in every thousand, annually affected by gouty arthritis, especially the ones aged >45 years.[1,3] On the other hand, the occurrence of hyperuricaemia is prevalent in females, particularly in the post-menopausal ones. The rate of incidence is no lesser in the USA where almost 3 million self-reported cases of hyperuricaemia were documented in a survey.[14] The high financial burden is linked to an increased prevalence of gout in the UK due to suboptimal treatment and management.[15] In New Zealand, around 9.3% to 13.9% of Maori men and 14.9% of Pacific island men suffer from severe gout.[16] A study conducted using nationwide data showed that the rate of gout incidence has substantially increased in the entire New Zealand population and the frequency is more (>25%) in the elderly Pacific and Maori men.[17] Higher number of hospital visits due to gout is reported in Asian than Caucasian subjects. The frequency of gout occurrence is reported to be high in mainland China,[18] while in Germany, the adult population shows >1% of gout patients. Not only European countries exhibit an alarming prevalence of high serum uric acid levels, but it is also evident is Asian countries, like Indonesia (18%), Taiwan (10-52%), Turkey (12%), China (6-25%), South Korea (5%) Thailand (9-11%) and Saudia Arabia (8%).[19] Till date, exact number of gout cases in Pakistan are not known and epidemiological statistics are required in order to evaluate risk factors and to have improved diagnosis.[20] Pathogenesis of the gout: Gout is a metabolic disorder resulting from the augmented formation of uric acid. It was first documented by Egyptians in 2640BC and it was known as the "disease of kings" as it is mostly associated with lifestyle. The term gout is coined from Latin word "gutta" meaning drop.[21] The heightening level of uric acid (>7mg/dl), primarily an end-product of purine metabolism, is the result of a disorder. Normally within the body, purines are transformed to the hypoxanthine, and then further transformed to uric acid by the action of hypoxanthine oxidase. Uric acid is converted to allantoin through the action of uricase, an enzyme excreted by the kidneys in mammals. The fundamental mechanism for the development of gout is an amplified serum level of uric acid following a reduced renal excretion.[22] The excretion of uric acid is mainly governed by renal secretion and absorption. The reabsorption process of uric acid is carried out by urate transporter-1. An amplified formation and dwindled excretion lead to a rise in the

serum concentration of uric acid, which successively converts into monosodium urate crystals.[5] The presence of uric acid subsists as needle-shaped crystals, open for identification and consumption by the neutrophils and monocytes. The inflammatory response is initiated via the release of interleukin 1 (IL-1) and added cytokines, subsequently initiating an acute gout attack. This follows the action of neutrophils that with the ingested crystals grow closer and forming a tight packing. This ultimately advances to cell death, led by a unique pattern, presenting a phase specified as tophaceous gout.[23] The inflammosome encompassing a multi-molecular structure is a pro-cytokine, responsible for activating IL-1 that in turn exhibits the inflammatory response. Supplementary mediators are also part of the inflammation constitutes of IL-6 and alpha-tissue necrosis factor. Conversely, IL-1 inhibitors impede the discharge of IL-1 and, therefore, contribute to receding the inflammatory response. There were many mechanisms discovered by which uric acid stimulates the inflammation and have influence on innate immunity, and, hence, they are also known as "danger signal". However, further investigations are needed to know the cellular and molecular basis of the pathogenesis which would be helpful in recognising the new sites for drug-binding that can be beneficial in the treatment of gout.[24]

Clinical presentation and diagnosis: Acute gout manifests with symptoms of swelling, intense pain and soreness around the joints. An asymptomatic period may be experienced between the gout attacks that are referred to as inter-critical gout.[25] Acute gout is reported with high fever, leukocytosis and shedding skin throughout the inflamed area, closely resembling cellulite. The term "podagra" is specifically reserved for acute gout, referring to the condition when the very first metatarsophalangeal joints are influenced by the urate crystals. Acute gout comes with clear signs of flares with a distinct fashion presenting as immensely inflamed area accompanied by discomforting pain lasting for around 5-10 days.[26] The asymptomatic hyperuricaemia can continue for a couple of years, while flares may dissolve within this duration. The crystals, on the other hand, may display propagation and intense pain accompanying inflammation, and ultimately may enter into the phase of chronic gout. In the case of chronic gout, production of tophi with unique features occurs that can be traced and diagnosed via physical examination and various imaging techniques. These tophi can be located in certain regions, namely cutaneous tissues, bones and articular spaces.[27] The presence of flare and pain makes routine activities and movement challenging for the patients, followed by permanent disability that adversely affect the patient's QOL.[2,5] The urate crystals are not limited to a particular organ, and, instead, may develop chalky deposit in the eyes though asymptomatic. A variety of eye pathologies, such as ulcerative keratitis, may occur following the crystals piling up in the cornea. This is a rare condition though.[28]

The diagnosis of the disease is based on the presence and identification of urate crystals coming through a smart and active clinical approach. This, besides being the gold standard diagnosis, is barely practised in routine. Failing to perform the synovial aspiration on a regular basis, the clinical diagnosis and judgment is based upon physical examination and patient history.[29] Some of the tools aiding in the detection of crystals are readily available, such as ultrasonography (USG) and microscopy. Another sensitive approach is a non-invasive dual-energy computed tomography (CT) technique that detects uric acid crystals. It offers diagnostic imaging by producing coloured images of crystals visible for a distinct identification of the subclinical tophus and the tophus volume. However, there is a need to refine the diagnostic methods.[30]

Prevention and treatment: High incidence of gout across the globe makes it necessary to have immediate identification of associated risk factors and lifestyle modifications to offer better prevention. Dietary habits, such as daily consumption of coffee, soft drinks and sugar, specifically fructose, increases the chances of gout. A controlled diet with partial or complete removal of precipitating factors and supported by healthy lifestyle promises prevention. Precautionary measures against gout incorporate the intake of more fluid and having a diet with low animal protein.[31] Routine ingestion of fresh vegetables, whole grains, nuts, fruits and dairy products gives an added advantage. A healthy routine with regular exercise, controlled body weight and use of vitamin C supplements, also limit the chances of gout. The management and treatment protocols of gout revolve around bringing down the serum level of uric acid, i.e., as low as 6mg/dl. In order to attain this status, medicines, like allopurinol and probenecid, play a pivotal role.[32] Drugs, for example, aspirin, diuretics, nicotinic acid, lactate infusion, testosterone, xylitol, ethambutol and pyrazinamide, should be taken cautiously as these may stimulate increased uric acid production and may worsen the gout. The regularly-acquired medicines to counter gout also include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and adrenocorticotropin hormone.[33] In addition, xanthine oxidase inhibitors, together with uricosuric, are

frequently used. For the management of acute gout, the use of systemic corticosteroids stands out as the most effective means of treatment that comes with no substantial adverse effects.[34] In case of patients either resistant to or contraindicated with the use of allopurinol can switch therapy to febuxostat as a substitute drug for the treatment of gout.[35]

The current review does have a few limitations. It is a non-systematic review that included only articles related to human studies. Also, manuscripts for which full text was not available and that ones that were not published in the English language were also excluded.

Recommendations

It is suggested that advance molecular studies should be carried out to further explore the gout pathogenesis which would be helpful in recognising the targeted areas of drugs to counteract the disease.

Moreover, exploration of literature revealed that comprehensive epidemiological studies are not available, especially with regard to the developing countries. Such studies, as such, are recommended so that geographical variation, related risk factors and rate of morbidity and mortality with treatment outcomes over time can be evaluated.

Conclusion

The distribution of gout, remains uneven, with developed countries more likely to face the economic burden via its negative influence of patients' QOL. There is a dire need for optimised treatment strategies.

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Phytoconstituents and Pharmacological Profile of *Echinacea purpurea*

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Key words: Anti-inflammatory, Cytotoxic, *Echinacea purpurea*, Immune-modulatory, Psychotic.

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Abstract

Echinacea purpurea (Asteraceae) is a medicinal herb that has broad spectra of pharmacological properties. It is a perennial herb with immune-stimulant and anti-inflammatory properties. Due to its vast pharmacological properties, this plant has attracted the attention of scientists to evaluate other beneficial biological effects. The plant has shown antidepressant, anxiolytic, anti-mutagenic, cytotoxic, antifungal and antibacterial properties. The objective of this review is to highlight the importance of *Echinacea purpurea*. Different databases were used to search literature in the English language. Clinical studies are still not found due to its adverse effects. But some plant studies have shown the best biological responses, with no serious side effects, while some studies have reported severe adverse effects on the skin such as rashes, urticaria and itching, abdominal cramps, pain, nausea and labored breathing. Cichoric acid and alkamides analysis have been developed by high-performance liquid chromatography (HPLC) by using different detectors, for example, coulometric detectors, ionization mass spray detectors and Uv-vis detectors. Instead of controversial results of different studies on this plant, some activities show the best results, But some questions are still there. *Echinacea purpurea* plant has a lot of work that needs to be done in the future by considering the mechanism of action.

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Introduction

Echinacea purpurea is one of the medicinal herbs of the Asteraceae family, with the habitat of eastern North America. It was the first time used by native Americans to enhance body immunity (Mckeown, 1999). Traditionally, it was being used to cure toothache, arthritic pain, worst skin conditions, snake venom bite and cancers (Grimm and Muller, 1999). The plant also has shown the best result in chemotherapy of many diseases. The same species of this family have been used to treat respiratory tract infections (cold, flu) and urinary tract infections (vaginal yeast infection) (Patel *et al.,* 2008).

Scientists isolated its major compounds and elucidated their structures. Alkamides, caffeic acid derivatives, and polysaccharides were major plant constituents. Many studies were conducted to check the pharmacological activity of the extract. Immunomodulatory activity is due to alkamides (Goel *et al.,* 2002; Gertsch *et al.,* 2004). Anti-inflammatory activity was estimated due to the presence of polysaccharides in extracts (Laasonen *et al.,* 2002).

Some other species of *Echinacea* genus, such as *E. angustifolia*, *E. pallida*, and *E. purpurea* are reviewed in past papers according to chemical, pharmacological, and clinical properties (Barnes *et al.,* 2005). According to some reviewed papers on the medicinal properties of the plant, further research studies can be conducted on it (Barrett, 2003).

This paper is reviewed different extraction techniques, and phytochemistry, biological and pharmacological activities of *E. purpurea species. Paper is also reviewed about* psychoactive and mosquitocidal effects of extracts.

Properties

Extracts of *E.Purpurea* possess many pharmacological properties in which most important is its immune-modulatory property. *Echinacea Purpurea* plant is being used since ancient times to treat inflammation and swelling of the skin by reducing the level of cytokines in the epithelial membrane. It has many other properties such as anti-venome (in snake bite), mosquitocidal property (aegypti larvae), antifungal (against *Saccharomyces cerevisiae* and *Candida albicans*) and antibacterial (Clifford *et al.,* 2002; Stojicevic *et al.,* 2009; Saiednia *et al.,* 2011).

It also has the property of enhancing immunity in colds and flu. For this purpose, a standardized solution of *Echinacea Purpurea* plant is being used commonly (Sharma *et al.,* 2009).

This formulation also possesses anticancer, anxiolytic and anti-viral properties (Chicca *et al.,* 2007; Sharma *et al.,* 2010).Experimental studies of secondary metabolites such as polysaccharides, glycoproteins, caffiec acid and alkamides show immune-stimulatory activity (Barnes *et al.,* 2005).

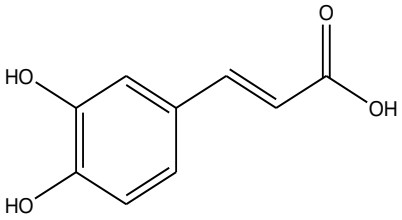
The plant *Echinacea purpurea* possesses enormous properties (Bergmann, 1995).

Constituents of Echinacea Purpurea

Plant extracts contain polysaccharides, chicoric and caffeic acid, alkyl amides and flavonoids.

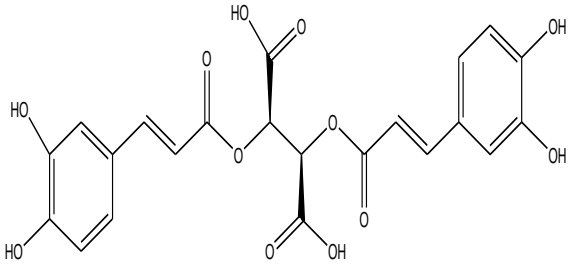
Caffeic acid

Caffeic acid is the main constituent of extracts which is an important metabolic product in plants. Chemically it is 3,4 dihydroxycinnamic acid which is phenolic acid. Derivatives of phenolic acid are monomers and oligomers of caffeic acid, and these are water-soluble (Barrett, 2003).



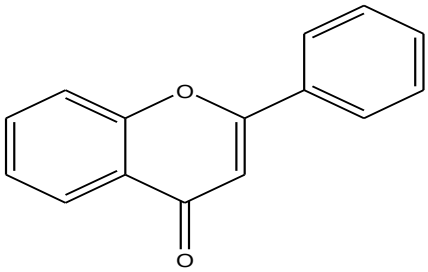
Chichoric acid

it is one of the main components of extracts, identified in 1958. It contains anti-viral (anti-HIV), anticancer and anti-obesity properties (Hao *et al.,* 2015).



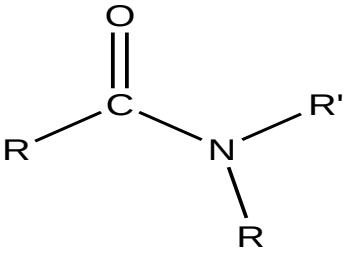
Falvonoids

Nicotiflorin and rutin are two major flavonoids found in *Echinacea purpurea* extracts.



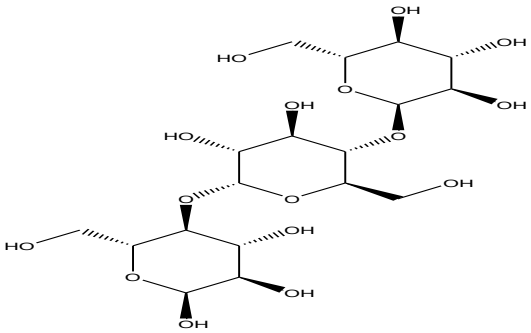
Alkamides or alkyl amides

Lipophilic component alkamides, show phagocytosis property when inserted orally in rats (Jungmin *et al.,* 2013).



Polysaccharides

Results of studies on mice showed its influence on nonspecific immunity. EP also enhances cytotoxicity against tumor cells (Kreft *et al.,* 2014).



Pharmacological activities

Echinacea purpurea is used anti-viral properties

Some studies show an aqueous fraction of flowers, leaves and stems of echinacea purpurea contains anti-viral properties against herpes simplex virus and influenza virus because ethanol and ethyl acetate present in leaves and stems are anti-viral (Steinmüller *et al.,* 1993).

Anti-oxidant activity

It also contains anti-oxidant properties. These oxidants are chichoric acid, rosmarinic acid and flavonoids.

These anti-oxidants are extracted from the fruits, and flowers of the plant.

Cytotoxic activity

The chichoric acid, which is extracted from flowers of *Echinacea purpurea* is used to inhibit the human colon cancer lines n-hexane, which is obtained from the roots of *Echinacea purpurea,* also shows anticancer activity (Shaffique *et al.,* 2018).

Anti-inflammatory activity

Some studies show EP is an anti-inflammatory agent which can reduce the symptoms of respiratory infections against many bacteria like *Streptococcus pyrogens*, *Hemophilus influenza*, *Legionella pneumophila*, *Staphylococcus aureus* (Manayi *et al.,* 2015).

Ailment for upper respiratory tract

Some results of many days study on the subject shows that Echinacea and tea can reduce the symptoms of the upper respiratory tract includes the portion of the larynx below the vocal folds, trachea, bronchi and bronchioles (Canlas *et al.,* 2010).

Immune-suppressant activity

It is the most popular herb used as immune-stimulants in North America and Europe. Some studies show it has anti-immune-suppressant properties when it is used on mice.

These studies showed that EP could increase immune functions (Shaffique *et al.,* 2018).

Immuno-stimulant capacity

The Native Americans consume the *Echinacea purpurea* L. as a medicinal plant to treat: infections related to the respiratory tract, wound curing, and boost the immune system. The metabolite contents were enlisted, which are polysaccharides (162.2±8.4), total phenolic content (22.3 ±1.0 mg Gallic acid/g of TP), total flavonoid content (86.0 ± 4.6 mg quercetin equivalent/g of TF) in the extract of *Echinacea purpurea* plant, which was made in ethanol 55% to distilled water (1:10). The outcomes of in vitro study were concentration-dependent for NO production, TNF- α and cell viability by the use of chicken peripheral blood mononuclear cells (PBMCs), and RAW 264.7 macrophages were 89% and 81% individually (Lee *et al.,* 2010).

Effect of Echinacea purpurea on antibody and immune cell response

To check the antibody and immune cell response against the snake venom by the administration of root of the aqueous plant extract. The results were remarkable; there is an increase in antibody production in the body against the venom. The in-vitro study also showed there was an uprise in lympho-proliferation when the root extract and lectin were used combined (Chaves *et al.,* 2007).

Effect of Echinacea purpurea as anti-oxidant on markers of aging

The outbreak against the oxidation was the consumption of active constituents of natural sources. The effectiveness of water and ethanol extract of the root of the plant on mice was tested against different parameters such as superoxide dismutase (SOD) and glutathione-s- transferase (GST), liver functions, total cholesterol, lipoprotein, triglycerides levels, blood hemoglobin and hematocrit counts. The plant extracts have the potential to keep the level within the range (Soudi *et al.,* 2010).

Efficiency of Echinacea purpurea on total anti-oxidant activity

The total anti-oxidant activity, which is composed of prevention of oxidation and scavenging of free radicals, was conducted in broiler chicks. The dried aerial parts of Echinacea purpurea (EP) were given in powder form against an antibiotic (flavophospholipol). The response of the activity was absent in the aerial part but, at the dose of 10 g/kg the activity was impressive (Wang *et al.,* 2008).

A first clinical trial was led to figure out the immune response of *E. purpurea* on volunteer females. These patients were treated with different residues of plant: purpurea/E. angustifolia or *E. purpurea/E. angustifolia* plus larch arabino-galactan, after the period of four weeks the properdin rises which was an immune-stimulant.

The active compound extracted from the butanol fraction of stem and leaves was tested for its proteomic profile on the mouse in dendritic cells primary cultures, maturation of phenotype of dendritic cells remains unaffected and the uprise of expression of anti-oxidant and cytoskeletal proteins (Ghalamkari *et al.,* 2011).

Cytochrome p450 activity

The cytochrome P450 (CYP) was inhibited by the tincture of Echinacea in *in-vitro* testing. While *in vivo* testing, the roots of the plant were checked with the CYP substrate drugs: caffeine (CYP1A2), tolbutamide (CYP2C9), dextromethorphan (CYP2D6), and by oral and intravenous route midazolam (hepatic and intestinal CYP3A). The various effects were observed with Echinacea that are: it diminishes the oral clearance of caffeine and but no consequence on the tolbutamide and dextromethorphan.

Anti-viral activity

The aqueous extract of aerial parts of the plant: stems, leaves, and flowers have potent anti-viral activity against herpes simplex virus and influenza virus. These can be used in the cure of UTI and also possess immune-enhancing properties.

The ethanol and ethyl acetate soluble fraction from leave and stem detected thiophenes, alkaloids, complex quinones, polysaccharides, and cichoric acid

might be the potential component for their action against viruses, which was lacking in the flower extract (Vimalanathan *et al.,* 2005).

Toxicology and adverse effects

The studies on different parts of the plant of *E. purpurea*: root extract, aerial parts, and pressed juice reported few unwanted side effects or toxicity (Mengs *et al.,* 1991).

Anti-leishmanial effect

The study reported that plants improve the immunity against leishmaniasis: the ethanol extract of the root of the plant was leishmanicidal at the concentration of 50 mg/ml (Lee *et al.,* 2010).

Other pharmaceutical uses

Acid indigestion, chronic fatigue syndrome, diphtheria, dizziness, gum disease, malaria, migraine, syphilis, tonsillitis, urinary tract infections and vaginal yeast infections (Barrett *et al.*, 2003).

Conclusion

Medicinal plants have remained the source of attraction since ancient, to treat people in all disease cases. Even they don't know the mechanism of action of the plant, but they treat people with these extracts. Recent researches are based on a major mechanism of action which leads to its pharmacological use to prepare a formulation. Formulations or drugs which have a natural origin possess great pharmacological action potential with fewer side effects. It will be pharmaco-economic as compared to synthetically originated drugs. The *Echinacea purpurea* contain enormous phytochemicals with many pharmacological properties. So, it can be used in the pharmaceutical industry to produce a new variety of formulations to treat different diseases. This review of the plant is advantageous in future researches and may be helpful in pharmacy to produce drugs.

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Drug discovery and development: current practices and future

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Abstract

Drug discovery and development encompasses the entire procedure of recognizing a drug from its discovery phase until its launch to market. The field of drug design discovery and development is a multifaceted, high-risk, high octane, and probably highly illuminating and rewarding venture. The current study aimed to highlight the current practices and future of drug discovery and development. Various databases, including Scopus, Web of Science, and PubMed, were utilized to search the literature. Natural products are still the first choice of starting material for drug discovery despite recent advances, the rise, and the integral role of combinatorial chemistry in the lead discovery process. Recent analytical and computer technology developments have opened new avenues for processing complex natural products and using their structures to generate new and innovative drugs. In recent times, it has promised biotechnology as a forerunner in the path to the insurrection of human lives. Various products include novel vaccines, diagnostic devices, and new therapeutic strategies, are the achievements of biotechnology in the biomedical domain. Drug discovery is a multidimensional question. It must be evaluated during drug candidates' selection by several parameters such as safety, pharmacokinetics, and efficacy. For a drug entity to pass different stages of its development has to go through significant drawbacks and pitfalls.

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Introduction

Drug discovery is an innovative practice of discovering and identifying new drug entities and medicines. The process is carried out through knowledge and practice of various disciplines such as pharmacology, chemistry, and biology. Drug discovery and development encompasses the entire procedure of recognizing a drug from its discovery phase until its launch to market. The process might comprise series of steps involving potent drug identification through screening of combinatorial chemical libraries or from natural products or drug designing thorough understanding of drug targeting (Thomford *et al.,* 2018). The development phase involves various animal and microbial investigations and animal and human clinical trials, which all converge to the ultimate regulatory approval from concerned federal organizations. Currently, the pharmaceutical industry faces besiegement through strict perusal by the general public, the financial community, and different regulators. Consequently, the progression in drug discovery and new drug approvals is now showing a downward trend from the last decade. Furthermore, this scrutiny put by various groups mentioned earlier poses a big question mark on the safety of highly successful existing drugs (van der Greef and McBurney, 2005).

The field of drug design discovery and development is a multifaceted, high-risk, high octane, and probably highly illuminating and rewarding venture. Corporations involved in this arduous process burn cash to the tune of approximately $802 million per drug (Dickson and Gagnon, 2009). Drug discovery and development have observed an unprecedented predicament in the past ten years: few new drugs were produced and approved despite more available funding and investments. Historical experience has proven to be a significant point of initiation in the process and success of drug discovery. This is further reckoned by Sir James Black, a former Nobel laureate who stated the initiation of the drug discovery process from an old drug is the most fruitful basis for discovering a new drug. The pharmaceutical industry has reverted to the historical experience again to discover novel drug candidates from natural sources and traditional medicines (Corson and Crews, 2007) (Raju, 1999).

About the health of Chinese people amongst others who have been using traditional medicine from ancient times to maintain their health, it could be vividly considered that conventional medicine may have more indications for contemporary drug discovery process rather than new chemical drug entities. The past century's efforts of medicinal chemists have borne fruitful results in the form of accumulation of almost 170,000 drugs which is around 100 times more than the prospective drug targets, which pool around 1500 only. If we consider the point that ligand binding sites are much less varied and assorted than protein architectures, then we can be certain that existing drug candidates may have encompassed a significant number of potential drug targets (Kong and Zhang, 2009).

Nowadays discovery of drugs is grounded on lock-key drug theory which, focuses on a single potential candidate to hit one target to cure various associated diseases (Sams-Dodd, 2005). Conversely, the pathology of various ailments is multifaceted and comprises numerous aspects which make it difficult for a single drug target to defend and combat against polygenic illnesses (Zimmermann *et al.,* 2007). Additionally, inhibition of one target is a significantly less efficient non-selective approach resulting in fewer efficacies as the human body is a tremendously intricate and complex grid with a lot of redundancy in it and unexpected side effects might interrupt the balance of the grid. (Csermely *et al.,* 2005) (Reddy and Zhang, 2013). The modernization of medicine in America today has called for strengthening and development of the drug discovery process through bridging the gap bawling for mutual collaborations between industrial, academic, and philanthropic sectors. This will, in turn help in breaking the barriers to ultimate commercialization and translation by fetching superlative practices from industry to academic organizations, and this would occur not only by generating new generation translation

scientists but also by producing a novel force of skilled scientists in regulatory discipline (Strovel *et al.,* 2016). For the discovery of new disease targets and development of the next generation of disease interventions, biotechnological and pharmaceutical industries have been integrating chief high-tech scientific progressions at the phenotypic, genetic, and proteomic levels for more than 50 years. But despite all these remarkable biotechnological developments, there have been very few chief progressions in the average success rates for developing novel drug candidates and identifying first-hand drug targets. However, in recent times emergence of disruptive therapeutic modalities such as tissue regeneration, cell-based therapies, and gene therapy has given illuminating hope and could prove to be the novel therapies of the future (Kelm *et al.,* 2019). The current study aimed to highlight the current practices and future of drug discovery and development. Various databases, including Scopus, Web of Science, and PubMed were utilized to search the literature (Ashiq *et al.,* 2021; Kanwal *et al.,* 2018;).

Sources of drug compounds

Natural products are still the first choice of starting material for drug discovery despite recent advances, the rise, and the integral role of combinatorial chemistry in the lead discovery process. According to current data, in the past 25 years, almost 974 new drug entities were established, out of which 63% were either natural, semi-synthetic, or natural inspired drugs. Natural products may prove to be an important tool as a source for new drug entities for advanced methods of development for certain treatments such as anti-inflammatory, antimicrobials, antihypertensive and anticancer drugs (Ashiq *et al.,* 2021; Harvey, 2008; Tanveer *et al.,* 2019).

Plant-derived bioactive materials

In the western world, before the advent of Paracelsus, most of the diseases were cured traditionally by crude drugs, which were mostly of plant origin. This has led to the formation of a genetic pool of info full of curative potential of botanical species, thus building them as an essential point of initiation for the discovery of novel drugs. The new drugs are discovered from plant secondary metabolites, which are delocalized in various anatomical parts of the plant (i.e., leaves, bark, roots, and flowers, etc.).

It requires strong botanical knowledge for the accurate identification of these bioactive plant ingredients (Balunas and Kinghorn, 2005; Latif *et al.,* 2020; Qayyum *et al.,* 2020.

Microbial species with bioactive metabolites

The main source of antimicrobial drugs are microbes which through their competition for nutrient, living space and their ability to survive the harsh conditions (i.e., prevention of proliferation of competing species) have finally passed the test of times and has proven itself to be the preferred source for the antimicrobial treatment plan. For example, *Streptomyces* species use as a source of antibiotics. However, it's crucial to mention the classical discovery of Penicillin in 1928, a Nobel antibiotic present in the bacterial culture of penicillium fungi used as a defense mechanism against another microbe (Alagarsamy, 2013; Sharma, 2020).

Marine invertebrates as a source of bioactive compounds

Currently, there is a shift towards the marine environment as a potential source of bioactive agents and drug discovery. In the 1950s, arabinose nucleosides were discovered from marine invertebrates, which demonstrated that sugar moieties other than deoxyribose and ribose could harvest novel bioactive nucleoside structures. Although 2004 marked the year of discovery of the first approved marine drug. Prialt, a ziconotide toxin extracted from cone snail, was the first FDA (Food and Drug Administration) approved marine drug used for the treatment of severe neuropathic pain. Numerous bioactive derivatives of the marine source are now going through clinical trials for the treatment of various ailments such as inflammation, pain, and cancer. Bryostatin-like agents are one such example of marine drugs under investigation as anticancer drugs (Alagarsamy, 2013; Kiuru *et al.,* 2014).

Traditional knowledge and drug discovery

The ancient ancestral knowledge is the non-documented and verbal form of treasure communicated from generation after generation and is being nurtured by ethnic societies in common and has an association with ferny floor and red lateritic soil of Purulia District of W.B and various forests. For efficient, sustainable development, good health is one of the crucial factors for the sustenance of a steady population. But extremely high cost is one of modern medicine's main attributes, which makes maintenance of global health a difficult task to accomplish. This issue could be resolved by the production of natural lead drugs discovered through the asset of traditional medicinal knowledge that would, in turn, lead to eco-friendly sustainable progression at a lower price with low side effects (Sannigrahi, 2014).

Natural lead drugs have proven to be the most fruitful basis for the progression and discovery of novel therapeutic drugs. Furthermore, due to the wider application of various molecular biological techniques, an upward trend is shown in the accessibility of new drug compounds that are expediently generated in yeast or bacteria. Also, different combinatorial methodologies focus on natural product-based scaffolds, which are in turn utilized to create screening libraries resembling drug-like compounds. This suggests that it could be expected that effective and efficient progression and application of natural products will also advance and improve the drug discovery process (Harvey, 2008).

Global traditional medicine usage and knowledge are pretty varied and diverse; however, Ayurveda, Chinese traditional medicine, and tib or Unani medicine are amongst the most popular and widely used ones. The term Ayurveda is composed of 2 Sanskrit words Ayur, meaning life and Veda means science, collectively it refers to the science of life and is dedicated towards the holistic management of disease and health. The most crucial role played by Chinese medicines and Ayurveda is the bioprospection of new drug molecules. Both holistic approaches utilized research in varied fields such as pharmacology, pharmacognosy, and chemistry (Patil *et al.,* 2014). As a result, many secondary plant metabolites have been reported which have various indications e.g. alkaloids from *Rauwolfia serpentina* have been reported for their use against hypertension, alkaloids from holorrhena for amoebiasis, curcumin as an anti-inflammatory, *Mucuna pruriens* for Parkinson's disease, piperidines for enhancing bioavailability, picrosides for hepatic protection, guggulsterons as hypolipidemic agents, baccosides for mental retention, withanolides and many other steroidal lactones and their glycosides as immunomodulators and phyllanthins as anti-viral (Patwardhan, 2005).

Tibb (also known as Unani-Tibb or Unani medication) is a widely practiced, traditional style of healthcare that draws on the basic standards of care established by Hippocrates, Galen, and Ibn Sina, the three proponents of persuasive pharmaceuticals (Avicenna). A number of axioms underpin Tibb's 'A science of pharmaceutical, the craftsmanship of care.' One is the individuality of each person, so this is a crucial part of Tibb diagnosis and treatment since it is expressed as temperament (Bhikha and Glynn, 2017). Another is the idea of Physis, or the body's natural ability to heal itself. Rather than only treating symptoms, Tibb focuses entirely on promoting inner health. The concept of body humor is the third axiom, while lifestyle Factors are the fourth. Temperament touches on humor and lifestyle Factors have a lot in common. Realistic lifestyle guidance, natural drugs, and adequate diet therapy are all part of the treatment. Tibb isn't a new or esoteric style of therapy; it has origins in traditional medicine that date back hundreds of years to ancient Greece and Persia. When the body's functions maintain a proper balance of temperaments, structure, and functions, it is said to be healthy. A temperamental imbalance, a humoral imbalance, or a tissue structure problem can all manifest as a disease. The concept of Physis is central to health, disease, and survival in Tibb. It plays a key role in the body's self-healing and self-repair processes and actively counteracting influences that cause injury and illness. It ensures that one's

health is kept at its peak. Physis corrects various lifestyle factors that cause alterations in humoral balance (Bhikha and Glynn, 2017).

The importance of lifestyle factors in sustaining the ideal qualitative condition demanded by a person's overall temperament is critical to achieving optimal health. Similarly, in the management of illnesses, restoring the proper humoral balance through appropriate application of the lifestyle factors is critical, as this tackles the symptoms and the causes. Tibb therapy fully complies with physis operation. The concept of temperament, essential to diagnosis and treatment, is also adhered to in Tibb. Temperament is a combination of personality, physics, and behavioral characteristics that makes us unrivaled. The two fundamental temperaments are a composite, a primary (dominant), and a secondary one (subdominant). Humor preserves the ideal qualitative condition of a person's temper (Shirbeigi *et al.,* 2017). The right amount and quality of humor in the body and a balance between them are health results. The illness is caused by imbalances in a person's humor composition. Physical philosophy, temperament, and humor, as well as the principle of cause and effect of Ibn Sina, testify to medical science and the art of care, which offers an understanding of the etiology, the underlying pathology, and how it is digested, and ultimately which treatments are chosen. Tibb's philosophical principles are the principles of physicality, temperament. Tibb is an ideal partner for integrative medicine because the main principles of conventional therapy are not contradictory (Bhikha, 2017).

Current practices

Since time immemorial, plant therapeutic properties have been recognized. Several pathologies with plant-derived medicines have been treated. Those medicines can be used without isolation from active compounds as concentrated plant extracts. However, modern medicine calls for one or two active compounds to be isolated and purified. But there are many global health challenges in the face of diseases such as cancer, degenerative conditions, HIV/AIDS, and diabetes, which are difficult to cure in modern medicine. The "active compound" isolation has been ineffective many times**.** Drug discovery is a multidimensional question that needs to be evaluated during drug candidates' selection by several parameters, both natural and synthetic such as safety, pharmacokinetics, and efficacy (Mohs and Greig, 2017). The development of state-of-the-art technology, which improves hypotheses of drug design such as artificial intelligence, the use of organ-on-chipping, and microfluidic technologies, makes automation part of pharmaceutical discovery. As a result, the safety, pharmacokinetics, and efficacy of candidate compounds were increased rapidly in medicinal research and analysis, while new drug design and synthesis solutions based on natural compounds were developed (Moderator *et al.,* 2015). Recent analytical and computer technology developments have opened new avenues for processing complex natural products and using their structures to generate new and innovative drugs. In fact, in the era of molecular computational design, we use natural products (Grimme and Schreiner, 2018) (Ashiq and Ashiq, 2020). The detection of molecular targets of natural products and their derivatives has contributed through predictive computational software. In the future, there will be few false-positive results in drug development using quantum computing, computational software, and databases for modeling molecular interactions and foreseeing the features and parameters needed for drug development, for example, pharmacokinetic and pharmacodynamic (Thomford *et al.,* 2018).

Spaceflight offers a complex and intellectually stimulating medical environment with complex biological and developmental changes. We learned a tremendous amount in the last century about adapting people to microgravity and the strictness of interplanetary travel. But that's only the starting point of that clinical frontier, and much has to be learned as people travel to space and invest extra time in space. Earth-based medical care has long led to the selection of prophylactic and curative disease strategies. This worked well on missions near the

earth when consultation can be made, communication can be relatively constant, and returns to earth are a viable option (Velasquez, 2021). However, the presence of a doctor will constantly broaden the capacities of medical care during the flight, irrespective of whether ground support is available. Ground-based medical treatment will no longer be possible when critical medical decisions are necessary as we investigate our solar system. In the meantime, a highly qualified physician with different medical and surgical skills will be needed before the permanent habitation of space stations or lunar bases with specialist doctors and modern surgical equipment. These opportunities to move are available to emergency physicians, who should perform the function of a space physician in the distinctive medical setting of space (Hinkelbein *et al.,* 2017).

The deep-sea biological system could be the source of one kind of way. It is chiefly collected as living substances that are highly valued and are therapeutically diverse. Marine therapy could be a scientific theory of improving, maintaining, and restoring well-being by anticipating and treating seafarers. The major sources of biomedical compounds are pharmaceutical, marine sponges, shellfish, green growth, Corals, Ascidians, Bryozoans, and Vertebrates. There seems to be an initial phase in the prevailing situation in India, but steps are being taken to develop a significant source of unutilized drugs. The most emphasis is given in the search for a cure for the dangerous disease. The introduction to the deep sea exposes jumpers to a series of physiological hazards. Marine remedies are the subject of clinical trials which associate long-running safety studies with a therapy protocol history. The newly discovered drug passes through a thorough testing protocol, first in the laboratory and thus through many layers of patient testing before this drug is authorized for use by the wider populace; the marine life has a vast diversity that is still untapped. Marine medicine offers new mechanisms for combating men's most vulnerable diseases, such as HIV, pathology, Alzheimer's disease, and cancer (Deshmane *et al.,* 2020).

In recent times, it has promised biotechnology as a predecessor in the path to the insurrection of human lives. Various products include novel vaccines, diagnostic devices, and new therapeutic strategies for the achievements of biotechnology at the biomedical level. However, for a drug entity to pass different development stages, it must go through significant drawbacks and pitfalls (Ravichandran and Verma, 2021). Due to the unlimited ability of the stem cells to self-renew and differentiate to generate cells and tissue from the whole of the human body, stem cell technology has revolutionized medical biotechnology over the previous decades. To rectify or replace injured cells or tissues, many attempts have been devoted to providing state-of-the-art stem cell therapies to ultimately heal serious illnesses (Lukomska *et al.,* 2019). This technological innovation guarantees the trust of serial entrepreneurs in the economic future of products and services based on stem cells. A study characterized the state-of-the-art applications of several adult stem and embryonic applications and induced pluripotent stem cells in biotechnology that represent entrepreneurial opportunities. While stem cells contribute considerably to medical research, several barriers still need to be overcome, including ethical and regulatory issues, e.g., the functional maturation of stem cell progenitors, strict guidelines on production, immune disruption, and tumorigenicity (Jossen *et al.,* 2018).

The publication has nevertheless led to the development of successful models of human-based multi-potential stem cells based health, disease-restraining mechanisms of pathology, drug detection, and toxicity testing, microfluid, "organ-in-a-dish," and 3D bioprinting medicines. It's worth noting that, as the goals of computational chemistry and bioinformatics expanded, assistance was required to reduce the number of molecules to be tested in vitro or in vivo. In recent years, there has been a surge in the number of enterprises and start-ups focusing on bioinformatics and machine learning worldwide. Furthermore, veterinary medicine is widely used in biotechnological applications today and human

therapy in stem cell-based biotechnology ushers in a new era (Leelananda & Lindert, 2016). Finally, scientists with strong entrepreneurial thinking are critical for achieving economic value in medical biotechnology. As a result, we should educate the next generation of entrepreneurs and collaborate directly with institutions and financial institutions to ensure that the next generation of students is recruited and formed in a successful translation process (Duelen *et al.,* 2019).

Conclusion

Based on their history and their known vast potential for activities and structure and function variety, this study highlights the importance of plant-derived NPs as the most important source for therapeutic development. On the other hand, the new research approach is aimed at developing pharmaceuticals based on natural mixes, which are purportedly more beneficial due to potential synergistic effects, a reduction in unpleasant side effects, and an increase in the costs of single molecular medicine.

Conflict of interest

The authors declared no conflict of interest.

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An updated review: The year 2020 and coronavirus disease-19 pandemic

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ABSTRACT

The recent scenario with an outbreak of novel coronavirus has led to dramatic upsurge in mortality and morbidity rates all around the globe. The objective of consolidated article is to provide an updated insight on coronavirus disease (COVID-19) based on the current literature, and it is anticipated that it may serve as a perspective reference in future studies. Scopus, Science Direct, MEDLINE, PubMed, and Google Scholar databases were used to search the literature. For the current review, both research and review articles issued in the English language were considered. The mode of Corona virus disease transmission is through direct contact or inhalation of infected respiratory droplets. The length of period of incubation varies from 2 to 14 days with maximum patients presenting mild symptoms and sign, that is, cough, fatigue, fever, and sore throat. The infection could be worst and life threatening in elderly and immuno-compromised patients. Special diagnostic molecular tests are available for detection and identification of virus. Till date, no cure is available and treatment of patients is only supportive therapy. Preventive measures such as physical isolation, hand washing, and wearing of mask should be followed. Even though, strict measures are taken into account, prevalence of COVID-19 continues to escalate worldwide and coming course of this novel virus is still not known.

Keywords: Coronavirus disease-19, Pandemic, Virus, Infection, Quarantine

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in People's Republic of China (Hubei Province) but later erupted on a larger scale affecting people worldwide. With its similarity with Severe acute respiratory syndrome (SARS), it was initially catered as acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Soon after identification, the World Health Organization (WHO) titled it as COVID-19 and Emergency Committee of WHO classified it as an emergent and critical situation globally on 30th January 2020 following the grown cases not only in China but all across the globe.[1] Coronaviruses (CoVs) belong to a very diverse category of viruses which are enveloped and have single stranded RNA with a positive sense.[2] SARS-CoV-2 emerged on the world platform after it had already witnessed severe cases of acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) in 2002 and 2012, respectively. The current pandemic has brought humans to face the third induction of extreme epidemic invasion of corona virus on large-scale in the midst of the present day century.[3]

Origin wise, it is likely to be an event of zoonotic transmission coming straight from the one of the largest seafood markets, also trading in wild animals. Post identification of person to person transmission, measures are taken at wide scale to prevent the further spread whilst the current outbreak. A keen plan is observed and implied to protect the children and old, presenting themselves as the most susceptible population.[4]

The symptoms identified in most of the patients are mild, that is, fever, cough, dyspnea, and fatigue. Some of the trending presentations from confirmed COVID 19 patients include; upper respiratory tract obstruction with dyspnea,

dry cough with sputum production, a lymphopenia alongside myalgia/arthralgia, high lactate dehydrogenase, raised levels of C reactive protein and prolonged prothrombin time. In terms of severe/critical case ratio and median to intensive care admissions reported includes about 7–10% and 9.5–10.5 days, respectively. However, the mortality of 1–2% is observed with varied geographically.[5] In complete absence of suitable antiviral drugs or vaccines, with prevailing carriers and without any clear symptoms, innuendo of traditional health interventions fail to be completely effective.[6]

Further, the world is not prepared to face such a challenge and failed to learn from any of the last two epidemics of CoV as seen by the ill-preparation. The future research should bring in use the effects of the cyberspace technologies for tracing contagion. Mutual sharing of information and knowledge among various geographical locations and disciplines is the only key to combat the current situation.[7] However, various vaccines are under consideration, including; nucleic acid vaccines, viral vaccines, and recombinant protein subunit vaccines.[8] Although, the team of researchers working and aiming at the progression of a suitable vaccine against coronavirus however at the same time they are facing both logistical and scientific challenges. With this, the pressing challenge in development of vaccines remains the response of the immune system, both to pathogens and the vaccine.[9] In this time period, over 500 articles have been released in print or digital version on a weekly basis from January 13, 2020. A major portion of the article covers clinical manifestation and treatment modalities yet a great number focuses on structural elucidation, viral transmission, mechanisms/dynamics involved along with diagnostic techniques, and future antiviral treatments.[10]

With known casualties linked to COVID-19, a serious risk has been posed to the economy, triggering an ever increasing global risk and need to counter the spread. At the present time, many diagnostic kits for detection of COVID-19 are made available and have shown tremendous clinical support. In the meantime, globally institutions have stepped up with working on vaccine development, also taking it to clinical trials.[11] In this article, we aim to present a comprehensive review on COVID-19 and this review may serve as a reference for coming studies.

ONSET OF COVID-19 AND ITS EPIDEMIOLOGY

December 2019, marked an identification of a group of patients presenting pneumonia like symptoms of concealed source, initially seen in the seafood market in China (Wuhan). The unidentified disease led to blockade of human airway epithelial cells which on further investigation confirmed a novel form virus of corona family, named 2019- novel CoVs (nCoV). It belonged to subgenus sarbecovirus clade and sub-family of orthocoronavirinae. Two known variants of the same family, affecting humans were found to be different, that is MERS-CoV and SARS-CoV while 2019-nCoV stands as the seventh family member of CoVs welcoming more surveillance and investigation.[12] Phylogenetic analysis revealed its zoonotic potential along with the structural make, that is, a specific nucleic acid sequence from known human CoV (HCoVs) species, showing some similarity to that identified in bats.[13,14] Subsequent isolation from human samples followed by molecular analysis brought forth information on a new CoV, initially titled as 2019-nCoV. Following this WHO named the disease as COVID-19.[15]

To explain further, *Coronaviridae* family includes two subfamilies, that is, Torovirinae and Coronavirinae. The latter comes with a considerable number of pathogens of mammals, causing a great variety of diseases including pneumonia. Within humans, CoVs lie in a spectrum of viruses causing flu-like symptoms and majorly affecting the respiratory tract, akin to SARS and MERS, both being zoonotic in nature. While the former, Torovirinae, possess pathogens of both aquatic and terrestrial origins. Genus Torovirus entails species that is equine torovirus (Berne virus), initially isolated from a horse presenting diarrhea symptoms, while Breda virus, when isolated from neonatal calves also presented with diarrhea.[16] Further known facts include that CoVs are divided into four genera that count for α−/β−/γ−/δ-CoV. α- and β-CoV, all capable of infecting mammals, while γ- and δ-CoV are seen to cause infection in birds.[14]

Study of the incubation period presents many useful information regarding infectious diseases of respective pathogens, including tips for surveillance, control, dynamic monitoring, and modeling. For sake of active monitoring, the potentially exposed persons are required to meet the health authorities and report their health updates. An understanding of the span of vigorous monitoring is required to limit infections which is important for health departments to bring in use all limited resources.[17] Recent available evidence brings into light that approximately it takes 3–7 days for an epidemic to double in size.[18] However, more epidemiological research is needed which allows a starting point for the proceeding investigation of this outbreak and overall impact on society.[19]

In the transmission, young people may serve as asymptomatic or mildly affected individuals, contributing to silent transmission while people with a high rate of geriatric may also show impact and morbidity come mortality rates similar to that of China. Such countries include Japan, Italy, the United States and Australia. Where Australia has an elderly population of about 16% with people aged >65 years while it is 9% when compared to China. It is also important to note that there is an epidemiological similarity between the current outbreak of COVID-19 to that of SARS in 2002–2003. Prospects of limited spread still appear for Italy and Iran while open European Union may lead further transmission across Europe. This situation may also be true for countries sharing borders like Iran and its other neighbors such as Pakistan, Iraq, and Afghanistan.[20] An increased number of cases in China posed a threat to both China and others, as it exported viruses worldwide. While they managed it well with stringent policies and strengthened systems, special efforts are required for other countries, especially one possessing a high ratio of vulnerable populations. Knowledge of unascertained cases has a major contribution to continuing surveillance and interventions opted subsequently.[21]

STRUCTURE OF COVID-19

CoVs are found to be enveloped in non-segmented positive-sense RNA coming from a known family of *Coronaviridae* and

order Nidovirales. They are known for affecting humans and other mammals.[22] In terms of size, it presents a high genome size of approximately 30 kilobases. This is in harmony with other CoVs playing a part in encoding for multiple structural and non-structural proteins. HCoVs usually present a single-stranded RNA viruses consisted of positive sense. Spike (S), Envelope (E), Matrix (M), and Nucleocapsid (N) are the structural proteins [Figure 1] of this virus while non-structural proteins are RNA dependent RNA polymerase (RdRp) (nsp12). Here, RdRp acts as a crucial enzyme in the life cycle of RNA viruses and point of target in anti-viral therapies, such as Hepatitis C Virus, corona virus, and Zika Virus. In CoVs, The active site of RdRp is immensely conserved which depicts two successive aspartate residues that protrude from a beta-turn structure. It makes their surface available across the nucleotide channel where the free nucleotides can pass.[23] The protein envelope spike (S) is crucial for CoV as the S protein allows the receptor binding, mediating the membrane fusion and also deciding factor for host transmission capacity along with the tropism. Usually, the function of the S protein is divided into S1 and S2 domain, where they perform for receptor binding and serve the purpose of cell membrane fusion, respectively. It is suggested from the structure analysis that the receptor binding domain shows its composition as a core surrounded by an external sub domain. An Angiotensin converting enzyme 2 (ACE2) was believed to be a cell receptor for SARS-CoV. Just like SARS-CoV, SARS-CoV-2 also utilizes ACE2 as an entry receptor in the ACE2 expressing cells which also indicated that SARS-CoV-2 might share a similar life cycle with SARS-CoV.[24]

TRANSMISSION AND PATHOGENESIS

20th January 2020, was marked by the National Health Commission of China with a confirmed case of human-to-human transmission of the Wuhan outbreak (COVID-19).[25] The usual routes of transmission of MERS-CoV, SARS-CoV and highly pathogenic influenza were through either direct contact or spread of respiratory droplets.[26] The clinical characteristics presented in pregnant women with COVID-19 pneumonia were

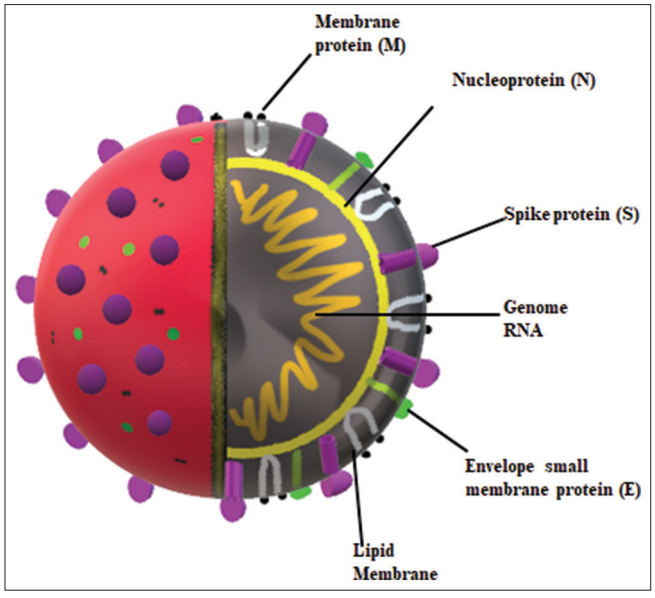

Figure 1: Structure of coronavirus disease-19

replicas of those reported in non-pregnant COVID-19 patients. The findings originating from small groups also presented the fact that no evidence is seen for intrauterine infection caused by vertical transmission among women who were developing COVID-19 pneumonia in late pregnancy.[27,28] Moreover, no evidence has brought to light the surviving capacity of SARS-CoV-2 exterior to the body for prolonged time. Although data achieved from, MERS-COV was presented with sturdiness and a considerable surviving capacity, exterior to body.[4] Thus, it can be concluded that rapid spread of COVID-19 could have originated from indirect spread through fomites, congested public places such as elevators and restrooms.[29]

Wide acceptance prevails in terms of transmission of CoVID-19 in humans and that pathogenesis mainly comes from general interactions. This includes a series of events such as virus attachment, recognition of receptor, protease cleaving followed by the involvement of S-protein (transmembrane spike glycoprotein) membrane's infusion and binding affinity of the host cellular transmembrane serine protease (TMPRSS) with COVID-19.[30] The pathogenic CoVs among human with SARS-CoV and SARS-CoV-2 has ability to bind to their target cells via ACE2. This in turn is expressed by epithelial cells of the intestine, blood vessels, lung and kidney. Expression of ACE2 is prolifically enhanced in patients with type 1 or type 2 diabetes and receiving ACE inhibitors and angiotensin II type-I receptor blockers (ARBs), for treatment purposes. The treatment of hypertension also implies ACE inhibitors and ARBs, which may cause up regulation of ACE2. ACE2 may also experience a rise by use of thiazolidinediones or ibuprofen. All this brings to consideration that the expression of ACE2 is higher in diabetics and also that treatment with ARBs and ACE inhibitors increases ACE2 expression. As a result, the infection with COVID-19 is facilitated with increased expression of ACE2.[31] ACE2 is an enzyme that physiologically counters the activation of Renin-Angiotensin-Aldosterone System (RAAS) which serves as a functional receptor to COVID-19. Data from clinical studies suggest RAAS inhibitors may raise ACE2 expression with rising concerns on safety of Covid-19 patients. However, data remain insufficient in explaining its translation among humans with no effect of study depicting the effects of RAAS inhibitors in Covid-19. Clinical trials are up taken to check for RAAS modulators, including efficacy and safety, also, use of recombinant human ARB losartan and ACE2 in Covid-19. Sudden withdrawal of RAAS inhibitors in high-risk patients, as one with myocardial infarction, may lead to unstable health and adverse outcomes. Until provision of sufficient data, one may use RAAS inhibitors in stable conditions for ones at risk with Covid-19.[32] Further, studies suggested coherence with the fact that a rise in temperature and humidity brings down the transmission of SARS and influenza, indicating that summer and rainy seasons in the northern hemisphere will considerably lessen the transmission of the COVID-19.[33]

Little study and data on MERS-CoV and SARS-CoV is a major setback. Antigen presentation consequently allows stimulation of the body's humoral and cellular immunity, run by the B and T cells. However, the antibody profile against SARS-CoV virus follows the usual pattern of Immunoglobulin M (IgM) and Immunoglobulin G (IgG) production as seen in other viral infections. The antibodies are normally produced after PRRs (pattern recognition receptors) detects PAMPs

(pathogen-associated molecular patterns) which are the microbial structures that serve as ligand for host pattern recognition. However, the major difference where SARS-CoV AND MERS-CoV deviate from this traditional approach is that they induce production of double-membrane vesicles for extensive replication, that don't possess PRRs which helps them camouflage the detection of their dsRNA by the host.[34]

SIGN AND SYMPTOMS

A wide clinical spectrum of SARS-CoV-2 infection has been witnessed worldwide. It has presented with mild respiratory infections to severe upper respiratory tract illness with pneumonia like symptoms or with respiratory failure and even death. While a large population also has been asymptomatic altogether with many hospitalized with pneumonia-like complaints as majorly found in Wuhan.[35] To elaborate, symptoms entail cough, fever, malaise, fatigue, shortness of breath and respiratory distress.[36] Moreover, frequent respiratory complaints have been registered, which has exhibited severe threats in the older and younger population, alike. This has been critical with ones presenting cardiovascular complaints.[37] Symptoms of fever, dry cough seen with COVID-19 including others like shortness of breath share commonality with previously reported SARS in 2003 and also to that of Middle East respiratory syndrome in 2012. However, the point of difference buds off from some added unique features of COVID-19 that includes incidence of diseases such as abdominal discomfort, nausea, diarrhea, and vomiting. These less frequently experienced symptoms are seen in a significant number of people with either a premature inception preceded by the conventional respirational signs.[38] With an experience of previous epidemics, corticosteroids are not recommended. This comes from the established fact that these might exacerbate COVID-19-associated lung injury and could worsen the condition.[39]

DIAGNOSIS

Epidemiological history, clinical manifestations alongside critical data originating from auxiliary examinations (like immune identification technology [Point-of-care Testing (POCT) of IgM/IgG, blood cultures], nucleic acid detection, enzyme-linked immunosorbent assay [ELISA], and computed tomography [CT] scan) serves as the main source for the diagnosis of COVID-19. It is found that the medical signs and symptoms of patients presented with SARS-CoV-2 were extremely varied and uncommon, making auxiliary examinations and epidemiological history a compulsion for prompt an accurate diagnosis of COVID-19.[34] Real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing are two most commonly used nucleic acid detection techniques implied for SARS-CoV-2.[40] It can also not be ignored that application of high-throughput sequencing technology in clinical diagnosis is limited owing to high cost and reliance on its equipment. This leaves with the option of RT-qPCR, commonly utilized with a simple and straightforward method of detection through blood and respiratory secretions.[41]

Many clinicians end up proposing CT scans with necessary auxiliary diagnostic methods to increase the sensitivity with reliable results. While patients presenting a high working hypothesis (clinical suspicion) of SARS-CoV-2 infection however false/negative screening results of RT-qPCR, bring in the need of combined and frequent RT-qPCR investigations alongside CT scan of chest. In particular, high-resolution CT for chest is a must for early diagnosis and evaluation of the severity of disease in SARS-CoV-2 patients.[42] However, with shortcomings established for currently used nucleic acid detection along with CT scans for the diagnosis of COVID-19, some immunological detection kits should be implied by the diagnostic laboratories. It helps target the viral antigens or antibodies in minimal possible time. In current times, ELISA kits and POCT of IgM/IgG have been tested and has establish advanced rate of detection than nucleic acid analysis assays yet no published list of products is available. Upon comparison.

Sensitivity of SARS-CoV S-based IgG ELISA is far less (58.9%) as compare to the results of SARS-CoV N-based IgG ELISA, that is, 94.7%.[43]

TREATMENT AND PREVENTION

The spread of COVID-19 has been rapid so far while scientists are trying day in and day out to come up with effective treatment through suitable discovery of drug or vaccine. At present, no effective treatment option is available as such, only means to boost immunity are adopted. A number of drugs, including ribavirin, interferon, corticosteroids, lopinavir-ritonavir, have been utilized in patients with SARS or MERS. Even still the efficacy of many of these drugs remains unclear.[2] Chloroquine phosphate stands out as one of the old drugs used for treatment of malaria. It has proven efficacy with reasonable safety levels against COVID-19 associated pneumonia as tested in multicenter clinical trials conducted within China.[44] Many antiviral drugs are checked for their ability of inhibiting SARS-CoV-2 replication of SARS-CoV-2 in cell culture. Among these, the drugs which have presented favorable inhibitory effects are chloroquine (CQ) and remdesivir (GS-5734). CQ holds a renowned status of effectiveness in treatment against autoimmune disease and malaria while GS-5734 is another drug which is one of the experimental drugs aimed for the treatment of infection caused by Ebola virus; the other being.[45]

Ribavirin, Remdesivir, and Sofosbuvir may be effectively utilized against the nCoV, presenting a new strain. Furthermore, the derivatives of Group Transfer Polymerization may be catered for specific inhibition of COVID-19.[23] On testing the active form (CHEMBL2016761) of Remdesivir, a perfect dock is revealed from the docking site with an overlapping region of the NTP binding motif, bringing it out as a potential therapeutic agent. However, need of clinical trials still remain for the need of confirmation of the curative effect.[46] Studies have also established the formation of antibodies against the N protein of SARS-CoV. It stands as an immunogenic protein with an immense expression in the infection and is commonly seen among viral infected patients. Besides the effectiveness of these antibodies, they have shown a shorter lifespan in the recovering individuals. Along with specific humoral immunity, responses of CD4+ and CD8+ have been found to be seen with long-lasting protection against COVID-19. The cell immunity is equally important with antibody-mediated immune response, in these infections. Peptides and epitopes

are some of the desired candidates for vaccine development as can be produced easily with little infection potential and relative chemical stability. A number of pathogenic factors and mechanisms are to be considered including above for successful vaccine formation against COVID-19.[47]

The use of serum, convalescent plasma and/or hyperimmune immunoglobulin is also found useful in treating severe acute respiratory infections of viral origin. Many of the activities including plasma donation against SARS-CoV-2, just as SARS-CoV is seen in convalescent patients.[48] Corona viral infection has turned out to be the leading hazard to not only healthcare systems, but also economies, affecting health modalities both directly and indirectly. A number of vaccines reached clinical status with the earliest Phase 1 vaccine trial tested in a synthetic DNA-based candidate. Furthermore, many new compounds plus those licensed for other conditions have been tested *in vitro* for efficacy against 2019-nCoV. Some are being tested in clinical trials against MERS-CoV and SARS-CoV, while others have been listed for clinical trials against 2019-nCoV yet no fruitful combination of individual antiviral has been proven sound for the treatment. Imperial College London published a report with respect to the stance of the UK government towards COVID-19, shifting it from "herd immunity" to more of a "pragmatic approach".[49,50] Hefty measures are implemented to cut down one to one contact hindering COVID-19 chain of transmission, especially in young and old communities.[4] To implement this classical health measures are up taken including social distancing, self-isolation, quarantine and community containment to bring to end the pandemic with underlying these respiratory symptoms.[51]

Post SARS-CoV event in 2003 calling global public health response highlights the immediate need for effective and rapid strategies of infection control. In the case of nCoV is the great potential for nosocomial transmission and risk with immune-compromised patients. Viral transmission is seen at rise due to aerosol-generation from bronchoscopy and intubation. Thus, a need of strict hospital hygiene practices is critical to prevent and control nosocomial outbreaks.[52] As per available data the close proximity between different individuals in mid of December 2019 has been massive reason for person to person transmission. Preventive measures and efforts are to be applied in regions with patients at high risk.[53] It is also rational to put on a protective face mask even especially when heading outside to prevent transmission, be it symptomatic or asymptomatic. Furthermore, the vulnerable populations should wear masks when required. In the meantime, it also is bringing in the need for research on use of masks and future production to meet mass needs.[54]

The WHO recommends the individuals who have been confirmed from laboratory as a COVID-19 patient to quarantine themselves for 14 days from the last exposed date. For implementation of quarantine, a contact person is defined as one who involved in any of the given from 2 days prior to and up to 14 days post onset of symptoms in patient: Exposed face-to-face with a COVID-19 patient within 1 meter of distance and time frame of >15 min, involved in the provision of direct care to the COVID-19 patients without implying protective garments. Residing in close vicinity to a patient infected with COVID-19 patient as in an office or home or public gathering for even the shortest of time is not sound. Moreover, travelling in close proximity is to be avoided as certain distance is mandatory in the pandemic situation. Furthermore, one should regularly disinfect surfaces coming in frequent use like bedside tables, bed frames and other furniture. It can be practiced once or twice everyday using bleach solution which has been diluted 1–99 parts of water. Otherwise 70% ethanol could be used as a substitute for bleach for surfaces that does not complement with use of 1% dilute bleach. It is important to disinfect the lavatories and its sanitary ware, at least once daily by implying domestic disinfectants or bleach. Also clothes, towels and linens should be washed with surfactant and water at 60–90°C (140–194°F) with common laundry detergent, and dry thoroughly. Disposal of waste should also be managed through sanitary landfill or any suitable method opted at the gross level to check unmonitored open areas. The personnel involved in cleaning should use gloves and protective wears when dealing in products soiled with body fluids, and they should perform disinfection and hand wash.[55]

CONCLUSION

COVID-19 is a hot issue in these days and poses a great risk to mankind health and safety. It is highly infectious and spread drastically all across the world. Till date, no treatment is available and production of vaccine is under the process. It is recommended that precautionary measures should be seriously followed to avoid infection, reduce death rates and to flatten the epidemic curve of COVID-19 virus.

CONFLICT OF INTEREST

There is no conflict of interest among the authors.

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ETHICAL CLEARANCE

Not required.

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Knowledge, Attitude and Practices Assessment of the Gout Patients Residing in Lahore, Pakistan

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Knowledge, Attitude and Practices Assessment of the Gout Patients Residing in Lahore, Pakistan

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ABSTRACT

Background: Gout is the most prevailing type of inflammatory arthropathy and its incidence has risen in recent decades. As previously no such research was found through an extensive literature survey, the current study aimed to evaluate gout patients residing in Lahore, Pakistan.

Methods: To conduct this cross-sectional study, n=203 responses were obtained by a simple and objective-oriented questionnaire devised for the collection of data. Dependent variables association was measured by the Pearson Chi-square. A *p*-value ≤0.05 was considered statistically significant.

Results: A total of n=203 responses results had shown that male patients were predominant 127 (62.56%) and most patients were elderly and obese. Respondents were suffering in ignorance for a long time and many of their joints were affected by gout. Outcomes regarding the severity of pain were based on patient experience, including mild (40.39%) moderate (31.52%) and severe (28.07%). In terms of treatment, 101 (49.75%) were on Allopurinol/ febuxostat/ colchicine, 31(15.27%) followed by diet modification. 190 (93.6%) reported that gout treatment puts an extra financial burden on them. Restricted mobility was experienced by 173 (85.2%), 157 (77.3%) patients preferred to visit the rheumatologist for a checkup, and 91 (44.8%) seemed help from the pharmacists.

Conclusion: Gout severely affects both physical and physiological health (*p*=0.001). The overall burden of gout is substantial and may be increasing with time. The risk rises in all gender with age and factors like obesity while adoption of a healthy lifestyle and some modifications can reduce the issue and underlined pain in joints.

Keywords: Gout; Arthritis; Inflammation; Allopurinol; Hyperuricemia.

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INTRODUCTION

Gout is known for a long time as one of the chronic inflammatory conditions of the joints. It is also known well as "men's disease" because of the high rate of incidence amongst males than the females[1]. Gout may also be defined in terms of raising serum uric acid levels, i.e., hyperuricemia with levels as high as 6.8mg/dl. The increase in serum uric acid levels causes the creation of urate crystals that is quickly followed by the formation of renal stones. It is also at times backed with tophi that ultimately lead to gouty arthritis[2]. Acute gout also manifests with a couple of symptoms that included high pain, swelling, and soreness found all around the joints. The patient might also experience an asymptomatic period between the gout attacks that are designated as inter-critical gout. Another term referred to as "podagra" is typically reserved for acute gout that aims at explaining a condition where the very first metatarsophalangeal joints are affected by the urate crystals. Also, acute gout symptoms come with visible signs of the flares that are exhibited distinctly[2]. There are presented clearly as a majorly inflamed region that causes discomforting pain in the patient which lasts for about 5-10 days. However, the asymptomatic hyperuricemia continues for quite some number of years, even when the flares may dissolve during this duration[1].

On the other hand, the crystals may exhibit propagation along with inflammation and intense pain that eventually enters a phase of chronic gout and tophi will appear. Such tophi can be found at multiple sites such as bones, cutaneous tissues, and articular spaces[3,4]. The routine activities of a gout patient might be affected by the presence of pain and moving a complete challenge with even partial or permanent disability. This in turn severely affects the patient's quality of life. Gout also presents a major association with comorbidities which accounts for stroke, diabetes, myocardial infarction and hypertension, and a few others to the list[5]. From the epidemiological data, it is found that an incidence and prevalence of gout have an overall seen accelerating increase in the past few years[6]. Still enough data, especially in the emerging countries for gout is not available, thus demonstrating a need for more research regarding the disease to dig out incidence about a geographical variation with other related risk factors. Previous studies have demonstrated that patients typically receive little education on lifestyle modification and medication adherence[7,8].

This study investigated gout with the intent of evaluating the understanding of patients suffering from gout within the region of Lahore, Pakistan as lately, no such research was found through an extensive literature survey. The research hypothesized that considerable numbers of patients are unaware of the basic understanding of the disease and the importance of medication adherence and lifestyle modifications. A better knowledge of such issues would help tackle the barrier and ensure a better quality of life. The results of current research could be informative for the clinicians and shall serve as a guideline.

METHODS

The study was descriptive cross-sectional research on sample size (n=203). The data was collected from September 2020 to March 2021. The data collection questionnaire was simple, easy to understand, and representative of the research objective. All the patients were briefed about the purpose of the study before the collection of the data. Ethical approval was obtained on December 10th, 2019 from the Institutional Review Board (IRB) of the University of the Central Punjab Lahore, Pakistan (Ref: UCP/FOP/368/1219).

In inclusion criteria, gout patients (serum uric acid more than 6mg/dl) living in Lahore were the subjects of the study. Only those participants were considered that were willing to contribute. In exclusion criteria, patients other than Lahore were not considered for current research. Also, patients unwilling to participate were excluded.

A simple and objective-oriented questionnaire was devised for the collection of information about subjects. The questionnaire was divided into different sections to collect comprehensive data regarding gout from the patients. The credibility of the questionnaire was tested by Cronbach's Alpha which is found to be 0.72 revealing that the data collection form is reliable. The data collection tool was prepared after the study of previous literature [9,10] and divided into the following sections: 1. It consisted of patient consent and willingness to participate in this research. After approval from patients, they were further directed to fill out the questionnaire. 2. This section was added to collect the basic demographics information i.e., gender, age and marital status. 3. This section was devised to have clinical information from patients suffering from gout. This included: patient weight, uric acid level, gout previous attacks, number of joints affected, management, and treatment. The uric acid level was taken from the patient's diagnostic laboratory report to ensure that patient was suffering from gout. 4. This section was made to assess the basic knowledge, perception, and practices about gout.

The data were analyzed using the software SPSS (Statistical Package for the Social Sciences IBM, version. 22). Descriptive statistical analysis was performed to determine the frequencies, percentages, and standard deviations. Dependent

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variables association/correlation was measured by the Pearson Chi-square. A *p-value* ≤0.05 was considered statistically significant.

RESULTS

A total of 203 responses were obtained. The results of the undertaken study showed that male patients were predominant 12a7 (62.56%) as compared to females76 (37.44%) as shown in Figure 1 and all patients were above 30 years (Table 1).

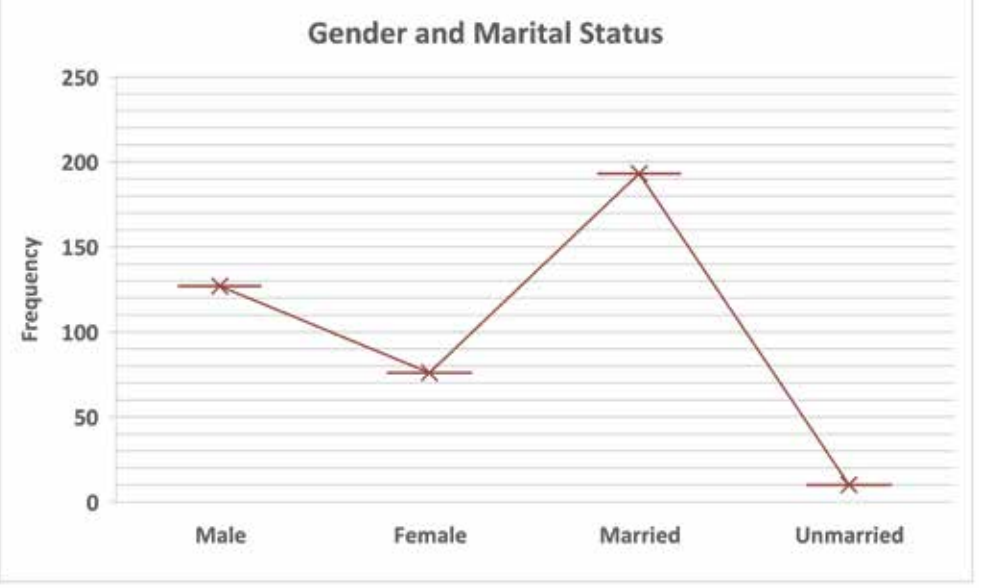

Figure 1: Gender and marital status of the participants.

Table 1: Descriptive statistics of the demographic, anthropometric and general information of the patients.

Parameters								
Age n (%)								
31-35	**36-40**	**41-45**	**46-50**	**51-55**	**56-60**	**61-65**	**66-70**	**71-75**
31 (15.27)	29 (14.29)	35 (17.24)	22 (10.84)	25 (12.32)	32 (15.76)	16 (7.88)	11 (5.42)	2 (0.99)

Weight (Kg) n (%)									
61-65	**66-70**	**71-75**	**76-80**	**81-85**	**86-90**	**91-95**	**96-100**	**101-105**	**106-110**	**110-115**
11 (5.42)	25 (12.32)	22 (10.84)	38 (18.72)	29 (14.29)	39 (19.21)	19 (9.36)	16 (7.88)	3 (1.48)	0	1 (0.49)

Uric acid level (mg/dl) n (%)		
7.0-8.0	**8.0-9.0**	**9.0-10.0**
121 (59.61)	72 (35.47)	10 (4.93)

Gout diagnosed (years) n (%)							
<1	**1 -2**	**2 -3**	**3 -4**	**4 -5**	**5 -6**	**6 -7**	**>7**
3 (1.48)	22 (10.84)	44 (21.67)	42 (20.69)	41 (20.2)	35 (17.24)	10 (4.93)	6 (2.96)

Number of gout attacks in the past years n (%)					
2 to 4		**5 to 8**		**9 to 12**	
52 (25.62)		113 (55.67)		38 (18.72)	
No of joints affected due to gout n (%)					
3 joints	**4 joints**	**5 joints**	**6 joints**	**7 joints**	**8 joints**
20 (9.85)	42 (20.68)	30 (14.77)	41 (20.19)	20 (9.85)	50 (24.63)
Severity of pain n (%)					
Mild		**Moderate**		**Severe**	
82 (40.39)		64 (31.52)		57 (28.07)	
Current gout treatment n (%)					
Allopurinol/ febuxostat/ colchicine/NSAIDS		**Diet modification or other natural treatment**		**Both**	
101 (49.75)		31 (15.27)		71 (34.97)	

Most patients fall between 40 to 45 age groups followed by 46 to 50. Information regarding patients' weight in table 1 showed that all patients weighed were more than 60 kg. Most of the population weighs 86 kg to 90 kg.

In addition to this, clinical information obtained from the gout patients is also summarized in Table 1. All patients who presented high uric acid levels were raised and the maximum range was found between 9mg/dl to 10mg/dl. A positive correlation was found between the risk of developing hyperuricemia and obesity as weight is a dependent factor. History of all patients since diagnosis was evaluated to check chronicity of the disease and it was found to be as 2 year-3 years (21.67%)>3 year-4 years (20.69%)>4 year-5 years (20.2%)>5 year-6 years (17.24%)>1 year-2 year (10.84%)>6 year-7year (4.93%)> more than 7 years (2.96%)> Less than 1 year (1.48%). The results have revealed that most of the respondents were suffering from gout for a long time. Patients were also assessed in terms of the number of their joints affected by gout. Most of the patients 50 (24.63%) affected the number of joints was eight and on opposite extreme 20 (9.85%) minimum of three joints was affected. Outcomes regarding the severity of pain based on patient experience are mild (40.39%)>moderate (31.52%)>severe (28.07%). Related to treatment 101 (49.75%) were on Allopurinol/ febuxostat/ colchicine, 31(15.27%) followed diet modification or other natural treatment 71 (34.97%).

Outcomes of knowledge, attitude, and practices of patients towards gout were gathered and plotted in Table 2. All patients confirmed that they knew about their disease. While 185 (91.1%) patients had no previous family history of gout with 18 (8.9%) patients having a family history. However, a positive correlation was demonstrated between family history and developing hyperuricemia. Twenty-three patients (11.3%) showed the habit of smoking. A negative correlation is found between the serum uric acid level and smoking habit. Patients (72.4%) knew that gout is caused by higher uric acid levels as compared to the 56 (27.6%) who lacked any information on the subject. Only 129 (63.5%) were familiar with signs and symptoms of gout and reported them, such as inflammation, pain, and swelling of the joints while 174 (36.5%) patients were failed to define their disease presentation. Patients (100%) agreed that a healthy lifestyle can reduce the risk of gout. Herbal medications (12.3%) were used for the treatment of gout while 178 (87.7%) did not. Patients (94.1%) claimed that gout affects their daily routine and 190 (93.6%) reported that gout treatment put an extra financial burden on them. All patients claimed that gout has affected their mental health. Restricted mobility was also experienced by 173 (85.2%) while 30 (14.8%) did not experience it yet. Patients (77.3%) preferred to visit the rheumatologist for treatment and their routine checkup while 46 (22.7%) used to visit primary health care providers or homeopathic doctors. Thus, patients (44.8%) seek help from the pharmacist for the counseling or management of disease as compared to 112 (55.2%).

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Table 2: Knowledge, attitude and practices assessment of the patients.

Perspectives	Frequency (n) (%)		Mean±SD	*p*- Value
	Positive	Negative		
Smokers	23 (11.3)	180 (88.7)	0.11±0.32	0.005
The patient was similar with the term gout	203 (100)	0	1± 0.00	.000
Family history of the gout	18 (8.9)	185 (91.1)	0.09±0.29	0.55
Do you know that gout is caused by a high uric acid level in the blood?	147 (72.4)	56 (27.6)	0.72±0.45	.000
Do you aware of the sign and symptoms of the disease?	129 (63.5)	174 (36.5)	0.64±0.48	.000
Do you think a healthy lifestyle can reduce the risk of gout?	203 (100)	0	1.00±0.00	0.004
Have you ever used herbal medications for the treatment of gout?	25 (12.3)	178 (87.7)	0.04±0.21	0.696
Gout affects your daily routine	191 (94.1)	12 (5.9)	0.94±0.24	.000
Treatment of gout put an extra financial burden	190 (93.6)	13 (6.4)	0.06±0.25	0.416
Do you feel depressed due to chronic pain associated with gout?	203 (100)	0	1.00±0.00	0..03
Gout causes a restriction in your mobility	173 (85.2)	30 (14.8)	0.01±0.28	0.001
Gout treated by Rheumatologist (yes); others (No)	157 (77.3)	46 (22.7)	0.77±0.42	.000
Seek help from the pharmacist for the management of gout	91 (44.8)	112 (55.2)	0.01±0.32	.000

**All titles p-value was found to be <0.05 which showed the statistical significance of the data.*

DISCUSSION

Gout is one of the oldest and most prevalent forms of inflammatory arthritis. The incidence of this disease has been rising over the past decades, suggesting an alarming public health concern. Yet the incidence of the disease is found to be uneven across the globe with most cases in the Pacific regions[9]. A part is played by the genetic factors in the development of gout while some ethnic groups are prone to gout in comparison to any other. This together gives a rising rate of mortality and puts down the life expectancy rate[10]. The outcomes of this research revealed that men are more affected than females. Men are at four times higher risk as compared to women. Females enjoy this leverage due to the presence of the estradiol that antagonist the synthesis of urate crystal[11]. The thirties are described as the minimum age when gout was first reported and most of the patients. While most patients were found in the range of 41 years to 45 years which indicates now disease appears at an early age. Gout mostly occurs at age 65 plus and one of the main reasons for gout appearance at an early age is obesity[12].

Most of the patients were found to be obese with raised levels of serum uric acid. This study showed a positive correlation between weight and developing hyperuricemia. Higher obesity and weight gain were found as strong risk factors for gout in men, while weight loss is protective[13,14]. Only a small fraction of the patients 3 (1.48%) have a gout diagnosis history of less than 1 year and remaining all the patients (98.52%) reported that they were suffering from gout for last many years. This explains the chronicity of the disease. In this research, the range of affected number of joints by gout is 3 to 8 and experiences severe pain. Gout is a chronic disease with several stages. Over several years the duration and patients with untreated gout may evolve from monoarticular or oligoarticular acute gout attacks to more frequent and recurrent polyarticular attacks, and chronic tophaceous gout may ensue[15]. Concerning the treatment, many patients were using one or a combination of drugs which included allopurinol, febuxostat, colchicine and non-steroidal anti-inflammatory drugs (NSAIDs). Evolution in the evidence base used for allopurinol, colchicine, and oral glucocorticosteroids administration has been validated, improved and found to be a cost-effective treatment strategy for most patients[16,17].

Few of the patients only relied on intake herbal medications and dietary modifications along with a reasonable number of patients with allopathic treatment followed with change lifestyle and diet modifications. A controlled diet with fractional or full removal of risk factors along with a support of a healthy lifestyle promises prevention[18]. Herbal medications are chosen in clinical practice to enhance uric acid removal which can be useful for the cure and management of gout but more research is required to ensure the efficacy of herbal treatment[19-21].

A small number of the patients were found to be smokers. No correlation was found between smoking and the risk of developing hyperuricemia. Earlier studies showed that smoking is not associated with developing gout, but the results remain debatable and further studies are still needed to endorse outcomes[22]. Few patients have claimed that they have a family history of hyperuricemia and a positive correlation is existing between family history and developing hyperuricemia. Major advances have been made in understanding the link between inherited susceptibility to gout and altered renal urate disposition[16].

Results showed that the patients agreed that gout affects their daily routine activities, disease put an extra burden on them, also reported that restriction in mobility makes them dependent on others and the mental health of all the patients is badly affected. Acute pain, subcutaneous tophi, and persistence of low-grade inflammation for a longer time cause deformation of joints, restricted mobility, and permanent disability that negatively influence the patient's QoL. Self-management of gout is quite complex. To effectively manage gout, patients should be aware of the influence of medication, daily routine and diet on their current medical condition. The deficit in patient education may result in medication non-adherence and poor quality of life[23-25]. Most of the patients preferred to go to rheumatologists instead of primary health care providers for their routine checkups and seek help from the pharmacist for better management of the disease[24].

Besides the treatment of bone-related disorders, rheumatologists are increasingly willing to discuss areas that are not directly related to drug treatment of joint diseases, such as quality of life and education of patients[26,27]. Enhanced pharmacy services have been identified as a mechanism to address medicines and drug-related problems. In the management of gout patients, the role of pharmacists in primary health care should be elaborated especially in the area of the current provision of education to people living with gout and in monitoring medication adherence in patients[28-30].

CONCLUSION

Gout is seen to be a prevalent form of inflammatory arthropathy and predominately males are affected as compared to females. The risk rises in all gender with age and obesity while adoption of a healthy lifestyle and some modifications can reduce the issue like pain in the joints, swelling, and movement disability. Better diagnosis, timely treatment, and integration of pharmaceutical care can better the patient's quality of life, overall bringing down the rate of mortality and morbidity.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

Ethics clearance (Ref: UCP/FOP/368/1219) was obtained from the Institutional Review Board (IRB) of the University of the Central Punjab Lahore, Pakistan.

PATIENT CONSENT

The data was collected after the consent of the patients.

AUTHORS' CONTRIBUTION

KA has designed the study. MA, MQ, AS, ST and RK collected the data. KA, SA, AM and FA have performed the statistical analysis and interpretations. KA, SA, AY and RK wrote the manuscript. MA, MQ, AS, ST and FA have edited the final document. All authors have read equally contributed and approved the final version of the submission.

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A Cross-Sectional Analysis of Knowledge, Beliefs and Practices Regarding Traditional Medicine Use among Pharmacy Students of Different Private and Government Universities of Lahore...

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Original Article

A Cross-Sectional Analysis of Knowledge, Beliefs and Practices Regarding Traditional Medicine Use among Pharmacy Students of Different Private and Government Universities of Lahore, Pakistan

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Abstract

Background: Students' understanding regarding traditional medicine is a part of pharmacy curriculum. In Pakistan, be it students or healthcare professionals, little is known about the general importance of traditional medicine. ***Objectives:*** The aim of this study is to assess the students, enrolled in Doctor of Pharmacy Program, regarding their beliefs, knowledge and practices for use of medicinal plants. ***Methodology*:** The questionnaires were distributed among the Doctor of Pharmacy (Pharm-D) students. The data was analyzed using SPSS software (IBM, version. 22) and different statistical tests were applied, including descriptive analysis, t-test and Pearson chi squared test. ***Results:*** Total 254 responses were obtained in the study. While the outcome indicates that the majority of the participants (n=237: 93.3%) acknowledge the usefulness of traditional medicine. 151 (59.4%) participants believed that the traditional medicine is safe but 103 (40.6%) concerned about the side effects of herbal remedies. 187 (73.6%) reported the use of some type of medicinal plants in their life. Easy availability of traditional medicine was reported by 186 (73.2%) participants and 176 (69.3%) claimed the medicinal plants as inexpensive alternatives. The physician was kept informed about the concomitant administration of herbal with allopathic medicine in only 43 (16.9%). Stomach pain (14.17%) was most common sickness for which participants utilized traditional treatment, followed by cough (12.6%) and flu (10.63%). Mint (10.24%) was found to be the most commonly used medicinal plant, followed by aloe (9.84%) and ginger (7.48%). ***Conclusion:*** Detailed studies are still required to evaluate not only the students but also health care professionals about their understanding, prescribing practice and dealing with patients already using medicinal plants. This will help in improved management of the disorders and may lead further advancement in the field of natural product research and cutting off ill effects of allopathic treatment.

Keywords: Medicinal plants; Traditional medicine; Knowledge; Pharmacy; Students

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Introduction

Medicinal plants are widely used around the globe for the treatment of various acute and chronic ailments[1]. Modern healthcare facilities are not available everywhere in low- and middle- income countries. More than 70% of the Asian population of developing countries are using the medicinal plants for the treatment of the various diseases[2, 3]. According to a study, approximately 57% of the Pakistan population relies on the traditional medicine for the treatment

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of multiple disorders[4]. However, less consideration is paid on education of the traditional medicine and medicinal plants in Pakistan[5]. The main reason of major population using the medicinal plants is based on the belief and perception of treating different ailments in an economical way while avoiding side effects[6]. Many low- and middle- income countries are striving to inculcate the traditional medicine system into their national health system and programs. Asia seems to be more progressive in this venture of instilling the traditional health system to national health policy and China achieved this agenda successfully[3]. The assessment of the data, questions evaluation, testing of different hypothesis and various anthropological aspects regarding traditional medicine would be proved beneficial to reach a definite conclusion and foster the bond between natural, medical and social sciences[1]. Around the globe, many researchers are actively doing research on medicinal plants and documented the available information regarding traditional medicine and its uses[7]. Beliefs, knowledge and training of pharmacy students about the traditional medicine and medicinal plants currently gain a substantial importance as in depth knowledge is required for safe and effective use of traditional medicine[8]. Hence, it is the need of hour to evaluate pharmacy students about familiarity, attitude and viewpoint regarding traditional health system and cure through medicinal plants[9, 10]. The aim of the current study is to assess the knowledge, beliefs and practices of pharmacy students both private and government sectors about the traditional medicine. The outcomes of this would be helpful in devising the pharmacy curriculum, national education policy, better treatment outcomes and development in drug design and discovery.

Material and methods

Study Design and Settings

For the current study, a descriptive cross-sectional research method was chosen. The data were collected from June 2019 to September 2019. Our respondents were pharmacy students from three different universities of Lahore, Pakistan. Out of three universities, two were of private sectors (Uni 1 and Uni 2) and one was from the government sector (Uni 3).

Data Collection Instrument

A simple and objective oriented data collection questionnaire was devised for the collection of data. The questionnaire was divided into the different sections in order to collect comprehensive information regarding traditional medicine. The sample collection tool was divided into the following sections:

Section 1

This section was about the basic demographics i.e. age, gender, marital status, area of residence and name of university currently enrolled.

Section 2

This section was devised to assess the basic knowledge, perception, beliefs and practices about the traditional medicine. It also included the common medicinal plants use for the cure of disease and side effects (if any experienced).

Participants

Data were collected from the pharmacy students. The inclusion and exclusion criteria for the participants is mentioned below

Inclusion criteria

All the students who were enrolled in the Doctor of Pharmacy (Pharm-D) program of both private and government universities of Lahore region were the subjects of this study. Only those participants were considered for the current research that were willing to contribute.

Exclusion criteria

All the students enrolled in other than Doctor of Pharmacy (Pharm-D) program and studying outside Lahore were excluded from this study. Those students who were not willing to participate were also not considered.

Data Collection

Total 500 copies were distributed and 254 responses were obtained. To have reliable results, sample size of 218 or more was required based on the desired accuracy with a confidence level of 95%. Before collection of the data, all participants were briefed about the study. Written consent was taken from the subjects for this research. Sufficient time was given to the participants for their response and they were asked to submit filled forms to the faculty office of the Pharmaceutical Chemistry Department, Superior University Lahore, Pakistan till September 30, 2019. After the due date, the collected sampling instruments were segregated into the private and government universities respondents for the purpose of comparative analysis.

Data Analysis

The data were analyzed using software SPSS (Statistical Package for the Social Sciences IBM, version. 22). Descriptive statistical analysis and t-test were used for the results calculations. The dependent variables association was measured by the Pearson Chi-square. An alpha value ≤0.05 was considered to be statistically significant.

Ethical Clearance

This is a cross-sectional survey study and does not need ethical approval. This research has been conducted after obtaining suitable informed consent from the volunteers. After approval from the participants, data were collected and confidentiality of the information was secured.

Results

Table 1 illustrates the basic demographic information of the respondents. 254 students participated in the study, aged between 15 to 35 years with maximum participants (52%) having ages between 21 to 25 years. Among the total 254, a vast majority of the participants (95.28%) were unmarried. 28.7% (73) of the total participants were males and the rest 70.5% (179) were female.

Table 1. Basic demographic information

Parameter	Frequency	Percentage (%)
Age		
15-20	118	46.5
21-25	132	52
26-30	2	0.8
31-35	2	0.8
Gender		
Male	73	28.7
Female	179	70.5
Marital status		
Married	12	4.724
Unmarried	242	95.28
Residence		
Urban	152	59.84
Rural	102	40.16

Homes (50%) were the major source of information regarding the use of medicinal plants, followed by relatives (26%) (Table 2).

Table 2. Major source of information regarding the use of medicinal plants

From where you heard about herbal medicine or treatment?	Frequency (%)
Home	127 (50%)
Neighbors	17 (6.7%)
Relatives	66 (26%)
Others	44 (17.3%)

Participants' responses to various questions regarding traditional medicine have shown in Table 3 and Figure 1. Most of the participants (n=237: 93.3%) admitted the worth of traditional medicine in disease treatment. 151 (59.4%) participants believed that the medicinal plants are harmless but 103 (40.6%) denied it and were concerned about the side effects linked with the use of traditional medicine. Out of 254, 187 (73.6%) reported the use of some type of medicinal plants in their life. Easy accessibility of traditional medicine was reported by 186 (73.2%) participants and 176 (69.3%) claimed the traditional medicine as low-priced alternative. More than half of the participants (66.5%) had taken traditional medicine with allopathic medicine. The physician was informed about the concomitant administration of traditional and allopathic medicine in only 43 (16.9%) cases as compared to the 211 (83.1%) uninformed cases. The use of medicinal plants gave satisfactory results according to 187 (73.6%) participants whereas 67 (26.4%) participants were not satisfied with traditional medicine. A comparative analysis among universities was performed (Figure 2) and a minor difference is noticed in responses that has taken from the participants.

Table 3. Respondents' assessment about the traditional medicine

Statement	Traditional Medicine related knowledge(n=254)		
	Yes	No	p value
Have you ever used traditional medicines (home remedies/ Tibb e Nabvi/ Hikmat)?	187 (73.6%)	67 (26.4%)	0.496
Do you think traditional medicines are useful in treating diseases?	237 (93.3%)	17 (6.7%)	0.85
Do you know traditional medicine have side effects?	103 (40.6%)	151 (59.4%)	0.506
Traditional medicines are easy to obtain or assessable?	186 (73.2%)	68 (26.8%)	0.726
Do you think traditional medicines are inexpensive?	176 (69.3%)	78 (30.75%)	0.318

Statement	Traditional Medicine related knowledge(n=254)		
Have you ever taken traditional medicine with allopathic medicine?	85 (33.5%)	169 (66.5%)	0.299
If you have taken traditional medicine with allopathic medicine then have you informed your physician?	43 (16.9%)	211 (83.1%)	0.216
Did you experience any adverse drug reaction when taken traditional medicine with allopathic medicine?	21 (8.3%)	233(91.7%)	0.109
Do you think traditional medicine treatment gives satisfactory results?	187 (73.6%)	67 (26.4%)	0.547
Do you know the brand name of any traditional medicine?	119 (46.9%)	135 (53.1%)	0.017

When the respondents were asked about the medical condition for which they used traditional medicines, varieties of diseases were reported as shown in Table 4 and data were also illustrated in Figures 3 and 4. Stomach pain (14.17%) was found to be the most common ailment for which participants seek traditional treatment, followed by cough (12.6%) and flu (10.63%). Other common diseases for which patients chose traditional treatment include sore throat, acne (5.51%), constipation (5.51%), sunburn (4.33%), diarrhea (3.94%), obesity (3.94) and tooth ache (3.15%).

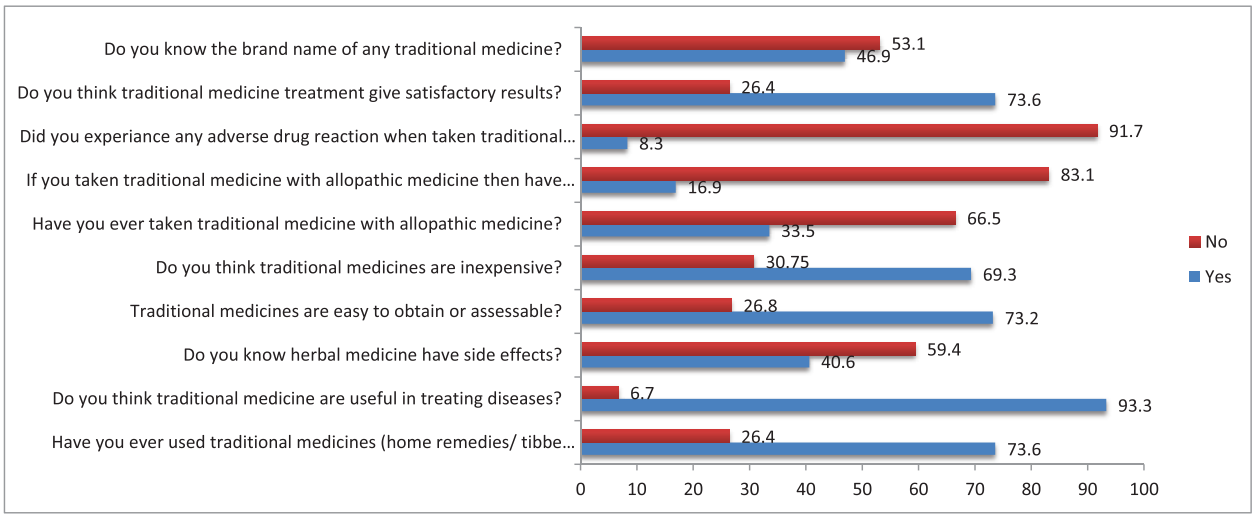

Figure 1. Respondents' assessment about the traditional medicine

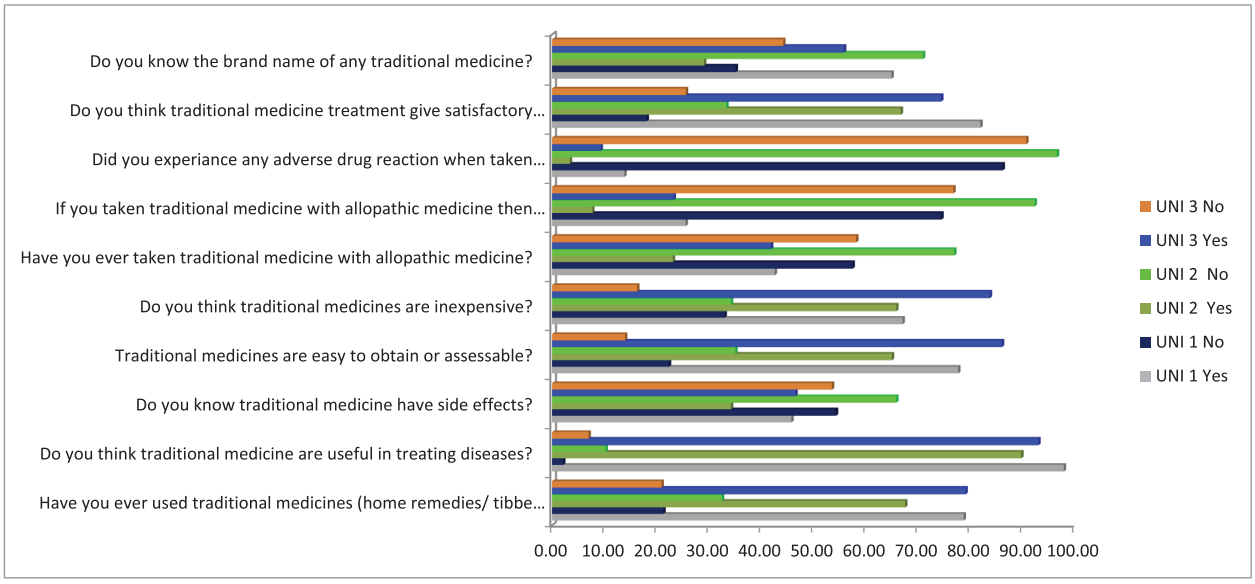

Figure 2. Responses among universities about the traditional medicine

Table 4. Respondents' assessment about the medical condition for which they used traditional medicine

Disease	Total	Percentage (%)
Acne	14	5.51
Arthritis	3	1.18
Asthma	2	0.79
Bronchitis	4	1.57
Constipation	14	5.51
Cough	32	12.60
Dandruff	3	1.18
Diabetes	4	1.57
Diarrhea	10	3.94
Face wrinkles	1	0.39
Fever	4	1.57
Flu	27	10.63
Gum Swelling	1	0.39
Hair fall	5	1.97
Hypertension	6	2.36
Itching	3	1.18
Jaundice	5	1.97
Kidney pain	1	0.39
Liver infection	2	0.79
Motion sickness	2	0.79
Mouth ulcers	2	0.79
Muscle pain	3	1.18
Nervous disorder	4	1.57
Obesity	10	3.94
Pollen allergy	2	0.79
Sore throat	16	6.30
Stomach pain	36	14.17
Sunburn	11	4.33
Toothache	8	3.15
Typhoid	1	0.39
Weakness	1	0.39

Table 5. Respondents' assessment about medicinal plants used for the treatment of diseases

Medicinal plants	Response n=254	Percentage (%)
Ajwain	13.00	5.12
Aloe	25.00	9.84
Black seed oil	3.00	1.18
Cardamum	4.00	1.57
Cascara	3.00	1.18
Cinnamon	7.00	2.76
Clove	12.00	4.72
Coconut oil	1.00	0.39
Euclyptus	8.00	3.15
Fennel	15.00	5.91
Garlic	13.00	5.12
Ginger	19.00	7.48
Glycerrihza	11.00	4.33
Gram flour	1.00	0.39
Green chilli	2.00	0.79
Green tea	9.00	3.54
Honey	7.00	2.76
Ipecac	3.00	1.18
Isapaghol	10.00	3.94
Joshanda	17.00	6.69
Lemon grass	10.00	3.94
Mint	26.00	10.24
Neem	4.00	1.57
Nux vomica	2.00	0.79
Olive oil	10.00	3.94
Safron	1.00	0.39
Sandal	6.00	2.36
Senna leaves	1.00	0.39
Sahtoot	13.00	5.12
Sohanjana	2.00	0.79
Turmeric	6.00	2.36
Valarian roots	4.00	1.57

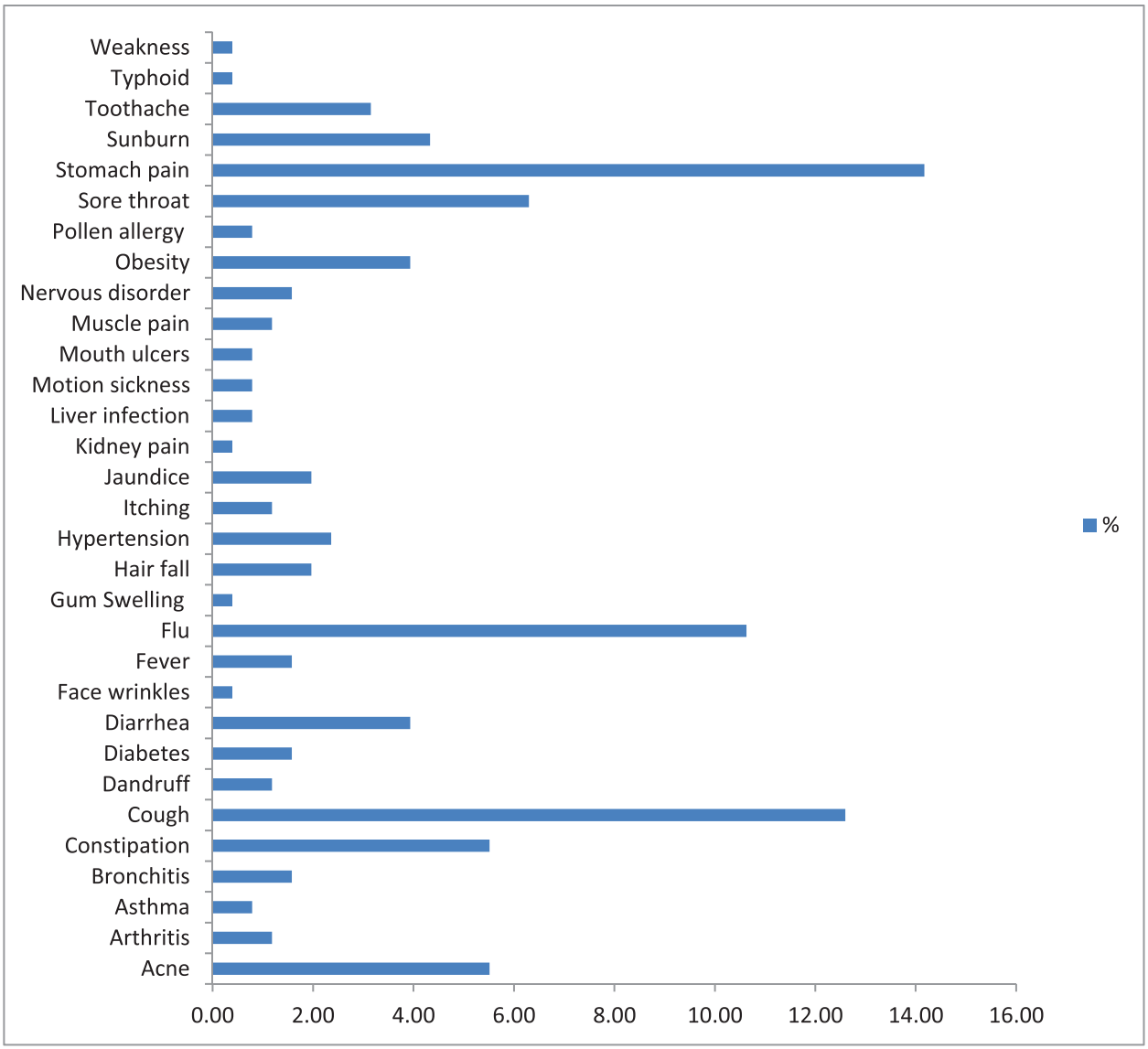

Figure 3. Respondents' assessment about the medical condition for which they used traditional medicine

Approximately half (46.9%) of the participants had the knowledge about different medicinal plants and were able to quote some names (Table 5, Figures 5 and 6). Mint (10.24%) was found to be the most commonly used herb, followed by aloe (9.84%) and ginger (7.48%). Other commonly used medicinal plants quoted by the participants include joshanda (6.69%), fennel (5.91%), ajwain (5.12%), garlic (5.12%) and shahtoot (5.12%).

Discussion

In the recent past, traditional medicine has taken a boom which is comparable to its practice in the ancient centuries. A great proportion i.e. 80% of population has shown inclination to use medicinal plants, specifically as a home remedy to treat various disorders[3, 8]. However, the use finds its roots in culture and societal grounds as seen with Asian, in particular Pakistan[5, 9]. The data from the present study demonstrates that pharmacy students have a sound knowledge of traditional medicine, reflecting an understanding of benefits and/or side effects, consumption of medicinal plants in various diseased conditions and their names along with affordability and accessibility[10-13].

Results revealed that most of the well informed students took home and relatives as a primary source of information. Impact and influence of the family remain vital amongst the Asian population for use of traditional medicine and has been quoted in the past[14, 15]. On the contrary, many other sources have been playing a part in informing students and some of them are cited in the literature included social media, online websites and television advertisements[16, 17]. Amongst

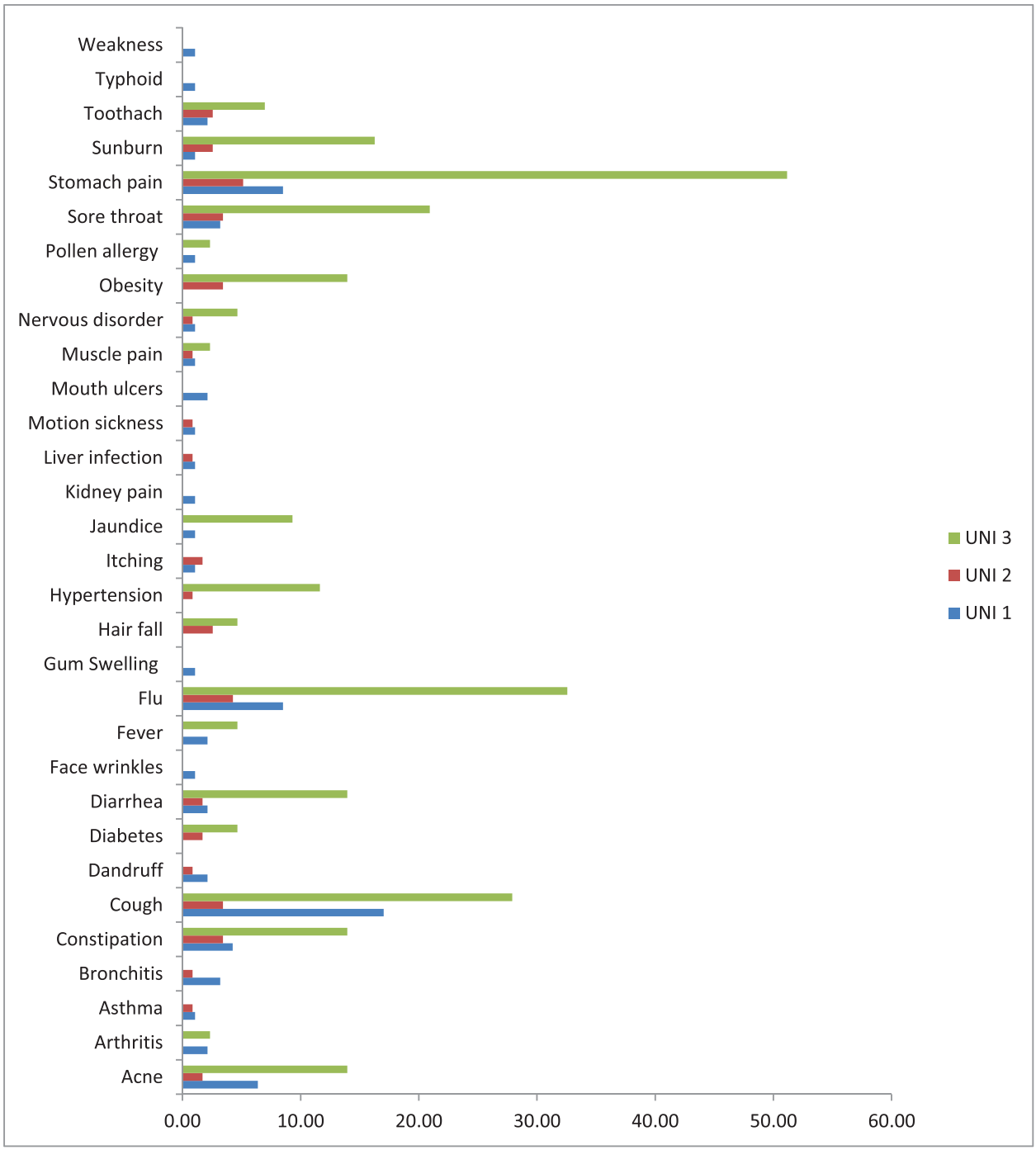

Figure 4. Responses among different universities about the medical condition for which respondents used traditional medicine

the students accustomed to the use of traditional medicine, a great deal agreed with its usefulness in the treatment and cure of diseases. A total of 93.3% (n=237) approved its benefits that subsequently attained in a diseased condition and the literature supports this through traditional medicine excessive use over various regions all around the globe[18-20]. Pupils were questioned for their perceptions about the safety and any concerns pertaining to side effects of the traditional medicine. The result was interesting as slightly more than half of the total count i.e., 151 (59.4%) participants considered traditional medicine as a safe mode of treatment. On the other hand, 103 (40.3%) respondents refuted on traditional medicine safety point and showing concern for associated side effects. The cost effectiveness and appreciable therapeutic effects are nothing new for traditional medicine and extensively discussed in previous

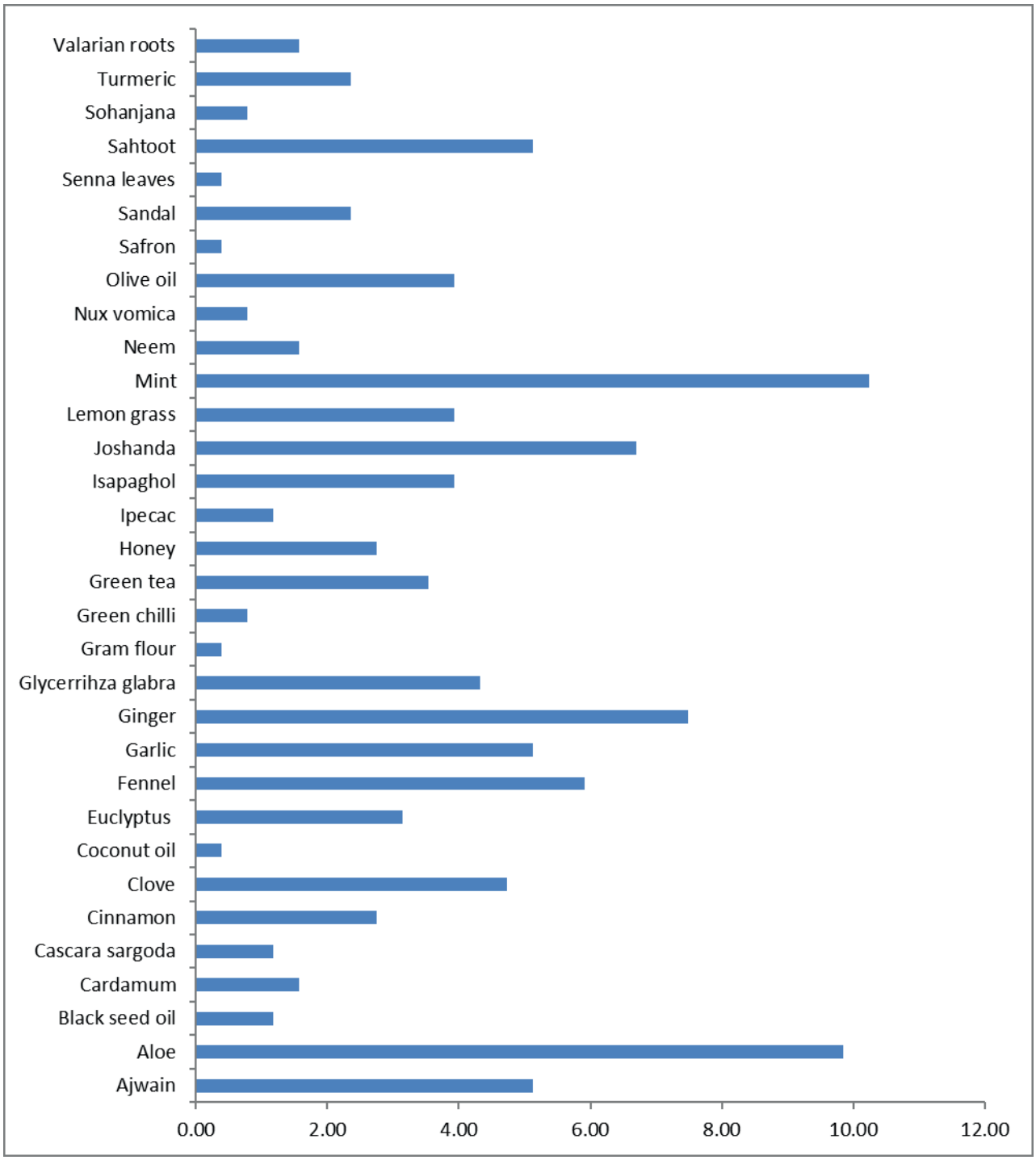

Figure 5. Respondents' assessment about medicinal plants used for the treatment of diseases

studies. Further, an insignificant difference among responses of all universities was observed through comparative analysis that demonstrates a uniform curriculum has followed to teach pharmacy students in all institutions [21, 22].

When participants were inquired about their knowledge of medicinal plants, almost half of the subjects were well familiar with the names of medicinal plants and their applications in treating various disorders. A total of 187 that constitutes the 73.65% of sample size reported in affirmation, later quoting names of some common medicinal plants. Many of the medicinal plants originated from household use such as mint found as highly used herbs, followed by aloe[23] and ginger. Other commonly used medicinal plants quoted by the participants included fennel, garlic, shahtoot and ajwain[24-26].

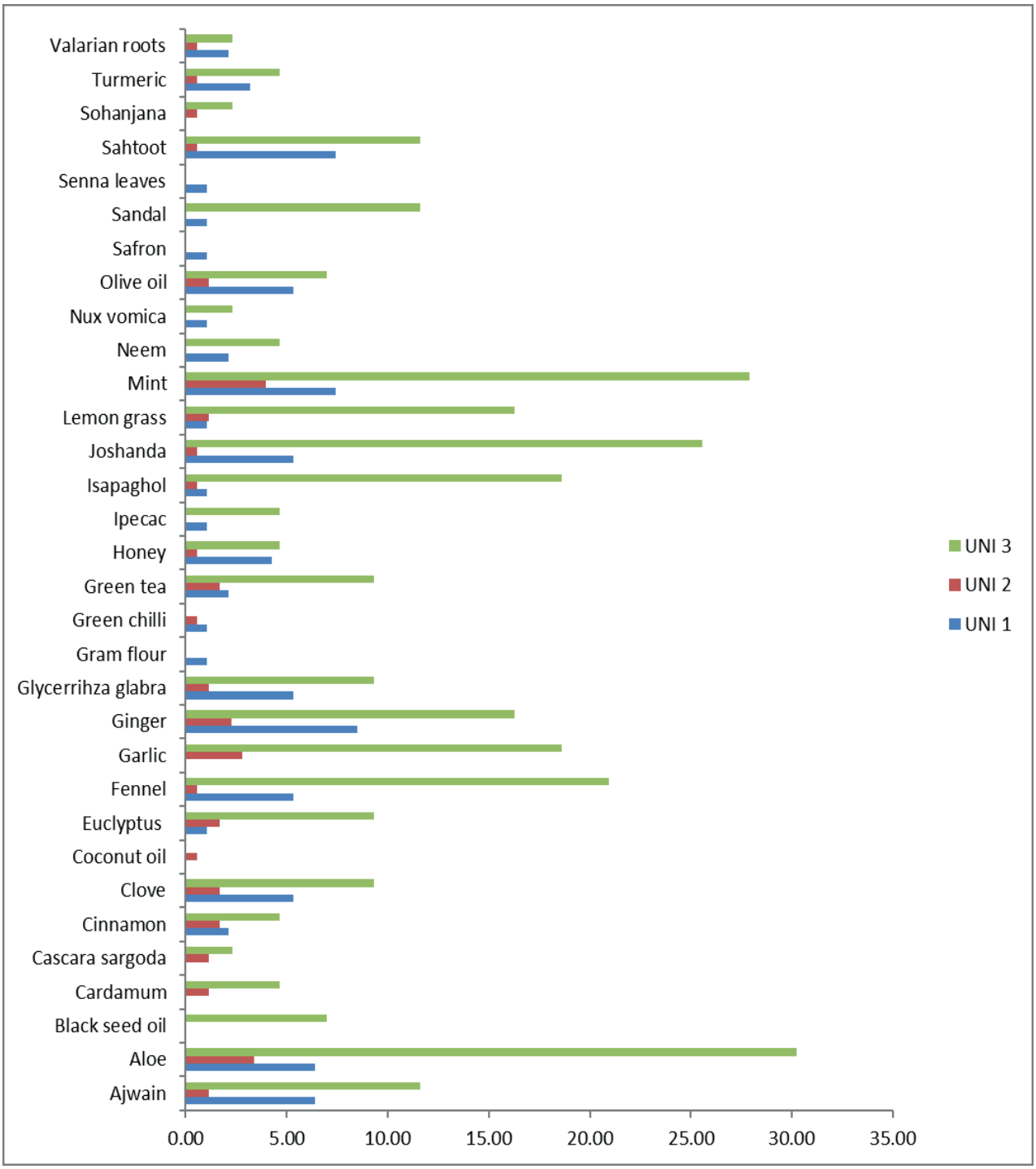

Figure 6. Responses among universities about commonly use medicinal plants

While analyzing the use and knowledge of medicinal plants, an interesting parameter of availability and accessibility was also evaluated. Though the costs of traditional therapies are not explored in this study, there is converging evidence that they are highly cost-effective[14, 16, 27].

Traditional medicine usage with allopathic has always been a point of debate and always causes confusion in the combined output of either mode of treatments. That combination of therapies could synergize the effect, potentiate or nullify, altogether. Keeping this in mind, pupils were evaluated for combined therapies and whether it was done with due consent and acknowledgment of the physician or kept hidden. The results revealed that a percentage greater than half of the total population had been taking allopathy and traditional medicine treatment in concoction. As

far as permission of the physician is concerned, it was done rarely and not practiced for most of the time[28, 29]. Previous data give an insight of the fact that well aware students with medical background, appreciate the advice of their physician for commonly applied traditional therapies and notifying interactions, if any[30]. A count of 187 (73.6%) participants reported their satisfaction with the results of traditional medicine. Traditional medicine has been excessively used with almost no threats to health as this stands consistent with various studies[31, 32]. In a previous study, people have reported a positive response to traditional medicine use, however, few people also showing reservations regarding its use. This hesitation could be attributed to the lack of scientific and phenotypic testing of the natural products[33, 34]. Altogether, researches previously carried, revealed a range in response varying from the positive reaction to skepticism with the use of traditional medicine[35, 36]. Candidates of the study were also assessed regarding medicinal plants utilization against day to day issues and diseases. The outcome of the current survey showed that majority of the participants were using medicinal plants to treat many ailments and previous studies also supported this investigation as medicinal plants are enriched source of phytochemicals that have potential therapeutic activities to cure diseases[37, 38]. However, many of the effects of medicinal plants are not completely understood, yet found effective as therapeutic agents and still there is a need to conduct more research in this area of study [39, 40].

Limitations

This study has a few limitations as mentioned below:

1. It is confined within the geographical region of Lahore.

2. Only includes pharmacy students, excluding all others.

3. Survey questions are limited to medicinal plants of daily use or commonly advertised.

Conclusion

Medicinal plants are widely used to treat various disorders around the world. Current study outcomes have demonstrated that the students have great interest in the field of traditional medicine. This research may turn to be useful regarding future recommendations in Pharmacy curriculum. Introduction of Clinical Pharmacognosy in Pharmacy curriculum could probably enhance the safe usage of natural products alongside allopathic medicine together with more phenotype based testing.

Conflict of interest

There is no conflict of interest among the authors.

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None

Authors' contribution

Data gathering and idea owner of this study: Kanwal Ashiq

Study design: Kanwal Ashiq, Sana Ashiq

Data gathering and Statistical Analysis: Kanwal Ashiq, Mayyda Asif Bajwa, Rabia Khokhar, Farah Abid, Samreen Tanveer, Mehwish Qayyum, Sana Jameel

Writing and submitting manuscript: Kanwal Ashiq, Sana Ashiq, Mayyda Asif Bajwa, Rabia Khokhar

Editing and approval of final draft: Kanwal Ashiq, Mayyda Asif Bajwa, Rabia Khokhar, Farah Abid, Samreen Tanveer, Mehwish Qayyum, Sana Ashiq, Sana Jameel

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Original Article

Assessment of pharmacists towards the use of herbal medicines in Lahore, Pakistan

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Objective: To assess pharmacists' knowledge of herbal medicines concerning their experiences and patients' interaction.

Methodology: A descriptive cross-sectional methodology was selected for the current study. The information, data, and facts were gathered from January to April 2021.

Results: The study has 253 responses. The study showed that 213 (84.2%) participants thought that herbal medication is nontoxic to use, 205 (81%) approved that herbal medicines had efficacy, 176 (69.6%) indicated that herbal medicines were cost-effective, 197 (77.9%) recommended herbal medicines to their clan members and 152 (60.1%) acknowledged that they guide patients on herbal medicines.

Conclusion: Pharmacists should be well informed so that they can guide patients about the safe and effective use of medicines. It is suggested, pharmacy curriculum must be updated so that students have adequate information about herbal medicines' benefits and their possible risks particularly when used with allopathic medicines.

Keywords: Pharmacists, herbal medicines, natural products, pharmacy, curriculum.

INTRODUCTION

Nearly 80% of the global population counts on natural drugs as they are perceived as benign and economical approach for the treatment of various ailments.[1] It is estimated that the herbal market has a 100 billion dollar share and is expected to witness an increase in this trend.[2] Although herbal drugs are considered therapeutically safe and effective, still this requires more evidence base research.[3] Thus it is a necessity of time to globally validate and ensure the safe use and utilization of herbal and natural drugs.[4] Worldwide consistent policies need to be established for the effective and standard utilization of herbal drugs.[5]

Most people in Pakistan live in tribal and rural areas in close proximity and utilize their ancestral knowledge for consuming herbal remedies for various treatments.[6] The profession of pharmacy is well recognized and is practiced to its full potential in developed countries, however it is underutilized in developing countries such as Pakistan.[7] Pharmacists are an accessible source for healthcare information.[8] The widespread sale of complementary and alternative medicines (CAM) in community pharmacies raises important questions regarding the responsibilities of pharmacists when selling complementary medicines.[9] This study assessed pharmacists' knowledge of herbal medicines with respect to their experiences and patients' interaction, as such sort of research has not been conducted previously.

METHODOLOGY

This descriptive cross-sectional study collected data from January to April 2021. We used an online survey since precautions have to be taken during the COVID-19 pandemic.[10] A Questionnaire was developed on Google Forms and consisted of three pages. Different online platforms were used for the distribution of sample performa. For assurance of the credibility of the collection tool, the Cronbach's Alpha was calculated and found to be 0.74 which showed the reliability of the data collection instrument.[11,12]

Qualified Pharm-D degree-holding pharmacists who inhabited in Lahore, Pakistan were considered for the study. Pharmacy technicians, students, non-pharmacy professionals, and general community were excluded from the study. Ethical clearance (Ref: PM/01/21) was obtained from the Institutional Review Board of Superior University, Lahore, Pakistan and all participants signed an informed consent.

Statistical Analysis: The data were analyzed using the software SPSS version 22. t-test, and ANOVA were calculated to evaluate the received data.

RESULTS

Total 253 responses were obtained. The demographic information is presented in Table 1. Participants' knowledge about herbal medicines (closed ended questions) is shown in Table 2. Mean analysis between employed and non-employed pharmacists is presented in Table 3.

Table 1: Demographic characteristics of participants (n = 253).

Parameter	Number	%	± SD	Parameter	Number	%	± SD
Age			1.02	**Nature of the Job Currently Doing (N = 161)**			2.05
20 – 25	180	71.1		Retail Pharmacist	32	12.6	
26 – 30	39	15.4		Community Pharmacist	24	9.5	
31 – 35	8	3.2		Hospital Pharmacist	33	13	
36 – 40	21	8.3		Academician/Researcher	19	7.5	
41 – 45	5	2.0		Clinical Pharmacist	23	9.1	
				Sale and Marketing	9	3.6	
Marital Status			0.36	Industrial Pharmacist	10	4	
Unmarried	212	83.8		Regulatory Affairs Manager	11	4.3	
Married	41	16.2		**Total professional experience**			
	253			No Experience	92	36.4	
Education			1.17	Less than 1 year	87	34.4	
M.Phil/MS Scholar	12	4.7		1-3 years	46	18.2	
M.Phil/MS	22	8.7		4-6 years	8	3.2	
PhD Scholar	4	1.6		7-9 years	12	4.7	
PhD	7	2.8		10-12 years	4	1.6	
Doctor of Pharmacy	208	82.2		More than 12 years	4	1.6	
Currently doing a job			0.5				
No	92	36.4					
Yes	161	63.6					

Table 2: Participants' knowledge about herbal medicines (closed ended questions).

Question*	Yes		No		May be		± SD
	N	%	N	%	N	%	
1.	193	76.3	28	11.1	32	12.6	0.697
2.	197	77.9	36	14.2	20	7.9	0.608
3.	213	84.2	0	0	40	15.8	0.731
4.	205	81	4	1.6	44	17.4	0.763
5.	176	69.6	41	16.2	36	14.2	0.731
6.	172	68	41	16.2	40	15.8	0.754
7.	152	60.1	16	6.3	85	33.6	0.933
8.	52	20.6	157	62.1	44	17.4	0.616
9.	144	56.9	69	27.3	40	15.8	0.749
10.	177	70	32	12.6	44	17.4	0.774
11.	172	68	21	8.3	60	23.7	0.851
12.	120	47.4	56	22.1	77	30.4	0.868
13.	125	49.4	44	17.4	84	33.2	0.896
14.	129	51	56	22.1	68	26.9	0.851
15.	180	71.1	12	4.7	60	23.7	0.854

***Questions:** 1. Have you ever used herbal medicines for personal use? 2. Have you ever recommend herbal medicines to your family members? 3. Do you think herbal medicines are safe to use? 4. Do you think herbal medicines are effective? 5. Do you think herbal medicines are cheap as compared to synthetic medicines? 6. Patients ask you about herbal medicine usage and information. 7. You counsel the patients regarding herbal medicines. 8. Have you ever guide doctors regarding herbal medicines. 9. Do you think available information regarding herbal medicines are adequate? 10. You tried to update your knowledge regarding herbal medicines. 11. Do you think manufacturer's reputation, and manufacturer's ability to give quality data regarding product were major factors influencing consumers? 12. You have adequate knowledge regarding potential interactions between herbal medicine and conventional medicines. 13. You or any of your patients inform doctor regarding concomitant use of the allopathic and herbal medicines? 14. Do you think that you have adequate knowledge and skills to counsel patients on herbal medicines? 15. Professional curricula should have more components on herbal medicines in order to equip with latest information.

Table 3: Mean analysis between employed and non-employed pharmacists.

Questions*		Mean	± SD	p-value**	Questions*		Mean	± SD	p-value**
1.	Yes	.31	.649	.237	8.	Yes	.90	.712	.090
	No	.41	.735			No	1.03	.516	
2.	Yes	.27	.582	.515	9.	Yes	.73	.784	.006
	No	.32	.631			No	.47	.699	
3.	Yes	.41	.811	.058	10.	Yes	.44	.771	.570
	No	.24	.647			No	.50	.779	
4.	Yes	.27	.690	.081	11.	Yes	.59	.892	.575
	No	.44	.814			No	.53	.816	
5.	Yes	.45	.725	.898	12.	Yes	.91	.851	.197
	No	.44	.738			No	.76	.880	
6.	Yes	.52	.772	.400	13.	Yes	.75	.899	.158
	No	.44	.738			No	.91	.890	
7.	Yes	.84	.991	.105	14.	Yes	.82	.877	.286
	No	.65	.874			No	.71	.827	

*Questions: see table 2 footnotes. **A p-value ≤ 0.05 was considered to be statistically significant.

Table 4: Participants' knowledge about herbal medicine (open ended questions).

Title	N	%
In your opinion, your patients are using herbal medicines for		
Acute illness	104	41.1
Chronic illness	36	14.2
Both	113	44.7
In your opinion, which of the followings you considered important to have reliable information regarding herbal medicines and other natural products.		
Scientific publications	45	17.8
Reference texts and books	48	19.0
Online websites	58	22.9
Conferences/workshops	32	12.6
Professional newsletters	15	5.9

In accordance with participants, for herbal medicine, the valued and consistent bases of evidence are as follows: online websites 58 (22.9%), references texts and books 48 (19%), scientific publications 45 (17.8%), conferences/workshops 32 (12.6%) and professional newsletters 15 (5.9%) (Table 4).

DISCUSSION

The practice of herbal medicine is more abundant in women and the well-educated public who were in their middle-ages.[13] Across the globe, herbal medicine and its preparations display a key role in the cure of diverse sorts of ailments such as liver disorders, memory disorders, diabetes, arthritis, etc. 76.3% of the current study participants advocated the use of herbal medicines. Pharmacists selectively used herbals, minerals, vitamins and other nutritional supplements, and endorsed some of the more commonly used products to patients, family and friends. The utmost

communal saga about these drugs is that they are entirely harmless and can be used up without prescription.[14,15]

Even though herbal medicines are mild, they might result in potential interactions when simultaneously used with synthetic medicines, and they possibly will have side effects as well.[16,17] In this study, 104 (41.1%) respondents believed that the bulk of the patients use herbal medicine for acute diseases on the other hand 36 (14.2%) believed that patients use herbal medicine for only chronic ailments and 113 (44.7%) were persuaded that patients use herbal medicine for all types of diseases either chronic or acute.

In a previous study, it was observed that the use of antipsychotic drugs (i.e. olanzapine, clozapine, and quetiapine) with natural medicine regimens (i.e. *Akebia caulis*, Fructus *schisandrae Chinensis*, *Radix* bupleur and *Fructus gardenia*) increases the risk of side effects almost 60%.[18] Across the world, complementary medicines are sold under the supervision of community pharmacists. In addition, patients usually rely on pharmacists' advice regarding the use of herbal medicines as the majority of such medicines are traded as over-the-counter (OTC) medicines.[19]

As pharmacists are the custodian of medicines, they should take responsibility to counsel patients regarding the safe use of natural products.[20] Many factors can influence consumer decision to purchase herbal medicines such as the reputation of the manufacturer company, requests and demands of consumer, and quality of the product.[12] Further, marketing of such products (via TV advertisement, website, and social media etc.) gives sufficient awareness to the customers and enhances sale of formulations based on natural ingredients.[21]

In regions where herbal medicines are extensively used, pharmacy students must equip and train in the field of natural products and their research.[22] It is suggested, the pharmacy curriculum must be updated so that students have adequate information about herbal medicines' benefits and their possible risks, particularly when used with allopathic medicines.

CONCLUSION

Pharmacists have adequate knowledge about herbal medicines. However, proper training and continuing education programs can boost their knowledge in this field.

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