Received: 8 July 2021 | Revised: 28 September 2021 | Accepted: 28 September 2021

DOI: 10.1111/jfbc.13967

Journal of Food Biochemistry WILEY

REVIEW

# Neuroprotective effects of oleuropein: Recent developments and contemporary research

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## Abstract

Neurological disorders are increasing at a faster pace due to oxidative stress, protein aggregation, excitotoxicity, and neuroinflammation. It is reported that the Mediterranean diet including olives as a major dietary component prevents and ameliorates neurological anomalies. Oleuropein is the major bioactive component in different parts of the Olive (*Olea europaea* L.) tree. Several mechanisms have been reported for the neuroprotective role of oleuropein including induction of apoptosis and autophagy, enhancing the antioxidant pool of the cerebral region, decreasing the unnecessary release of proinflammatory cytokines and chemokines by deactivating the microglia cells and astrocytes thus preventing the occurrence of neuroinflammation. Regular intake of oleuropein seems to be correlated with decreased risks of neural disorders including Alzheimer's, Parkinson's, strokes, depression, anxiety, epilepsy, and others. This review majorly discusses the chemistry, biosynthesis, and metabolism of oleuropein along with an updated vision of its neuroprotective role in counteracting the acute and chronic neurodegenerative and neuropsychiatric disorders. Moreover, mechanisms by which oleuropein may prevent neurodegeneration are reviewed.

**Practical application**

Neurological disorders are negatively affecting the health and life quality of individuals around the globe. Although various medicinal solutions are available to tackle such ailments, none has proven to fully cure and being deprived of side effects. In this respect, the prevention of such disorders using natural remedies may be an effective strategy to overcome the incidence of the increasing cases. Furthermore, the natural compounds provide a safer alternative to pharmaceutical drugs. Hence, oleuropein from olive tree products is found to be efficacious against neurological disorders. This review provides an updated insight on the positive effects of oleuropein against neurodegenerative and neuropsychiatric disorders. The diet practitioners

**Abbreviations:** 5-HT, Serotonin; 6-OHDA, 6-Hydroxydopamine; AD, Alzheimer's Disease; ALS, Amyotrophic Lateral Sclerosis; ARE, Antioxidant Response Elements; Aß, Amyloid Beta; BBB, Blood Brain Barrier; BDNF, Brain-Derived Neurotrophic Factor; CAT, Catalase; CNS, Central Nervous System; CVDs, Cardiovascular Diseases; DA, Dopamine; DALYs, Disability-Adjusted Life Years; DNA, Deoxyribonucleic Acid; EPCs, Endothelial Progenitor Cells; EPM, Elevated Plus Maze; FST, Forced Swim Test; GABA, Gamma-Aminobutyric Acid; GPx, Glutathione Peroxidase; HD, Huntington's Disease; ICH, Intracerebral Hemorrhage; MD, Mediterranean Diet; MS, Multiple Sclerosis; NDDs, Neurodegenerative Disorders; NDs, Neurological Disorders; NE, Norepinephrine; NFTs, Neurofibrillary Tangles; NPDs, Neuropsychiatric Disorders; Nrf-2, Erythroid Related Nuclear Factor 2; OFT, Open Field Test; OL, Oleuropein; OLA, Oleuropein Aglycone; OLE, Olive Leaf Extract; OS, Oxidative Stress; PD, Parkinson's Disease; PNS, Peripheral Nervous System; PTZ, Pentylenetetrazole; RNS, Reactive Nitrogen Species; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase; TST, Tail Suspension Test.

  

and nutraceutical companies may benefit from the provided information to design and develop strategies to improve the mental health of suffering individuals.

KEYWORDS
neuroinflammation, neurological disorders, neuroprotective, oleuropein, oxidative stress

## 1 | INTRODUCTION

Neurological or Neuro-affected disorders (NDs) refer to any kind of anomaly involving injury of the central nervous system (CNS); mainly brain and nerves or peripheral nervous system (PNS) (Choi et al., 2020). Some other factors involved may include alterations in certain biochemical aspects or some unknown factors causing obvious CNS injury (Rizk et al., 2018). NDs occur among all age groups and different geographical regions. They significantly contribute to morbidity and mortality around the world (Abbastabar et al., 2019). Globally, NDs are the leading cause of disability-adjusted life years (DALYs) contributing up to 11.6%, that is, 276 million DALYs and second leading cause of deaths contributing up to 16.5%, that is, 9 million deaths worldwide (Feigin et al., 2020).

Neuro-affected disorders can be further divided into two major sections a) Neurodegenerative disorders (NDDs) and b) Neuropsychiatric disorders (NPDs) (Bawa et al., 2016). NDs are generally characterized by progressive damage and loss in neural cells leading to compromised cognitive and motor functions. Major NDDs include Alzheimer's disease (AD) and Parkinson's disease (PD), Cerebral stroke, Huntington's disease (HD), Multiple sclerosis (MS), and Amyotrophic lateral sclerosis (ALS) (Cassano et al., 2020; Yan et al., 2020). AD and PD represent the prime health problem associated with the older population (Scheiblich et al., 2020). NPDs are associated with disorders of cognition and abnormal behavior arising due to direct effects of CNS injury, *for example*, depression, anxiety, and epilepsy. NPDs may also occur as a consequence of indirect effects of dysfunction of the neural system that might not involve neuropathology but may appear as associated symptoms of NDDs, for example, depression related symptoms are reported in AD patients with a prevalence of about 20% and at the time of diagnosis for PD and HD in about 30% of cases (Bray, & O'Donovan, 2018; Menculini et al., 2021; Salim, 2017). The co-morbid nature of NDDs and NPDs, especially the "pairing" of NDDs with NPDs intensifies the complications for the development of effective therapeutic strategies (Bawa et al., 2016; Cummings et al., 2019).

Neuroprotection is intended to ameliorate the brain dysfunction, regeneration of neuronal network and prevent the neural cell death in an effort to develop disease-modifying therapies (Naoi et al., 2019). Unfortunately, in spite of the tremendous devotion and efforts of researchers and scientists toward the development of neural protective drugs in the past era, no successful and effective drugs have yet been discovered to halt the adverse impacts of NDs (Sun et al., 2020). For example, Food and Drug Administration approved antidepressant drugs like fluoxetine, escitalopram, and citalopram are found to be associated with hepatotoxicity, oxidative stress, inflammation, and apoptosis of hepatocytes which can be positively attenuated by natural food components like olive oil and its bioactive constituents (Elgebaly et al., 2018). Recently, many researchers have turned their focus to the development of such drugs from natural origin, since from ancient times nature has been proven to be a hub of bioactive components with unique biomedical applications (Shazmeen et al., 2021; Silva et al., 2019). Several natural compounds have been observed for their promising potential in the management of different NDs and many are still under consideration and evaluation (Ikram et al., 2019). A large group of studies support the beneficial role of the Mediterranean diet (MD) in neuroprotection possibly due to its phenolic compound dense components in foods (Angeloni et al., 2017).

*Olea europaea* L. commonly known as olive worldwide is a key component of the MD (Díaz-Curiel et al., 2020). The olive plant is an abundantly cultivated species and a major portion of its cultivation comes from the Mediterranean region (Yazbeck et al., 2019). Moreover, it is also widely cultivated in central Asia, various parts of Africa, Australia, and North and South America as well (Gul et al., 2020). Olive tree is very special to mankind because its health benefits have been repeatedly emphasized in religious sayings and historically it has been used as an essential component in various traditional herbal medicines (Uylaşer & Yildiz, 2014). Olive fruits and leaves are full of phytochemicals that are known for their potent health benefits (Gorzynik-Debicka et al., 2018; Rigacci & Stefani, 2016). Likewise, popularity of olive oil is rising not only due to its organoleptic properties but also for its health promoting aspects that is evident by scientific findings (Debib et al., 2016).

Oleuropein (OL) is the major bioactive component found in the olive trees and is present in greater amounts in its leaves, unripe, and unprocessed fruits (Imran et al., 2019; Santini et al., 2020). Its range can vary from 113 to 100,000 mg/kg of fresh olive fruit on dry weight basis, and 50–23485 ng/mL of olive leaf extract, depending upon the ripening stage, extraction methods, and preservation methods used for storage purpose (Cecchi et al., 2015, 2020; Žuntar et al., 2019). Several clinical and preclinical studies conducted have identified its beneficial role against different human diseases. OL have been found to exhibit many pharmacological and biological effects such as cardioprotective (Çömez et al., 2020; Zhao et al., 2017), antidiabetic (Kamİloğlu et al., 2019; Karabag-Coban et al., 2017), hypolipidemic (Malliou et al., 2018), antiischemic (Esmailidehaj et al., 2016; Zhang et al., 2018), antioxidant (Ivanov et al., 2018), anti-inflammatory (Janahmadi et al., 2017), anticancer (Przychodzen et al., 2019), hepatoprotective (Cerig et al., 2016), nephroprotective (Geyikoglu et al., 2017), and neuroprotective actions (Benlarbi et al., 2020). The current review presents precise information about

the chemistry, biosynthesis, and bioavailability of OL alongside an updated vision from the past decade about its neuroprotective role in counteracting the acute and chronic NDDs and NPDs.

## 2 | OCCURRENCE, CHEMISTRY, AND BIOSYNTHESIS OF OLEUROPEIN

As a component of the traditional 'Mediterranean Diet', olive and olive oil are the most famous and popular foods (Žuntar et al., 2019). Olive leaf extracts, olive oil, and olive fruits are rich in phenolic compounds, tocopherols, phospholipids, and carotenoids (Gorzynik-Debicka et al., 2018). OL is considered as the main ingredient in olive drupe and its other constitutional parts, that is, pulp and peels. (Rostamzadeh et al., 2020). Factors affecting its concentration include cultivars of olives, employed processing system, climate, water stress, and time of harvesting. Altered content of OL depicts change in total phenolic compounds content of fruit and its concentration varies during maturation (Charoenprasert & Mitchell, 2012). There is no set recommended dosage for oleuropein intake per day but many studies have shown that olive leaf extract (containing approximately 20% oleuropein) at the dose of 1,000 mg/day depicted no observed adverse side effects (Breakspear & Guillaume, 2020; Clewell et al., 2016). OL is not solely a component of *Olea* genus, it also occurs in several other genera of *Oleaceae* family such as *Fraxinus chinensis* (Chang et al., 2020), *F. angustifolia* (Kasmi et al., 2021), *F. excelsior* (Sidda et al., 2020), *Syringa vulgaris* (Hanganu et al., 2021), *S. josikaea* (Damtoft et al., 1993), *Ligustrum vulgare* (Macková et al., 2013), *L. ovalifolium* (Hosny et al., 2009), and *Philyrea latifolia* (Tattini et al., 2000). Table 1 represents the oleuropein content in different parts/products of olive tree.

OL was detected for the first time in 1908 by Bourquelot and Vintilesco but its appropriate chemical structure was discovered and designed by Panizzi and his co-workers in 1960 (Cavaca et al., 2020). OL comes under the umbrella of secoiridoids, which are found in higher concentration in olive leaves up to 1,450 mg/100 g on fresh weight basis in comparison to olive oil and fruit having 23 and 110 mg/100 g respectively (Sivakumar et al., 2018). Secoiridoids are formed from iridoids via conversion of iridoid substrates which leads to formation of indole alkaloids. The skeleton of iridoids contains a cyclopentane ring that is fused to a six-membered heterocyclic ring (Yoon, 2018). OL is a glycosidic ester of hydroxytyrosol and β-glucosylated elenolic acid that portrays an oleosidic skeleton (a common structural skeleton of glycosidic secoiridoids of *Oleaceae*) (Genc et al., 2020). The chemical structure of OL is illustrated in Figure 1.

Biosynthesis of OL in olives occurs *via* mevalonic acid pathway. Following this pathway (Figure 2) branching of mevalonic acid leads to formation of geraniol, 10-hydroxygeraniol, and then the iridodial. This iridodial is then converted into an aglycone structure forming deoxyloganic acid, 7-epiloganic acid, and loganic acid that incorporates to form ligstroside. Ligstroside acts as the direct precursor of OL. Damtoft with his colleagues proposed the pathway for the biosynthesis of OL *via* deoxyloganic acid, 7-epiloganic acid, 7-ketologanic acid, 8-epikingisidic acid, oleoside 11-methyl ester, and then esterification of tyrosol with 7-β-1-$_D$-glucopyranosyl 11-methyl oleoside leading to the formation of ligstroside and ultimately OL (Damtoft et al., 1992).

Olive fruit maturation with special reference to alteration in contents of OL is usually distinguished in three phases. First "the growth phase" in which OL starts to accumulate in olive fruit, second "the green phase" in which the concentration of OL and chlorophyll starts decreasing and the third phase "the black phase" in which an increase in the concentration of anthocyanins and OL derivatives occurs with continuous decrease in OL levels (Ahamad et al., 2019; Farooqui & Farooqui, 2017). Hence, in the early maturation stages, OL occurs at its peak; in young fruits OL levels can be found up-to 14% of dry weight. Although OL starts decreasing with maturity but its concentration is still found to be very impactful in green-picked fruits while for black fruits OL rapidly decreases with the passage of time (Charoenprasert & Mitchell, 2012; Omar, 2010).

OL structure contains three subunits, that is, elenolic acid, a glucose moiety, and hydroxytyrosol. In presence of β-glucosidase OL undergoes enzymatic digestion result in breakdown of glucose molecule which leads to subsequent biotransformation of nonpolar oleuropein aglycone (OLA) because of keto-enolic tautomeric equilibrium which involves the ring-opening and formation of hemiacetal structure of elenolic acid and next more stable dialdehydic form (Poerschmann et al., 2013). These OLAs under an aqueous environment is transformed into decarboxymethyl elenolic acid linked with hydroxytyrosol which gets converted in elenolic acid glycoside and demethyloleuropein on action of endogenous esterase *via* hydrolysis of hydroxytyrosol esters or methyl esters respectively (Cavaca et al., 2020). Hence, as a result this enzymatic digestion leads to accumulation of two compounds elenolic acid glycoside and demethyloleuropein (Figure 3) (Cavaca et al., 2020; Romero et al., 2020). Olive fruits have appeared to accumulate only these glycosylated derivatives while other derivatives of OL such as non-glycosylated secoiridoids and di-hydroxytyrosol content were found in leaves (Yoon, 2018). Hydroxytyrosol is produced from the hydrolysis of OL while tyrosol is a hydrolytic product of ligstroside (Özcan & Matthäus, 2017).

Quality of phenolic compounds in olive is also affected during processing for extraction of olive oil. Quality of olive oil is determined through a series of factors such as olive tree, genotype, environment, agronomic practices, processing techniques, and storage. Among all, the processing plays a decisive role in quality determination (Gullon et al., 2020; Kalogianni et al., 2019). During olive processing, milling and malaxation are the most critical steps which affects the quality and composition of virgin olive oil (Jerman Klen et al., 2015). Oleuropein and ligstroside, the main secoiridoids of olives are degraded resultant to hydrolytic and endogenous enzymatic and non-enzymatic alterations. The enzymatic degradation occurs during crushing and hydrolytic degradation while leading to accumulation of decarboxymethyl aglycons while non-enzymatic degradation prevails during the storage and preservation of olive oil (Kanakis et al., 2013; Lanza & Ninfali, 2020; Migliorini et al., 2012). Similarly, during processing of table olives content of oleuropein is affected. Processing of

TABLE 1 Oleuropein content in different parts/products of olive tree

| Parts of Olive tree | Variety | Oleuropein content | Unit | References |
|---|---|---|---|---|
| Leaves (Dry Weight) | Domat | 155.47–165.33 | mg/g | (Topuz & Bayram, 2021) |
| | Edremit | 52.90–66.90 | | |
| | Trilye | 116–162 | | |
| | Arbequina | 63–73 | g/kg | (Lama-Muñoz et al., 2020) |
| | Royal | 66–71 | | |
| | Picual 1 | 56–65 | | |
| | Picual 2 | 43–49 | | |
| | Wild Type 1 | 79–83 | | |
| | Wild Type 2 | 115–122 | | |
| | Wild Type 3 | 81–85 | | |
| | Agizi Okasi | 45–122 | mg/100 g | (Kabbash et al., 2021) |
| | Agizi Shami | 85–101 | | |
| | Hamed | 15–116 | | |
| | Maraki | 32–36 | | |
| | Toffahi | 2.8–63 | | |
| | Watiken | 14–53 | | |
| | Monzanillo | 83–219 | | |
| | Picual | 22–111 | | |
| | Arbequina | 12–23 | | |
| | Kalamata | 19–85 | | |
| | Koroneiki | 12–92 | | |
| | Coratina | 36–151 | | |
| | Chetoui | 6.65 | mg/100 g | (Brahmi et al., 2014) |
| | Chemchali | 8.10 | | |
| Fruit (Dry weight) | Cornicabra | 6500–12000 | mg/kg | (Gómez-Rico et al., 2009) |
| | Morisca | 400–3000 | mg/ | |
| | Chetoui | 0.77 | mg/100 g | (Brahmi et al., 2014) |
| | Chemchali | 0.32 | | |
| | Kaissy | 630.5–638.7 | mg/kg | (Tayoub et al., 2012) |
| | Jlott | 1,019.7–1030.8 | | |
| | Sorani | 939.7–951.9 | | |
| | Dan Mawi | 724–736 | | |
| | Khodairi | 675–685 | | |
| | Istanbuli | 977–993 | | |
| | Nibaly | 659–671 | | |
| | Kato Drys | 4,539 | mg/kg | (Emmanouilidou et al., 2020) |
| | Korakou | 4,304 | | |
| | Ladoelia | 10,871 | | |
| | Memecik | 4590–9936 | mg/kg | (Yorulmaz et al., 2013) |
| | Edremit | 5100–15038 | | |
| Fruit (Fresh Weight) | Petrolia | 1.0 | mg/g | (Petridis et al., 2012) |
| | Smertolia | 1.5 | | |
| | Valanolia | 1.3 | | |
| | Megaritiki | 2.5 | | |
| | Kothreiki | 2.2 | | |

(Continues)

TABLE 1 (Continued)

| Parts of Olive tree | Variety | Oleuropein content | Unit | References |
|---|---|---|---|---|
| | Kalamon | 2.8 | | |
| | Pikrolia Kerkiras | 11.07 | | |
| | Thassitiki | 1.2 | | |
| | Maronia | 0.25 | | |
| | Romeiki | 3.00 | | |
| | Throubolia Aegaan | 0.8 | | |
| | Frontoio | 6,522.3 | mg/kg | (Cecchi et al., 2018) |
| | Arbequina | 4,115.6 | | |
| | Leccio del Corno | 7,339.6 | | |
| Stem (Dry weight) | Mission | 13.50 | mg/g | (Kishikawa et al., 2015) |
| | Picual | 22.30–58.02 | g/kg | (Ortega-García, & Peragón, 2010) |
| | Chetoui | 4.42 | mg/100 g | (Brahmi et al., 2014) |
| | Chemchali | 4.63 | | |
| Roots (Dry weight) | Picual | 1.93–6.05 | g/kg | (Ortega-García, & Peragón, 2010) |
| | Meski | 271–1795 | µg/g | (Mechri et al., 2019) |
| | Zard | 25–45 | mg/g | (Petridis et al., 2012) |
| | Ascolana | 14–75 | | |
| | Koroneiki | 25–75 | | |
| | Arbequina | 08–14 | | |
| Extra Virgin Olive Oil | NA | 0.49–0.55 | mg/g | (Huguet-Casquero et al., 2020) |
| | Frontoio | 95.3 | $mg_{tyr}$/kg | (Cecchi et al., 2018) |
| | Arbequina | 15.9 | | |
| | Leccio del Corno | 18.7 | | |
| Virgin Olive Oil | La Pepa | 137–143 | mg/kg | (Cioffi et al., 2010) |
| | Severini | 118–122 | | |
| Olive Oil Pomace | La Pepa | 137–143 | mg/kg | (Cioffi et al., 2010) |
| | Severini | 118–122 | | |

table olives is mainly done to remove the bitterness in taste due to oleuropein (Johnson & Mitchell, 2018) Purposely, several processing techniques like analytical hydrolysis or diffusion in brine are employed. Moreover, the bitter taste in olives is also reduced by semi-drying processing or enhancing the enzymatic degradation of oleuropein in olives *via* microorganisms like lactic acid bacteria which not only help in debittering the olive but also plays a role in fermentation process. In naturally processed olives (with brine fermentation/salt processing), the hydrolytic degradation of oleuropein and other phenolic compounds take longer time than lye treatment which involves complex mechanism for removal of oleuropein (Cillidag, 2013; Conte et al., 2020; Ozdemir et al., 2014).

## 3 | BIOAVAILABILITY OF OLEUROPEIN

OL on its metabolization in biological systems yields several other metabolites that possess particular biological properties and health benefits attributed to OL. Metabolism and bioavailability of OL are heterogeneous and greatly depend upon a number of factors such as formulation of its intake (either in form of capsule or liquid), route of administration and gender (García-Villalba et al., 2014). In a human study, it was observed that oral ingestion of OL is resistant to stomach acidic environment. Hence, it gets rapidly absorbed up to 50%–60% in the intestine and reached its peak levels in plasma in just 25–30 min based on the type of preparation, that is, liquid or capsule after ingestion in comparison to its conjugated metabolites such as glucuronidated and sulfated hydroxytyrosol that reached in plasma in about 64–93 min. These conjugated metabolites made up almost 95% of OL metabolites in plasma and urine after its complete metabolism (De Bock et al., 2013; Nediani et al., 2019). However, some studies have also reported minimal absorption of OL *via* intestines depicted by its minute concentration in portal plasma of rats when administered orally and increased excretion *via* biliary route when administered intravenously in comparison to other metabolites soon after

administration (Kano et al., 2016). Furthermore, a human study on pharmacokinetic aspects of OL absorption concluded that absorption of OL is heterogenous in comparison to other metabolites, and depends up on several factors, that is, preparation (liquid/capsule), gender, form (in fruit, extract or oil), and delivery route (De Bock et al., 2013). Therefore, various formulations like liposomal encapsulations are gaining attention for appropriate delivery of OL and to get its maximum health benefits (González-Ortega et al., 2021; Nassir et al., 2019).

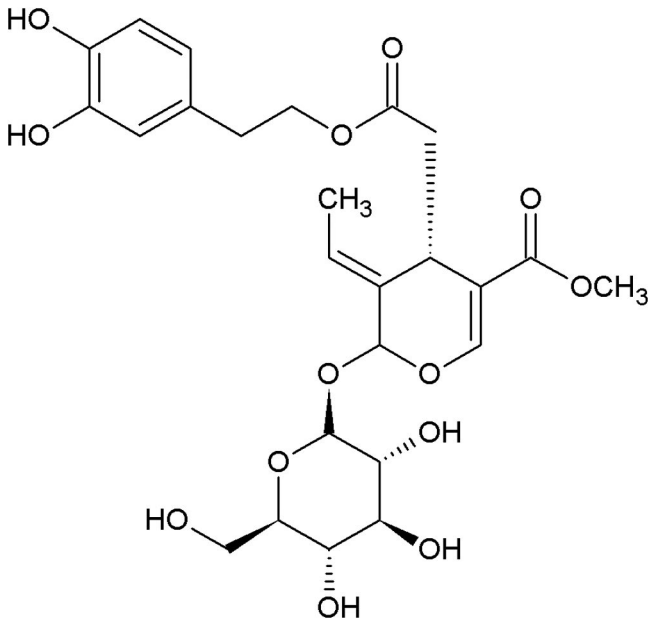


FIGURE 1 Chemical structure of oleuropein

OL gets absorbed *via* glucose transporter-mediated pathway involving Na-dependent transport carrier. Besides this, absorption of OL can also occur *via* transcellular passive diffusion or through the paracellular route (Farooqui & Farooqui, 2017). After absorption, OL gets distributed in various body organs and tissues such as the brain, liver, and heart. (Karković Marković et al., 2019). OL derivatives, ligstroside and OL itself are metabolized in liver and are converted into tyrosol and hydroxytyrosol and then excreted in urine either in their original form; its metabolites such as elenolic acid, OLA, and hydroxytyrosol; or as glucuronides by making conjugates with glucuronic acid (Lin et al., 2013; Mahmoudi et al., 2018). From all the metabolites of OL, OLA is the one that enters the brain tissue by crossing the blood brain barrier (BBB). BBB is extremely sensitive and selectively permeable for the compounds that can pass through it. The aglycone metabolites of OL cross this BBB by passive diffusion pathway and hence get readily absorbed than the glycated metabolites of OL (Angeloni et al., 2017). This mechanism of absorption has been observed in the brain parenchyma of rats after administering phenolic extract of olive cakes to rats (Serra et al., 2012). Absorption and bioavailability of OL may also be influenced by the gut microbiota, which is also recognized as metabolic organ, as these microbes can cause biotransformation of OL and its metabolites into some other active components which may help in ameliorating the consequences of bowel diseases (Noce et al., 2019; Žugčić et al., 2019).

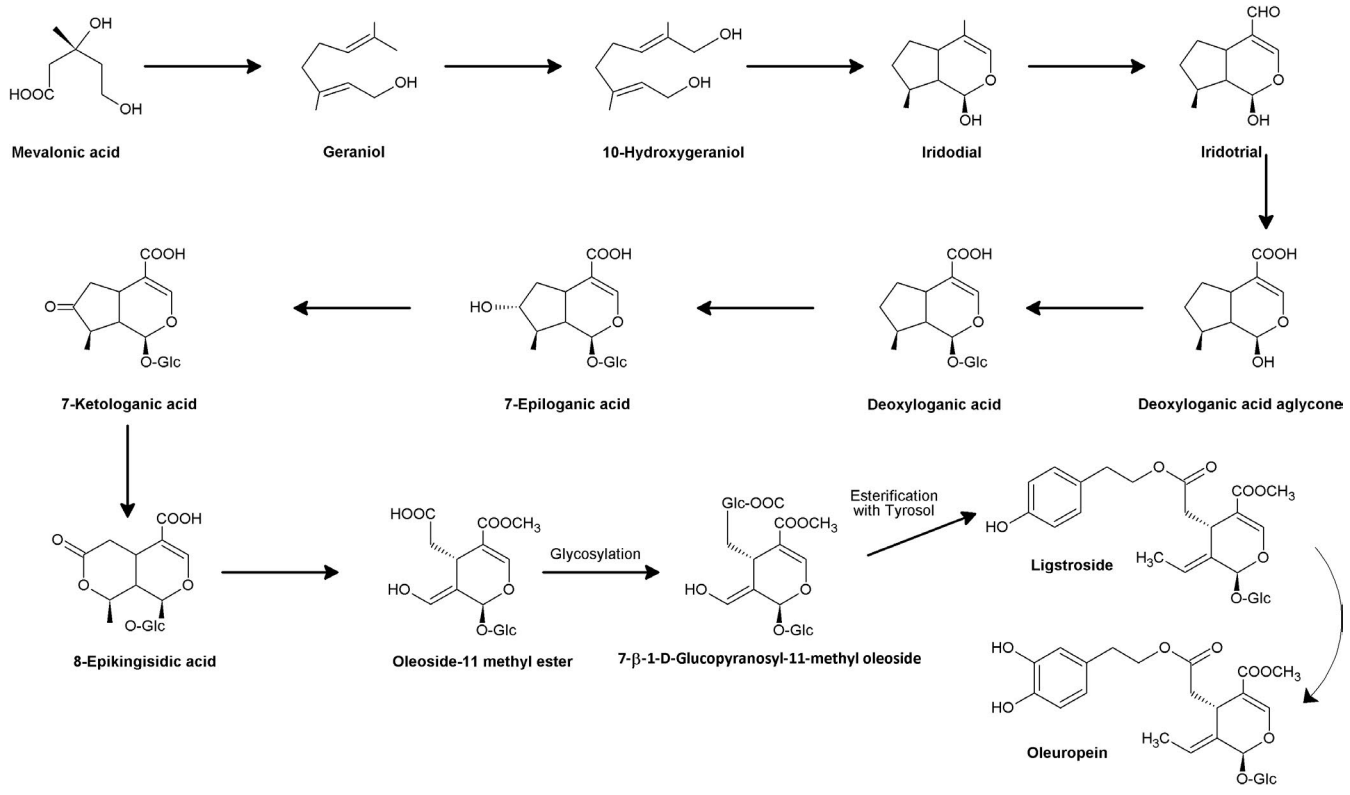


FIGURE 2 Biosynthesis of oleuropein

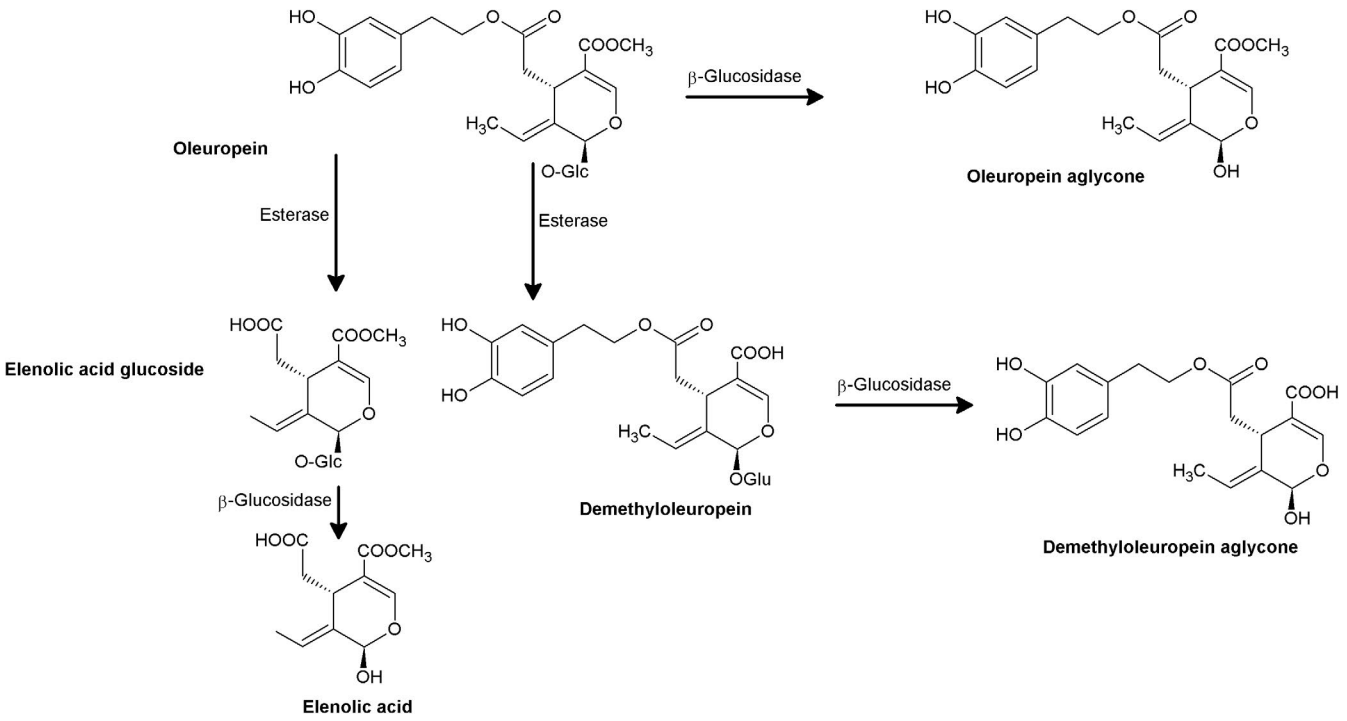


FIGURE 3 Catabolism of oleuropein

## 4 | PATHOPHYSIOLOGY OF NEUROLOGICAL DISEASES

The etiology of the pathophysiology of neurological anomalies is multifactorial and still far from being fully understood. Among the several factors involved, chronic and acute neuroinflammation, cellular senescence, genome instability, and proteostasis dysregulation are listed (Dugger & Dickson, 2017; Potì et al., 2019). Most often the progression of NDs has been linked to inflammation and oxidative stress (Ong et al., 2017; Pandareesh et al., 2018). This review focuses on the latter two main contributors in the pathogenesis of NDs.

### 4.1 | Oxidative stress

Oxidative stress (OS) plays a key role in the pathogenesis of countless diseases including cancer, arthritis, aging, cardiovascular diseases (CVDs), and NDDs. (Imran et al., 2020; Islam, 2017). OS mainly occurs as a result of an imbalance between the body's antioxidant pool and the oxidants produced by the body, for example, reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Rekatsina et al., 2020). These ROS and RNS also play an important role as part of healthy physiological processes occurring in the body, for example, defense system against pathogens, signaling pathways, and induction of mutagenic reactions. Overproduction of these ROS and RNS beyond their quantity required for healthy physiological functions or failure of the ability of body's natural antioxidant pool to counteract these effects leads to OS (Iahtisham-Ul-Haq et al., 2019; Manoharan et al., 2016). Key ROS produced and involved in OS are hydroxyl radicals, superoxide anion, and hydrogen peroxide while those of RNS include peroxynitrite and nitric oxide that participates in induction of OS in CNS and whole body (Ma et al., 2017; Tab assum et al., 2020). Nucleic acids are the major target sites of these ROS/RNS causing breakage of DNA strands, DNA-protein crosslinks, and leads to DNA mutation by modifying the purines and pyridine bases. They also impart contribution in tissue damage, inflammation, protein injury, and ultimately cellular apoptosis (Gandhi & Abramov, 2012; Lax & Jaros, 2012).

Among all the body organs, the brain and neurons are more susceptible to the adverse impacts mediated by ROS/RNS. Generally, the brain has a weak antioxidant pool, high energy demand, limited ability to regulate glucose uptake, and huge amount of mitochondria (Chourasia & Sethi, 2017; Latini et al., 2019). Accumulation of oxidation products of fatty acids particularly docosahexaenoic acid and arachidonic acid, increased metabolism of dopamine (DA), huge amount of ROS/RNS while reduced levels of antioxidant enzymes such as superoxide dismutase (Bansode & Gacche, 2019), glutathione (Fiest et al., 2016), glutathione peroxidase (GPx), and catalase (CAT) in brain are mainly responsible for neural damage leading to NDDs (Md et al., 2019; Silva et al., 2019). One of the main cell populations affected by the consequences of ROS/RNS is the microglia cells. Microglia cells get activated in the presence of ROS/RNS and they, if remain activated for a longer duration, themselves cause production of huge amount of ROS and RNS which suggests their involvement in neurodegeneration (Giacometti & Grubić-Kezele, 2020). Activated microglia also leads to secretion of cytokines, for example, interleukin 1 and TNF-α,

which together became sufficient for the induction of reactive astrocytes. These reactive astrocytes loses their ability to promote the growth and survival of neurons, phagocytosis, and synaptogenesis and ultimately leads to death of neurons and other glial cells (Liddelow et al., 2017).

### 4.2 | Neuroinflammation

Inflammation is usually a body's defense process in response to infectious pathogens, but it is also involved in pathogenesis of NDs. During an inflammatory process, several inflammatory chemokines and cytokines are released that maintains and amplifies the normal inflammatory responses (Pandareesh et al., 2018). Neuroinflammation is a term particularly referred to denote the inflammation of neurons and brain tissues. Acute neuroinflammation is the protective response of brain defense system which isolates injured brain tissues from non-injured ones, rebuilds extracellular matrix and causes apoptosis of injured neural cells. If this inflammatory process fails to work properly, brain tissue would be damaged rapidly due to physical injuries or infections caused by microbes (Killeen et al., 2014; Spagnuolo et al., 2018).

One of the most beneficial compartments of brain's anatomy is BBB covering which prevents the crossover of several microbes inside the brain. BBB is composed of endothelial cells that help in the maintenance of chemical balance in CNS by making a highly selective permeable outer covering (Fakhoury, 2015). This acute neuroinflammation process involves monocytes, lymphocytes, glial cells of CNS, and macrophages of hematopoietic system (Russo & McGavern, 2016). Among all these recruited components, activation of microglia cells has gained more attention. Microglia are basically the immune cells residing in brain tissues which gets activated in response to any kind of brain injury (Hong et al., 2016). These cells are assigned to protect and repair the injured neural cells *via* secretion of pro-inflammatory chemokines (Yacoubian, 2017) and cytokines such as interleukin (IL-6, IL-1ß, and TNF-α) (Noyce & Bandopadhyay, 2017), alongside the lipid mediators including neuroprotectins and resolvins (Ong et al., 2017).

Another type of glial cells that play a key role in inflammation are astrocytes and oligodendrocytes. Astrocytes cause the formation of glial scars and they participate in various physiological functionalities such as pro and anti-inflammatory actions under basic or diseased conditions such as cellular repair, steroid release, phagocytosis, and reduction of ROS/RNS (Nguyen & Ehrlich, 2020; Schain & Kreisl, 2017). Oligodendrocytes are responsible for the myelination of axons which enables the spinal cord and brain to stay fit in their limited spaces without affecting the rapid neural responses required for several tasks (Itoh, 2015). Myelin sheath is not just covering on neuronal axons but is metabolically active (Maiuolo et al., 2019) and its integrity is very critical for appropriate functioning of nervous system. Due to the distinctive metabolic requirements and critical functioning, oligodendrocytes are more susceptible under any neural pathological condition (Camargo et al., 2017; Papaneophytou et al., 2019). Oxidative stress, protein aggregation, and excitotoxicity are some of the major factors to oligodendrocytes' pathology leading to AD, PD, MS and neuropsychiatric disorders such as depression, anxiety, epilepsy etc. On the other hand, the chronic inflammation lingers for many years and causes severe damage to neural cells. This damage is closely linked with the prolonged hyperactivity of microglial cells and astrocytes leading to increased activation and expression of pro-inflammatory cytokines. These increased pro-inflammatory cytokines after a particular time duration, rather than exhibiting neuroprotective properties start to contribute to the pathology of NDs, for example, in Alzheimer's disease, consistent release of proinflammatory cytokines released from activated microglia, that is, IL-1ß further activates the production of TNF-α which triggers astrocytes activation. These activated astrocytes glia increases the cell volume and hence leads toward the chronic inflammation (Baune, 2015; Poletti et al., 2020; Schain & Kreisl, 2017). A systematic relation of different factors involved in neurological pathologies is depicted in Figure 4.

## 5 | NEUROPROTECTIVE ROLE OF OLEUROPEIN

A large number of studies have been conducted to explore the neuroprotective potential of oleuropein against NDDs and NPDs. The mechanisms of action of oleuropein (OL) in neural health promotion are enclosed in Table 2. OL has been observed to exert various neuroprotective effects by several mechanisms, that is, inhibition of the inflammatory enzyme, quenching and neutralization of free radicals, antioxidant and anti-inflammatory properties (Özcan & Matthäus, 2017; Talhaoui et al., 2018). The antioxidant and anti-inflammatory role of oleuropein is exerted by several mechanisms which enhances the neural defense against several stimuli. Morphine is well-known for induction of oxidative stress and apoptosis in different regions of brain especially the hippocampus (Osmanlıoğlu et al., 2020). Shibani and co-workers investigated the protective influence of oleuropein against the morphine induced hippocampal neurotoxicity and memory deficits in male *Wistar* rats. They observed that treatment with OL (15 & 30 mg/kg BW) improved the antioxidant's activity, that is, SOD and GPx, memory deficits and spatial learning in neurotoxic rats. OL also reduced the lipid peroxidation and apoptosis in brain cells by regulating the expression of Bcl2/Bax proteins (Shibani et al., 2019). OL exerts neuroprotective role by enhancing the protein kinase A mediated phosphorylation, surface expression of GluA1 and hence, enhances the intracellular calcium influx in mice hippocampal slices thus exerts beneficial effects in tackling the age-related memory impairments (Wang et al., 2020). Likewise, OL effectively counteracted the hydrogen peroxide induced stress in human glioblastoma cells and maintained the cell viability. OL also significantly regenerated the cellular total antioxidant capacity and glutathione content affected by hydrogen peroxide (Kucukgul et al., 2020). Deltamethrin, a synthetic pyrethroid insecticide, elicit neurotoxic effects *via* cellular

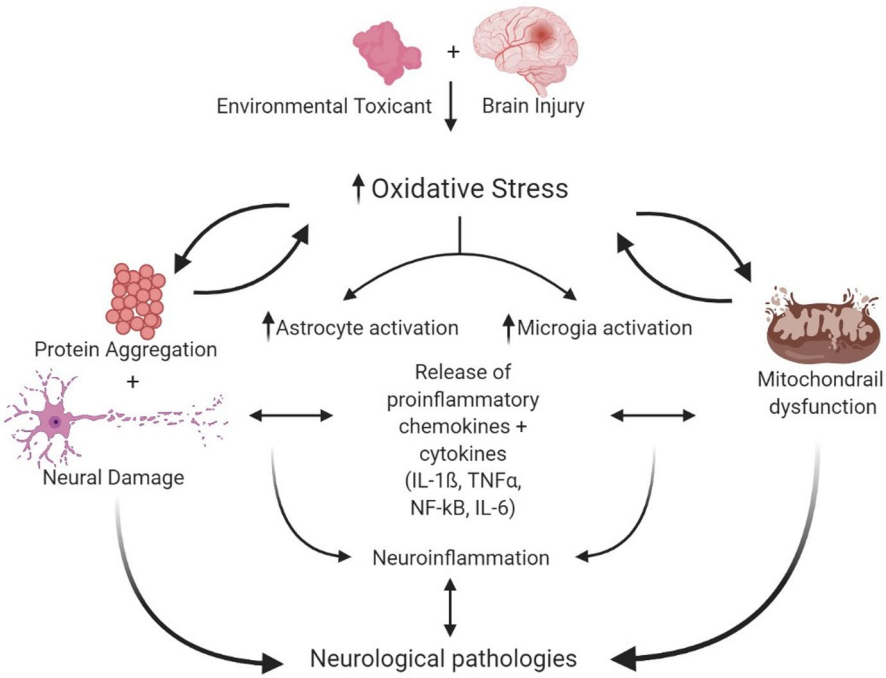


**FIGURE 4** Interlinking of oxidative stress and neuroinflammation in pathogenesis of neurological disorder

and molecular cascades including oxidative stress and inflammation (Guo et al., 2018). The protective impact of OL in ameliorating deltamethrin induced neural stress was exhibited by decrease in neural degeneration *via* regulating the immunohistochemical expression of Bcl-2/Bax proteins and reducing the histopathological alterations (Khalatbary et al., 2015). Later, Lee with his companions investigated the therapeutic potential of OL in a dose dependent manner against adverse impacts of single prolonged stress and post-traumatic stress model of rats. Stress induced memory impairments and declined levels of BDNF in hippocampal region of rat's brain were significantly reversed by OL administration. They proposed that this effect of OL was due to its anti-inflammatory properties as reduction in expression of pro-inflammatory cytokines was observed after OL administration (Lee et al., 2018). OL prevents inflammation of dopaminergic neurons *via* suppressing the pro-inflammatory response of activated microglia cells by inhibiting the mitochondrial fission (Impellizzeri et al., 2011; Park et al., 2017). Detailed mechanism of OL in protection of some major NDs is discussed in the subsequent sections and illustrated in Figure 5.

## 5.1 | Alzheimer's disease

Alzheimer's disease (AD), an age-related NDD, clinically can be identified as a rapid and progressive decline in memory and cognition (Swarbrick et al., 2019). AD is the most common neuro-degenerative disorder and leading cause of dementia affecting 40.2 per 1,000 persons over the age of 60, across the world (Fiest et al., 2016). As per World Health Organization (WHO), almost 74 and 114 million population will be affected from AD by 2030 and 2050 respectively (Borumandnia et al., 2020). Its etiology involves an array of complex risk factors such as age, alcohol intake, diabetes, smoking habits, CVDs, and other mental disorders in addition to other epigenetic and genetic risk factors (Crous-Bou et al., 2017; Irwin et al., 2016). Neuropathological indications of AD can be assessed both at macroscopic level, such as brain atrophy, and microscopic level, such as neurofibrillary tangles (NFTs) and amyloid plaques (Dá Mesquita et al., 2016; Panza et al., 2016). Amyloid plaques, the major indicator of AD, is the accumulation of amyloid-beta (Aβ) peptide (a 38- to 43-amino acid, originating from amyloid precursor protein) in the extracellular space of brain (Millan, 2017). Inside the plaques, Aβ are found in aggregated forms such as fibrils and oligomers (Doig et al., 2017). In body's basic physiological state, tau (a microtubule associated protein of mature neuron) binds to the tubulin to make microtubules stable (Iqbal et al., 2010). The microtubules exhibit multiple functions and among them, the important one in neurons is their involvement in formation of axons, dendrites, and the network connecting both (Valles et al., 2020). In AD, Tau presents a hyperphosphorylation signature, hence, is separated from the microtubules and is converted into paired helical filaments by undergoing self-aggregation. Resultantly, NFTs are formulated leading to dystrophic neuritis (Franzmeier et al., 2020; Tam et al., 2016). In addition to the formation of plaques and NFTs in AD, the other neuropathological hallmarks of this disease involve loss in synapses and neural cell death (Lista & Hampel, 2017).

Several in vivo studies have shown that OL is one of the most actively investigated biophenols that are potent amyloid inhibitors (Casamenti et al., 2015; Cordero et al., 2018). The major mechanism behind this action of OL is that it inhibits the formation of Aβ toxic aggregates and also causes a marked reduction in neuroinflammation

TABLE 2 Mechanisms of action of oleuropein in neural health promotion

| Neural disorder | Mechanism of action | Model of experiment | Source of Oleuropein and Dosage | References |
|---|---|---|---|---|
| Alzheimer's Disease | ↓ Aβ toxic aggregates | Mice | Olive leaf extract (50 mg/kg) | (Omar et al., 2019) |
| | ↓ Neuroinflammation and ROS/RNS production | In silico | Olive phenolic compounds | (Mubarakati et al., 2019) |
| | ↓ Production of Aβ toxic aggregates | Human SH-SY5Y neuroblastoma cells | Oleuropein (500 μM) | (Rigacci et al., 2011) |
| | ↓ Amylin peptide aggregation | Rat RIN−5F insulinoma cells | Oleuropein (1.8 μM) | (Rigacci et al., 2010) |
| | | Neuroblastoma SH-SY5Y cells. | Oleuropein Aglycone (20, 40, 100 and 200 μM) | (Leri et al., 2021) |
| | ↓ Tau fibrillation | P301L-Tau Protein | Oleuropein Aglycone (10 μM)<br>Oleuropein (10 μM)<br>Hydroxytyrosol (10 μM) | (Daccache et al., 2011) |
| | ↓ Aβ Plaque accumulation<br>↑ Autophagy | TgCRND8 mice | Olive leaf extract (50 mg/kg) | (Luccarini et al., 2016; Pantano et al., 2017) |
| Parkinson's Disease | ↓ αSyn toxicity | *Escherichia coli* BL21(DE3) | Oleuropein (0.3 mg/mL) | (Mohammad-Beigi et al., 2019) |
| | ↓ αSyn interaction with lipid membrane<br>↓ αSyn aggregation | Micelle-bound human a-synuclein monomer | Oleuropein Aglycone | (Borah et al., 2020) |
| | ↓ Mitochondrial fission<br>↓ Neuroinflammation | BV−2 murine microglial cells | Oleuropein (100 μM) | (Park et al., 2017) |
| | ↓ Cell damage, ROS/RNS<br>↑ Apoptosis | PC12 cells in vitro model | Olive leaf extract (400 and 600 μg/mL)<br>Oleuropein (20 and 25 μg/mL) | (Pasban-Aliabadi et al., 2013) |
| | ↓ Denaturation of DNA<br>↑ Antioxidant pool | PC12 cells | Oleuroein aglycone ($10^{-12}$ M) | (Achour et al., 2016) |
| | ↑ Locomotion<br>↓ Degeneration of dopaminergic neurons | *Caenorhabditis elegans* | Oleuropein (500 μg/mL) | (Brunetti et al., 2020) |
| Cerebral Stroke | ↓ Cerebral edema<br>↓ Plasma fibrinogen<br>↓ ACE activity<br>↑ SOD, GPx and Cat in brain | *Wistar* rats | Oleuropein (40 mg/kg BW) | (Mnafgui et al., 2021) |
| | ↓Bax/Bcl−2 (apoptotic/antiapoptotic protein) ratio<br>↓ Neuronal apoptosis<br>Suppression of caspase−3 activity | ICR Mice<br>*Sprague Dawley* rats | Oleuropein (100 mg/kg)<br>Oleuropein (100 mg/kg) | (Yu et al., 2016; Zhang et al., 2018) |
| | ↑ Neovascularization<br>↑ Endothelial recovery<br>Actvation of Nrf−2 pathway | Endothelial progenitor cells (EPCs) | Oleuropein (10 μM) | (Parzonko et al., 2013) |
| | ↑Structural and functional integrity of BBB | *Sprague Dawley* rats | Oleuropein (20, 40, 60 and 80 mg/kg) | (Shi et al., 2017) |
| Anxiety | Improved behavioral deficits<br>Regulates dopamine metabolism | *Wistar* rats | Olive oil (0.25 mL/kg) | (Perveen et al., 2013) |
| | ↑ Memory and locomotion<br>↑ 5-HT and DA | *Wistar* rats | Olive oil (0.1 & 0.25 mL/kg)<br>Olive oil (0.3 mL/day) | (Cheema et al., 2018; Perveen et al., 2016) |
| | ↑ BDNF<br>↓ pro-inflammatory cytokines | *Sprague Dawley* rats | Oleuropein (20, 50 & 70 mg/kg BW) | (Lee et al., 2018) |

(Continues)

TABLE 2 (Continued)

| Neural disorder | Mechanism of action | Model of experiment | Source of Oleuropein and Dosage | References |
|---|---|---|---|---|
| | ↑ Locomotion | *Sprague Dawley* rats | Oleuropein (100 mg/kg intraperitoneal) | (Lee et al., 2018) |
| Depression | ↓ Ca2+/calmodulin binding<br>↑ NE, DA, 5-HT | Mice<br>*Wistar* rats | Oleuropein (8, 16 & 32 mg/kg)<br>Extra Virgin olive oil (7.5 mg/kg BW) | (Badr et al., 2020; Bawazir, 2011) |
| | ↑ Locomotion | Mice | Oleuropein (10 mg/kg) | (Rabiei et al., 2018) |
| | ↑ BDNF and growth associated protein 43 | *Sprague Dawley* rats | Olive fruit juice | (Zhang, 2015) |
| Epilepsy | ↑ Siezure latency<br>↓ Oxidative stress and neuroinflammation | Mice<br>NMRI Mice | Oleuropein (20 mg/kg)<br>(**10**, 20 & 30 mg/kg) | (Asgharzadea et al., 2020; Rahimi et al., 2017) |
| | ↑ Cognition | *Wistar* rats | Oleuropein (10 & 20 mg/kg) | (Hosseini et al., 2019) |

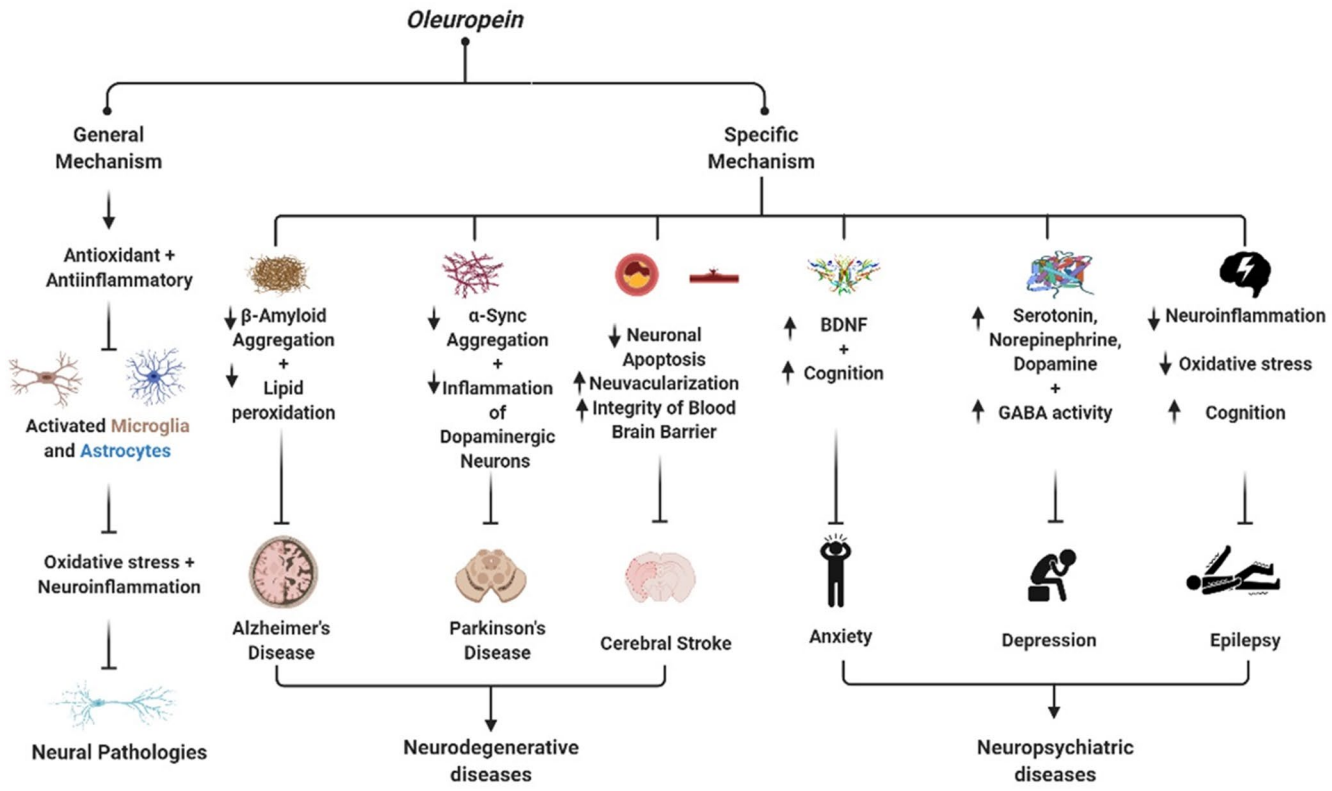


FIGURE 5 Schematic diagram for neural health promotion via oleuropein; alpha-synuclein (α-Sync); brain-derived neurotrophic factor (BDNF); gamma-aminobutyric acid (GABA)

and ROS/RNS production by mitochondria (Mubarakati et al., 2019; Omar et al., 2019). OLA has been found to interfere with the formulation of Aβ aggregates (Rigacci et al., 2011), amylin (Rigacci et al., 2010), and Tau (Daccache et al., 2011). Several studies conducted in this regard reported that OL disrupts the aggregation pathway followed by these amylin peptides by binding and inhibiting the action of aggregating molecules. This hinders the formulation of toxic species by converting those aggregates into nontoxic ones (Luccarini et al., 2014; Pantano et al., 2017). It has been observed that OLA could improve the clearance of Aβ by promoting autophagy. Autophagy is usually referred to as a process in which the undesired cellular compartments are engulfed by lysosomes for their degradation *via* hydrolytic enzymes (Brogi et al., 2020; Luccarini et al., 2016). Daccache and collaborators explored the preventive role of OL and its derivatives, that is, hydroxytyrosol and OLA against tau aggregation in AD. They reported that OLA inhibited the tau aggregation more actively than OL and hydroxytyrosol. The potential of OLA as a tau aggregate inhibitor (in both P301L and wild-type tau proteins)

was found similar to methylene blue (Reference tau inhibitor). They also observed that OLA inhibited the fibrillization of tau even at micromolar concentration due to the aldehyde group present in its structural skeleton (Daccache et al., 2011). Lately, another study demonstrated the inhibitory effects of olive leaf extract (OLE) [the richest source of oleuropein among different parts of olive tree] in Aβ aggregation in *Caenorhabditis elegans* (*C. elegans*). It was reported that OLE fed animals showed decreased deposition of Aβ plaque, reduced rate of Aβ toxic oligomers and paralysis, and an increased life expectancy in comparison to the OLE non-fed animals (Diomede et al., 2013). Besides this, several studies have reported the positive role of OL in improving cognitive anomalies in animal models. This improvement in cognition after OL intake was considered as its role in modulation of the autophagy pathways (Xu et al., 2018). To explore this hypothesis, the first effort was made by Grossi and his co-workers. They used the wild-type and TgCRND8 transgenic mice as models for AD and Aβ pathology (Grossi et al., 2013; Yang et al., 2011). In this study, they reported that diet of animals supplemented with 50 mg/kg OLA for 8 weeks caused a significant decrease in Aβ aggregates, astrocyte activation in AD relevant brain regions, Aβ toxicants mediated cognitive disabilities, and induction of autophagy (Grossi et al., 2013; Luccarini et al., 2015). In continuation of this study, Pantano and his co-workers explored the impact of different doses of OLA supplementation, that is, 0.5 mg/kg and 12.5 mg/kg in diet of TgCRND8 mice. They reported that later dose resulted in marked decrease in Aß plaques at cortex and lead to significant improvement in cognitive functions of mice (Pantano et al., 2017). Recently, Leri and coworkers investigated that OLA has potency for inhibition of amyloid assembly and mitigates the damaging effects of proinflammatory protein S100A9 in SH-SY5Y cells. OLA reduced the length of amyloid fibrils, its growth and overall amyloid load alongside enhanced the cell viability and provided protection against neurodegeneration (Leri et al., 2021).

## 5.2 | Parkinson's disease

Parkinson's disease (PD) is a progressive NDD associated with a decline in neural cells responsible for the production of DA in brain resulting in numerous complex symptoms (Bansode & Gacche, 2019). These symptoms do not appear until 60%–80% degradation and loss of dopaminergic neurons have already occurred (Emamzadeh & Surguchov, 2018). However, progression of PD is generally associated with movement disabilities such as shivering, muscle rigidity, bradykinesia (reduced control over voluntary movements), akinesia (temporary paralysis), and abnormal gait (Cechetto & Weishaupt, 2017; Jagadeesan et al., 2017). PD is the second most common NDD that affects about 1%–2% of older population with age above 65 (Liu et al., 2017). Number of PD affected people is expected to get doubled by the year 2030, imposing a great threat on economy of the societies having more elder population (Oliveira de Carvalho et al., 2018). Interestingly, amongst the PD cases, almost 90% are sporadic and are just not associated with genetics thus, suggesting that etiology of PD involves multiple factors (Ascherio & Schwarzschild, 2016). Alongside the aging, the leading risk factor of PD, several epidemiological studies have reported that excessive exposure to environmental pollutants such as metals, pesticides, and other toxic residues increases the risk of occurrence of PD (Agnihotri & Aruoma, 2020; Bellou et al., 2016).

A number of mechanisms have been found to be associated with the pathogenesis of PD that causes degradation and loss of dopaminergic neurons in substantia nigra pars compacta (Radhakrishnan & Goyal, 2018). Amongst them the most studied one is the accumulation of Lewy bodies. These Lewy bodies are the abnormal aggregates of proteins like ubiquitin and alpha-synuclein (αSyn) (Ha et al., 2012; Kouli et al., 2018). Formulation and accumulation of these αSyn aggregates is the major stimulation for the onset of degradation and dysfunction of dopaminergic neurons (Bellucci et al., 2012; Carboni & Lingor, 2015). Besides the accumulation of these aggregates, OS also plays a key role in the pathogenesis of PD (Collins et al., 2012). In particular, the nigral dopaminergic neurons are more prone to get adversely affected by OS as they actively perform under highly oxidant surroundings and reduced levels of antioxidants and increased iron content in nigral region (Chakraborty et al., 2013; Manoharan et al., 2016). OS is also an important stimulator for activation of microglia and astrocytes that subsequently enhances the ROS/RNS production (Qiao et al., 2016; Rizor et al., 2019). These activated microglia and astrocytes propagate and propel the feed forward cycle of neural cell death and also initiates the inflammation of dopaminergic neurons, hence, contributes in progression of PD (Gelders et al., 2018; Hirsch et al., 2012).

Several studies have reported the protective and preventive potential of OL in PD by inhibiting αSyn induced toxic impacts on dopaminergic neurons (Pasban-Aliabadi et al., 2013). Mohammad-Beigi and his companions reported in their study that OL and other structurally related compounds namely OLA, verbascoside, elenolic acid, dihydrooleuropein, 3-Hydroxytyrosol, rutin, and oleuropein glycosides reduces the toxicity of αSyn by directing αSyn oligomers into small αSyn monomers with less toxic effects (Mohammad-Beigi et al., 2019). Likewise, in the conformational study, Borah and his co-workers identified that OLA after binding with αSyn, interacts with its N-terminal region, making it unable to react with cellular lipid membranes, hence, prevents the formulation of toxic aggregates (Borah et al., 2020).

OL also prevents inflammation of dopaminergic neurons by suppressing the pro-inflammatory response of activated microglia cells by inhibiting mitochondrial fission thus, protects against microglial inflammation-mediated PD (Impellizzeri et al., 2012; Park et al., 2017). In an in vitro model of 6-hydroxydopamine (6-OHDA) induced PD, supplementation of different formulations of OLE with OL content as 20 and 25 μg/mL, in diet resulted in a marked decline in cell damage, OS, and apoptosis in adrenal pheochromocytoma (PC12) cells (Pasban-Aliabadi et al., 2013). Recently, another study supported this neuroprotective behavior of OL and reported that OL is effective in declining the 6-OHDA-induced

apoptosis in PC12 cells, even when administered in picomolar doses. They also found that OL causes a marked reduction in denaturation of DNA, mitochondrial production of ROS, and superoxide anion levels (Achour et al., 2016). In another study, OLA with its derivative hydroxytyrosol improved locomotory activities in rotenone induced PD model of *C. elegans* and also prevented degeneration of αSyn containing dopaminergic neurons (Brunetti et al., 2020).

OL being the major biophenol of olive leaves is mainly responsible for its beneficial health impacts (Nardi et al., 2017). Sarbishegi and collaborators observed that OLE is potent in protecting neural cells from the adverse effects of PD in male rats (Sarbishegi et al., 2018). They reported that OLE exhibits this protective role by decreasing lipid peroxidation, quenching excessive ROS/RNS and by increasing the activity of endogenous antioxidants in substantia nigra of midbrain thus prevents the neural cells from hallmarks of OS.

### 5.3 | Cerebral stroke

Cerebral stroke is a severe public health problem globally. Stroke is usually a sudden ND linked to part of or complete brain dysfunction. It occurs resultant to stopped blood supply to a particular region of brain preventing appropriate supply of oxygen and nutrients along with enhancing the cerebral necrosis (Radu et al., 2017). Strokes are of two major types: cerebral infarction/ischemic stroke accounting about 85% of all strokes, and hemorrhagic strokes which corresponds to 15% of cerebral strokes (Amarenco et al., 2013). OS has reflective effect behind the pathogenesis of strokes because of brain's high vulnerability to ROS induced alterations (Chen et al., 2011). A variety of pathways can induce the generation of free radicals after cerebral stroke among them two are the major ones. First, the decomposition of blood cells and the resultant products such as iron, heme and thrombin while second involves the activation of inflammatory cells, that is, neutrophils and microglia which promote ROS generation (Duan et al., 2016). Iron accumulation in brain resultant to hemorrhagic attack generates abundant ROS leading to neurotoxicity. These overlapped mechanisms result in neuronal loss and apoptosis, BBB disruption, gliosis, and permanent neurological deficits (Hu et al., 2016).

Oleuropein offers neuroprotection against cerebral stroke by increasing the superoxide dismutase (Bansode & Gacche, 2019) and catalase activity, clearing hydroxyl radicals and reducing the oxidative stress induced lipid peroxidation and its associated deteriorations (Mnafgui et al., 2021). In animal model of cerebral ischemic reperfusion (IRI), oleuropein had been observed to enhance the neurological and cognitive functions by reducing the neuronal apoptosis indicated by decreased Bax/Bcl-2 (apoptotic/antiapoptotic protein) ratio and also by suppressing the caspase-3 activity which was found higher in rats/mice after IRI (Yu et al., 2016; Zhang et al., 2018). Oleuropein not only prevents the occurrence of cerebral alterations after strokes but also participates in endothelial recovery of ischemic tissues. Parzonko with his companions (Parzonko et al., 2013) explored the protective effect of OL on endothelial progenitor cells (EPCs), which are responsible for the neovascularization of ischemic tissue and they explicated that protective mechanism of OL is not only due to its antioxidative property but the ability to activate the erythroid related nuclear factor 2 (Nrf-2) pathway which is the main antioxidant inducible regulator. The Nrf-2 activation plays a pivotal function in inflammation through the decrease in production of ROS and the macrophages regulating gene expression of antioxidant response elements (ARE). This activation of Nrf-2 not only prevents EPCs from further damage by OS but also increases the rate of endothelial recovery of injured walls of ischemic tissues. Later, OL was investigated for its preventive role in intracerebral hemorrhage (ICH) by Shi and his co-workers (Shi et al., 2017). They demonstrated that OL being the potent antioxidant attenuated ICH induced neurological deficits and also preserved the structural and functional integrity of BBB by alleviating the OS. Recently, it has also been observed that OL is effective in improving the post cerebral stroke cognitive anomalies. OL at the dose of 20, 50, and 100 mg/kg BW in PSD rat model showed spontaneous improvements in Morris water maize test, reduced the levels of choline acetyl transferase and acetyl choline while enhanced the phosphorylation of cAMP protein in a dose dependent manner (Gao et al., 2020).

### 5.4 | Huntington's disease, Amyotrophic lateral sclerosis, and Multiple sclerosis

Very few evidence links the beneficial role of OL in Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis compared with other NDs. Huntington's disease (HD) is destructive inherited and familial disease characterized by gradual loss of brain and muscular functioning. It occurs resultant to the genetically programmed neuronal degeneration causing loss of intellectual skills, uncontrolled movements, and emotional disturbances (Manoharan et al., 2016). Exact etiological factor behind occurrence of HD is unknown yet OS may play a major role (Sánchez-López et al., 2012). Several molecular events, for example, protein aggregation, mitochondrial dysfunction, and transcriptional dysregulation have been implicated with HD pathogenesis. Regarding OS, it is yet not clear either the OS initiates the occurrence of HD or itself occurs in consequence of the mentioned molecular events (Kumar & Ratan, 2016). Elevated OS usually plays a critical role in the pathogenesis of HD at later stages. Mitochondrial dysfunction and impaired electron transport chain are mainly involved in ROS mediated pathogenesis of HD (Paul & Snyder, 2019). Although in literature, no direct evidence regarding therapeutic potential of OL against HD can be found, its beneficial impact can be inferred from the positive role of extra virgin olive oil (Tasset et al., 2011) and olive leaf extract (Bigdeli, 2013) in ameliorating HD and its associated hallmarks. On the other hand,

oleuropein has been found effective in mitigating mitochondrial dysfunction (Achour et al., 2016), reversing transcriptional dysregulations (Messeha et al., 2020) and prevents cerebral structure and functional integrity from excessive oxidative stress (Asgharzadea et al., 2020) thus, can prevent the pathogenesis of HD.

Amyotrophic lateral sclerosis (ALS) is characterized by continuous loss of motor neurons in spinal cord and brain leading to paralysis or death (van Es et al., 2017). Almost 50% of ALS cases are associated with behavioral and cognitive impairments (Phukan et al., 2012). Traditionally, ALS has been classified as either the sporadic or familial form. One from the five familial cases, is found to be associated with mutation of antioxidant enzyme Cu/Zn-superoxide dismutase 1 (Renton et al., 2014). In a model of liver steatosis, OL preserved the SOD1 cytoplasmic localization (Santini et al., 2020). Like HD, direct role of OL in ALS is not clear but extra virgin olive oil being a source of OL had been found effective in improving motor coordination in transgenic mice model which overexpressed the human SOD1G93A variant (Oliván et al., 2014).

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of CNS, which diffuses neurodegeneration in entire brain and gives rise to lesions in gray and white matter (Lassmann, 2018). OS in response to excessive ROS generation mediates axonal damage and demyelination (Miller et al., 2013). OL is well-known for its antioxidant and anti-inflammatory properties. In this context, Giacometti and Grubic-Kezele (Giacometti & Grubić-Kezele, 2020) investigated the potential of olive leaf polyphenols against multiple sclerosis rat model. They concluded that OLE at the dose of 1,024 mg/kg containing OL as 45.96 mg/kg significantly reduced the oxidative stress in rats by decreasing MDA levels and upregulated the SOD1 and SOD2 genes alongside preserving the neuronal myelin integrity.

## 5.5 | Anxiety

Anxiety is an emotional disorder characterized by unpleasant mood accompanied by complaints, cautions, worries, and nervousness (Liu et al., 2019). Anxiety disorders as a group is the most prevalent mental health condition and sixth leading contributor of disability worldwide (Zimmermann et al., 2020). They contribute as leading cause of global disease burden. According to reports of "global burden of disease", about 275 million people are affected by either single or multiple anxiety disorders and approximately 42 million new cases are reported per year worldwide (Konnopka & König, 2020). Occurrence rate of anxiety disorders have been recorded to be two times higher in women than men (Davison et al., 2020). Anxiety disorders can be further classified into generalized anxiety disorder, obsessive compulsive disorder, panic disorders, post-traumatic stress disorder and phobic disorders depending upon the symptoms appearing and biological alterations (Coyle & Balu, 2018; Khan & Khan, 2017). For different kinds of anxiety disorders, the risk factors vary but some of general risk factors involved in occurrence and progression of anxiety disorders include genetics (Ressler, 2020), gender (Davison et al., 2020), chronic mental disorders (Riesel et al., 2019), separation from closed ones (Cao et al., 2020), adverse events in childhood (Lee et al., 2020), less education, impaired subjective health (Tamayo Martínez et al., 2016), stressful life events (Kingsbury et al., 2020), physical limitations in daily activities (Scott et al., 2016) and neuroticism (Paulus et al., 2016).

Pathophysiology of anxiety disorders is multifaceted involving complex interaction of environmental influences, biological factors, and psychological mechanisms (Schiele & Domschke, 2018). These disorders are usually characterized by multiple neural disruptions such as neuroanatomical, neurotransmitter, and neuroendocrine alterations (Bandelow et al., 2017; Martin et al., 2009). The neural systems involving regulation of three major monoamine neurotransmitters such as serotonin (5-HT) (Lawther et al., 2020), DA (Bandelow et al., 2016), and norepinephrine (NE) (Purvis et al., 2018) are the most extensively studied neural systems associated with progression of anxiety. These studies collectively summarizes that hyperactivation of noradrenergic system and under activation of serotonergic system are basically involved in pathology of anxiety (Montoya et al., 2016). However, anxiety related anomalies do not occur just due to deficiency of one or more monoamines but also interlinks the complete network governed by these neurotransmitters, for example, regulation of multiple feedback mechanisms and maintenance of complex receptor structures (Adwas et al., 2019).

Disruptions of neuropeptide Y (Soodan & Arya, 2015), gamma-aminobutyric acid (GABA) system (Li et al., 2017), and Amygdala hyperactivity (Lee et al., 2011) has also been considered as an important neural characteristic of anxiety disorders. These systems are regulated by different pathways of neuronal circuits and in return also regulate other pathways in various regions of CNS. Hence, disruption in these systems leads to physiological dysregulations in neuronal circuits and ultimately emotional disturbances (Bystritsky et al., 2013; Craske & Stein, 2016). Like many other diseases, oxidative stress is the major causative factor behind the pathogenesis of anxiety disorders. High levels of ROS generation and decreased antioxidant pool have also been observed to be associated with high anxiety levels in humans (Grases et al., 2014).

Anxiolytic potential of olive fruits (Zhang, 2015), olive oil (Cheema et al., 2018), leaves (Sarfaraz, 2019), and its bioactive components has been studied so far. Oleuropein and its derivatives being the major bioactive components of olives contribute to its anxiolytic potential. In a study, oral administration of OLE caused significant decrease in anxiety-like behaviors, in animal model of 6-OHDA induced PD (Hosseini & Hajizadeh, 2015). Anxiolytic effects of olive oil were reported in a research investigation where repeated administration of olive oil for 4 weeks regulated the dopamine metabolism and improved the behavioral deficits in stressed rat model (Perveen et al., 2013). Later, in continuation to this study, they observed that pretreatment with olive oil reduced depression and anxiety related behaviors, improved long-term memory and locomotion in forced swim test (FST), open field test and light/dark reaction tests in restraint mice (Perveen et al., 2016). In another study, olive oil administration of 0.1 mL/kg bodyweight to mice, for long duration markedly reduced anxiety and improved motor activity in elevated plus maze

(EPM) test and OFT along with an increase in 5-HT and DA levels (Cheema et al., 2018). Not many studies have explored the direct anxiolytic potential of extracted OL. The researchers explored the therapeutic potential of different doses of OL such as 20, 50, and 100 mg/kg for 2 weeks in single prolonged stress and post-traumatic stress model of rats. Stress induced memory deficits and reduction of brain-derived neurotrophic factor in hippocampus region of rat's brain were significantly reversed by 100 mg OL. They proposed that this effect of OL was due to its anti-inflammatory properties as reduction in expression of pro-inflammatory cytokines was found after OL administration (Lee et al., 2018). Later, reported the anxiolytic potential of OL in mice with post-traumatic stress disorder. Among the three doses as 10, 50, and 70 mg/kg, they found the latter dose of OL most effective in increasing the efficiency of mice in behavioral tests, that is, open arms visits and EPM test (Lee et al., 2018). Lately, olive leaf tea, due to high presence of OL, was found to cause a significant reduction in stress and anxiety related symptoms in mice model (Sarfaraz, 2019). OL administration reduced the anxiety and mobility complications after swimming in 6-OHDA induced neural affected rat model (Jafari et al., 2020).

### 5.6 | Depression

Depression is one of the most prevalent mental health anomalies among the general population which can be characterized by loss of pleasure and interest in normal activities, poor concentration, tiredness and fatigue, disturbed appetite and sleep, sadness, feeling of having low self-worth and being in guilt all the time (Fitzpatrick et al., 2017; Fried et al., 2016). Depression is categorized into three types namely, bipolar disorder, persistent depressive disorder, and major depression. WHO reports that almost 350 million people from different age groups have depression and over 800,000 people succumb to death yearly from suicide due to depression making it the leading cause of disability worldwide (Carlton et al., 2020; LeMoult & Gotlib, 2019). Suicide can be considered as the fatal hallmark of severe depression (Brådvik, 2018) and increases the risk of mortality (Gilman et al., 2017). Depression affects the quality of life more adversely in later years of life (Sivertsen et al., 2015). Globally 14% of people of 55 years and above age suffer from depression and among them 2% suffer from major depression (Kok & Reynolds, 2017). Depression increases the risk of several other non-communicable diseases such as diabetes, obesity, hypertension, cognitive impairment, frailty, and mortality (Buigues et al., 2015; Penninx, 2017).

Etiology of depression does not depend upon a single factor. A range of factors are involved in the pathogenesis of depression including biological, hormonal, environmental, socio-economical, socio-cultural, and genetic factors (Nagy et al., 2018; Schaakxs et al., 2017). From all the depressive cases, approximately one-third involve inheritance while the remaining two-third occur in response to above mentioned causative factors other than genetics (Saveanu & Nemeroff, 2012). The biological factors and mechanisms possibly involved in pathophysiology of depression may include neural plasticity, endogenous toxicant attacks leading to altered brain activities and decreased volume of frontal cortex & hippocampus. (Belleau et al., 2019; Verduijn et al., 2015). The major causative factor behind these structural and functional alterations in brain during depression is OS (Black et al., 2015). Large group of studies has reported that increased ROS/RNS and weak antioxidant defense pool in brain is mainly responsible for structural damages in brain and this hypothesis behind the OS induced depression is generally known as "oxidative stress hypothesis of depressive disorders" (Bhatt et al., 2020; Muraro et al., 2019). Besides OS, the up-regulation of inflammation is also involved in progression of depressive disorder by declining the concentration of monoamines, such as DA, 5-HT, and NE (Liu et al., 2018; Miller & Raison, 2016), and enhancing the catabolism of tryptophan which releases toxic compounds in brain (Dmitrzak-Weglarz & Reszka, 2017; Jenkins et al., 2016). Low levels of cerebral brain-derived neurotrophic factor (BDNF) and GABA is also one of the important pathophysiological mechanisms of depression (Bembnowska & Jośko-Ochojska, 2015; Nandam et al., 2020).

Olive oil is an important source of mono-unsaturated fat and a prime component of the MD (Tosti et al., 2018). The beneficial health effects of virgin olive oil are due to both its high content of mono-unsaturated fatty acids and its high content of anti-oxidative substances including oleuropein, tyrosol, oleocanthal, oleacin, and hydroxytyrosol (Farooqui & Farooqui, 2018; Kanakis et al., 2013; Karabag-Coban et al., 2017). MD has been well-reported for its antidepressant effects (López-Olivares et al., 2020; Sanchez-Villegas et al., 2019). Accordingly, the impact of olive oil on NE, DA, 5-HT, and GABA concentrations in different brain regions of rats was evaluated. The histological alterations in liver and kidney tissues were also observed after chronic administration of 7.5 mg/kg olive oil. Results of study showed that olive oil administration significantly increased the NE, DA, 5-HT, and GABA content in various brain regions (cerebral cortex, brain stem, cerebellum, hypothalamus, hippocampus and striatum) of rats. Olive oil inhibits the binding of $Ca^{2+}$/calmodulin that plays a key role in release of these neurotransmitters in different regions of CNS (Bawazir, 2011). Hryhorczuk with his collaborators found that intake of olive oil enriched diet (50% of total kcal/day) for 3 months protected the brain's integrity in rodents therefore, diet rich in olive oil can reduce the progression of depression-like behaviors (Hryhorczuk et al., 2016). Significant improvement in depression-like behaviors was also observed in patients of major depressive disorders after introducing MD to their normal routines (Opie et al., 2018).

Very few studies have been conducted to explore the direct impact of extracted OL against depression. A group of scientists explored the antidepressant effects of different doses (5, 10, and 20 mg/kg) of OL against reserpine induced depression in rats (Rabiei et al., 2018). They concluded that OL although possesses a prophylactic role in preventing occurrence of depression at all dose levels, but best results were found at 20 mg/kg. Pretreatment with OL injected intraperitoneally increased the mobility of rats in FST. OL also effectively prevents the downregulation of neural proteins including BDNF and growth associated protein 43 (Zheng et al., 2015). In

a recent study, Badr and his co-workers found that OL effectively ameliorates the OS causing agents like corticosterone induced depressive-like behaviors. They observed that OL at the doses of 16 and 32 mg/kg reversed the corticosterone induced decrease in biogenic amines, that is, 5-HT, DA, and NE. Supplementation of OL also increased immobility of rats in TST, OFT, and FST (Badr et al., 2020). Numerous other studies have reported that OL is potent in protecting the cognitive disorders due to its antioxidant and anti-inflammatory activities (Asgharzadea et al., 2020; Qabaha et al., 2018).

### 5.7 | Epilepsy

Epilepsy being the commonest brain anomaly affects more than 70 million people globally. It is usually characterized by a long-time predisposition generating sudden epileptic seizures and is associated with several cognitive, psychosocial, and neurobiological consequences (Thijs et al., 2019). Causative factors behind epilepsy are divided into six categories: infectious, structural, genetic, immune, metabolic, and unknown (Scheffer et al., 2017). In epilepsy, a wide spectrum of pathological changes in neurons and axonal sprouting, inflammation and gliosis occurs during the seizure-free latent period following epileptogenesis and may last for several years (Asgharzade et al., 2020). Brain OS and neuroinflammation with increased production of proinflammatory cytokines and activation of microglia have been implicated behind pathogenesis of epilepsy (Ho et al., 2015). Oleuropein increased the seizure latency in mice model of Pentylenetetrazole (PTZ) induced epilepsy. Anticonvulsant effects of OL are most likely to occur by modulating the GABAergic system and its anti-inflammatory and antioxidant properties (Asgharzadea et al., 2020; Rahimi et al., 2017). Epilepsy is commonly associated with cognitive impairments and memory loss. Hosseini with his companions (Hosseini et al., 2019) explored the positive impact of OL in improving the memory loss of PTZ induced epileptic rat model. The explicated that OL at the dose of 10 and 20 mg/kg BW of rats increased rat's periodic behavior in maze-Y test and also enhanced passive avoidance memory.

## 6 | CONCLUSIONS

The beneficial effects of OL in NDs have been investigated deliberately and are associated with different cellular pathways. The major activity in this regard has been found due to the direct antioxidant and anti-inflammatory properties of OL. OL is potent in normalizing the activities of reactive microglia cells and astrocytes. Concerning the NDDs, OL plays protective role in AD, PD, and cerebral stroke by interfering with the aggregation of beta amyloids, amylin, tau, αSyn and ubiquitin proteins, reduces neuronal apoptosis and activates several antioxidant defense pathways including Nrf-2 pathway. However, less evidence is available regarding direct influence of OL in HD, MS, and ALS. Among neuropsychiatric disorders the most common disorders include anxiety, depression, and epilepsy. The therapeutic potential of OL against these psychological disorders has been found to be associated with its role in regulation of neurotransmitters (5-HT, DA, and NE), growth factors (GABA and BDNF), cognitive behaviors, and neuronal endothelial recovery. Conclusively, OL has great potential in counteracting the multifactorial pathologies of NDs. In routine, the inclusion of olive fruit and its oil in diet can improve the overall health of an individual and prevent or delay the onset of different diseases. However, large scale clinical and observational studies are necessitated to observe more insight about the neuroprotective actions of oleuropein. Furthermore, extensive investigations are needed to elucidate the preventive/protective role of OL in NDs including Huntington's diseases, multiple and amyotrophic lateral sclerosis, schizophrenia, and bipolar disorders. On the other hand, the neuroprotective actions of oleuropein may result synergistic to other olive polyphenols such as hydroxytyrosol, oleuropein aglycone, and elenolic acid. Hence, epidemiological studies should be conducted for confirmatory impact of either single or mixture of polyphenols in neuroprotection.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## AUTHOR CONTRIBUTION

**MS Butt:** Data curation; Resources; Supervision; Validation. **Urwa Tariq:** Data curation; Investigation; Visualization; Writing-original draft. **Iahtisham Ul Haq:** Conceptualization; Software; Visualization; Writing-original draft; Writing-review & editing. **Ambreen Naz:** Validation; Writing-review & editing. **Muhammad Rizwan:** Investigation; Writing-review & editing.

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**How to cite this article:** Butt, M. S., Tariq, U., Iahtisham-Ul-Haq, Naz, A., & Rizwan, M. (2021). Neuroprotective effects of oleuropein: Recent developments and contemporary research. *Journal of Food Biochemistry*, 00, e13967. https://doi.org/10.1111/jfbc.13967