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Neuropharmacological insights of African oil palm leaf through experimental assessment in rodent behavioral model and computer-aided mechanism

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ABSTRACT

The present study aimed to investigate the neuropharmacological potential of methanol extract of African oil palm or *Elaeis guineensis* (MEEG) in Swiss albino mice and through computer-aided model. To identify the secondary metabolites in MEEG, standard phytochemical and GC-MS analyses were performed. Antidepressant activity of MEEG was assessed by forced swimming test (FST) and tail suspension test (TST) in Swiss albino mice. Besides, elevated plus maze (EPM), hole board test (HBT) and light-dark test (LDT) were used to investigate anxiolytic activities while for assessing sleeping disorder, open field test (OFT) and hole cross test (HCT) were performed. Additionally, computational and ADME/T analysis was performed using Schrödinger Maestro (v11.1) software and admetSAR online tools. The qualitative and quantitative phytochemical analyses revealed the existence of several secondary metabolites in MEEG. The oral administration of MEEG significantly reduced the immobility time in FST and TST. Similarly, promising dose-dependent anxiolytic effects were noted in all corresponding tests as compared to the control. As well, a significant decrease in the locomotion activities in experimental animals was noted during the OFT and HCT analysis. In case of computational and toxicological studies, most of the selected compounds were found considerably safe. Among the safe compounds, squalene showed promising binding energy for the antidepressant and anxiolytic activities, while stearic acid showed promising effects for the locomotion activity. The outcomes of the investigation recommend MEEG as a potential source of therapeutic candidate for the management of neurological disorders.

1. Introduction

Neurological disorders are becoming increasingly prevalent and, in turn, exerting significant personal and socioeconomic burdens. Depression is a state of neurological and mental disorder serving as the key basis of disability and self-destruction. Hypothesis based on the physiological basis of depression suggests that depression stems from the deficiency of monoamine neurotransmitters such as 5-hydroxy tryptamine (5-HT), noradrenaline (NE) and dopamine (DA). On the other hand, there is research-based evidence that reactive oxygen species (ROS) are elevated in the plasma and brain of patients with extreme depression, signifying that oxidative stress may be a potential etiology of depression (Eren et al., 2007; Sarandol et al., 2007). Nonetheless, antidepressants are widely available for the treatment of depression even though they are often with limited success and the side effects of such medications are usual and can be severe in some cases; therefore, more effective antidepressants with fewer side effects is the need of time (Schweitzer et al., 2009). Considerably, anxiety is the most common psychological condition and the pervasiveness of anxiety in the lifespan

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List of abbreviations

ADME	absorption, Distribution, Metabolism, Excretion
BDH	British Drug House
BW	Body weight
CNS	Central nervous system
DA	Dopamine
DW	Distilled water
EPM	Elevated plus maze
FST	forced swimming test
GC-MS	Gas chromatography-mass spectroscopy
HBT	Hole board test
HCT	Hole cross test
ICDDRB	International Centre for Diarrheal Disease Research Bangladesh
i.p.	intraperitoneal
LDT	Light-dark test
MEEG	Methanol extract of *Elaeis guineensis* jacq
NE	Norepinephrine
OECD	Organization for Economic Co-operation and Development
OFT	Open field test
PDB	Protein data bank
PO	Per orally
QSAR	Quantitative Structure Activity Relationship
RBC	Red Blood Cell
ROS	Reactive oxygen species
SEM	Standard error mean
SMC	Social Marketing Company
TST	Tail suspension test
WHO	World health organization
5-HT1B	5-hydroxytryptamine receptor 1 B

ranged from 10% to 25%. More than 30% of adults have had a sleeping problem, which is considered the second most common sign of mental suffering (Begum et al., 2020). According to WHO, diazepam is the essential medicine for anxiety and sleep disturbances with the most reconcilable record for both potency and health. Notwithstanding its excellent efficacy, diazepam has serious adverse effects, including violent behavior, hostility, and disinhibition due to paradoxical excitation. Hypotension and respiratory depression can occasionally occur at high doses, particularly in parenteral doses. Henceforth, new prescription drugs with fewer side effects and higher potency are most anticipated to control insomnia and anxiety.

Natural products play significant roles in preventing diseases and improving the health of humans and animals. Medicinal plant-based natural products are now offering a promising substitute for treating mental and neurodegenerative disorders. Numerous phytoconstituents of the medicinal herbs, fruits, or vegetables may potentially subdue neurodegeneration and improve the memory and cognitive function of the brain (Rehman et al., 2019). African oil palm (*Elaeis guineensis* Jacq.) is one of the most foremost medicinal plants in the life of traditional West African societies. Various parts of this plant are being used by the traditional healers for the management of several disorders. Specifically, the fresh sap is used as a laxative and partially fermented palm wine is offered to nursing mothers to enhance lactation. Fruit bush is used in the preparation of soaps used to treat skin infections and root decoction is utilized to treat cerebral pains in Nigeria. Also, spray roots are used to treat gonorrhea, menorrhagia, and bronchitis (Sasidharan et al., 2010). In addition, the various parts of the plant are being used as a remedy for headache, migraine and mental disorders (da Silveira Agostini-Costa, 2018; Olusola & Oyeleke, 2015). The leaves of this plant have been reported to be used for the treatment of various neurodegenerative disorders (Sonibare & Ayoola, 2015). However, most of these ethnopharmacological claims are yet to be validated with proper scientific approach. Not many research studies to date have been found to support the neuropharmacological potentials of the leaves of African oil palm. Therefore, the present study aimed to provide the scientific basis and investigate the possible neuropharmacological properties of methanol extract of African oil palm leaves in rodent behavioral models. Subsequent chemical characterization and computational model has been added to comprehensively justify the results found in the rodent model.

2. Materials and methods

2.1. Drugs and chemicals

Methanol was procured from Sigma Chemical Company, St. Louis, MO, USA. Standard drugs *i.e.*, fluoxetine HCl and diazepam were purchased from Square Pharmaceuticals Ltd., Bangladesh. Normal saline (0.9% NaCl) from Social Marketing Company Ltd., Bangladesh and Tween 80 was procured from BDH Chemicals (Leicestershire, UK). MEEG was dissolved in saline with 1% Tween 80, whereas all the other drugs were dissolved in isotonic saline solution (NaCl 0.9%) prior to use. All the chemicals and reagents used in this study were of analytical grade.

2.2. Extract preparation

Fresh leaves of African oil palm (*E. guineensis* Jacq.) were collected from south-eastern Chittagong, Bangladesh during winter season of 2019. The identification of the plant had been confirmed by a taxonomist and a voucher specimen (Accession no. DPH816) has been deposited in the Department of Pharmacy, International Islamic University Chittagong for future reference. Collected leaves were then shade-dried at ambient temperature (25 ± 1 °C), powdered by using a mechanical grinder to a mesh size of 1 mm (Sieve No. 10/44). The powder material (1200 g) was soaked in methanol at the ratio of 1:6 (plant sample: solvent) at 25 ± 2 °C for 72 h (Haque et al., 2019; Rashid Chowdhury et al., 2020). The supernatant was filtered by Whatman #1 filter paper (Whatman plc, Maidstone, UK) and then concentrated using a rotary evaporator (Buchi, R114, Switzerland) under reduced pressure to obtain 126 g gummy crude methanol extract. The crude extract was stored at 4 °C for subsequent investigation.

2.3. Experimental animals

Male Swiss albino mice (aged 5–6 weeks, weighing 22–30 g) were obtained from the animal research division of the International Centre for Diarrheal Disease and Research, Bangladesh (ICDDR, B). The animals were maintained under standard laboratory conditions (temperature: 23 ± 2 °C; relative humidity: 55–60%) with a 12 h natural day-night cycle and had free access to water and commercial pellet diet *ad libitum*. The experimental animals were acclimatized to the holding room for 48 h before conducting the experiment (Goni et al., 2020). The experimental protocol was investigated and approved by the Ethics Committee of the Department of Pharmacy, International Islamic University Chittagong.

2.4. Acute toxicity test

The acute toxicity test was performed by following the OECD guidelines and previously described protocol (Al-Araby et al., 2020; OECD, 2002). Swiss albino mice were divided into seven groups (control and tests), each group consisting of six mice (n = 6). The test groups

were orally administered with MEEG at the dose of 200–4000 mg/kg while the control group received 1% Tween 80 in distilled water. Afterward, mice were provided a commercial pellet diet and freshwater *ad libitum*. The animals were observed for possible behavioral changes, any allergic reactions and mortality for the next 72 h and up to the next 14 days.

2.5. Study plan

Experimental animals were separated into four groups (control, standard, and two test groups) each consisting of 6 mice. The standard drug diazepam (1 mg/kg, b.w, i.p.) was used in elevated plus maze (EPM) test, hole-board test (HBT), open field test (OFT), hole cross test (HCT) and light-dark test (LDT) whereas fluoxetine HCl (20 mg/kg, b.w, p.o.) was used for tail suspension test (TST) and forced swimming test (FST). The test groups were administered orally MEEG at doses of 200 and 400 (mg/kg, b.w, p.o.), respectively, whereas the control group received vehicle (1% Tween 80 in distilled water, 10 mL/kg, p.o.). The reference drugs (diazepam and fluoxetine HCl) were primarily administered at 15 min and MEEG (200 and 400 mg/kg) or vehicle at 30 min prior to the experiments.

2.6. Standard phytochemical analysis

Qualitative phytochemical analysis of MEEG was evaluated by following previously described method (Khan et al., 2020) to identify the presence of secondary metabolites, particularly flavonoids, alkaloids, quinones, glycosides, steroids, tannins, phenols, and terpenoids.

2.7. Gas chromatography-mass spectrometry (GC-MS) analysis

GC-MS analysis of MEEG was conducted using the GCMS-QP2010 SE (Shimadzu Corporation, Kyoto, Japan) equipped with a column and coupled to a mass selective detector. For GC-MS detection, an electron-ionizing mechanism was used with its ionizing energy of 70 eV. Afterward, 99.99% pure carrier gas (He) and then 1 μL of the sample was injected. The oven temperature was set primarily at 50 °C and increased up to 100 °C, pressure was kept at (89.7 kPa) with its flow rate of 12.2 mL/min, column flow rate was set as 1.20 mL/min, linear velocity was 40.8 cm/s and ejected flow was 5.0 mL/min, respectively. Mass spectroscopy was set with a scanning align of (40–350 amu) and the ionization approach was electron ionization. Mass detector was set with the time ranging from 5 to 50 min (starting/end). Interpretation on spectrum GC-MS was compared with the national institute of standards and technology (NIST) GC-MS library database (version 08-S).

2.8. Antidepressant activity

2.8.1. Forced swimming test (FST)

The FST method was used to perform the evaluation of the antidepressant activity of MEEG in Swiss albino mice (Cryan et al., 2005; Khan et al., 2020). The experimental animals were placed separately in an open cylindrical container (10 cm height × 25 cm diameter) containing 19 cm (depth) of water at 25 ± 1 °C. The test was recorded using a video camera (Geo Vision GV800-16, GeoVision Inc., Taiwan) for 6 min while the last 4 min was considered for the total duration of immobility followed by adapting for the first 2 min. Mice of all groups (control, standard, and two test groups) were treated as per the study plan mentioned in Section 2.5. Mice were recorded as immobile when they stayed floating motionless, except those movements needed to keep their head above the water. The decrease in immobility time during the test was considered as antidepressant-like activity.

2.8.2. Tail suspension test (TST)

The TST is considerably a simple and most consistent method to determine the antidepressant activity. The total duration of immobility induced by TST was measured according to the earlier described method (Khan et al., 2020; Machado et al., 2008). Mice were suspended 50 cm above the floor by cohesive tape assigning approximately 1 cm from the tip of the tail. The test was recorded using a video camera (Geo Vision GV800-16, GeoVision Inc., Taiwan) for 6 min while the last 4 min was considered for the total duration of immobility followed by adapting for the first 2 min. Mice of all groups (control, standard, and two test groups) were treated as per the study plan mentioned in Section 2.5.

2.9. Anxiolytic activity

2.9.1. Elevated plus maze (EPM) test

The EPM is comprised of two open arms with the area of 35 cm × 5 cm and two closed arms with the area of 35 cm × 5 cm × 20 cm. The arms were jointed with a centre square of 5 cm × 5 cm. The apparatus was raised to a height of 25 cm from the floor and two arms merged in a central platform denoted by the symbol of plus sign. The experimental mice were placed on the centre of the EPM apparatus after the 30 min administration of the dose with its head facing the open arms. The behavioral effects of the mouse were observed using a video camera (Geo Vision GV800-16, GeoVision Inc., Taiwan) for 5 min of the 6 min period where the first 1 min was considered as an initial adjustment time with two different kinds of parameter (time spent in open arms, the number of the entry in the open arms) (Abreu et al., 2018; Goni et al., 2020). Mice of all groups (control, standard, and two test groups) were treated as per the study plan mentioned in Section 2.5.

2.9.2. Hole board test (HBT)

The hole board apparatus was composed of a grid patterned box made of wood (20 cm × 40 cm) with sixteen equidistant holes, elevated to 15 cm in height above the floor. The distance of the centre of one hole to another was 10 cm and the floor of the hole board was positioned 25 cm above the ground. Thirty minutes after administering test doses, the experimental animals were placed in the box's centre and allowed for free movement (Abreu et al., 2018; Goni et al., 2020). Finally, head dipping numbers through the holes by mice were recorded using a video camera (Geo Vision GV800-16, GeoVision Inc., Taiwan) for 5 min of the 6 min period wherein the first 1 min was for adjustment. The head dipping of the experimental animals was counted if both eyes disappeared into the hole. Mice of all groups (control, standard, and two test groups) were treated as per the study plan mentioned in Section 2.5.

2.9.3. Light-dark box test (LDT)

The light-dark test can be advantageous for predicting the condition of anxiolytic or anxiogenic properties in experimental mice. Transitions were stated to be an activity-exploration index due to time habituations, and the time spent in each compartment was a reflection of aversion (Shahed-Al-Mahmud & Lina, 2017). It consists entirely of an automated observer-monitored panel. The light-dark box is an open-topped rectangular box with a area of 46 cm × 27 cm × 30 cm and divided into two areas, small (18 cm × 27 cm) and a large (27 cm × 27 cm) area with an opening door (7.5 cm × 7.5 cm) which is positioned at the centre of the partition at the floor level. The two compartments were painted with two colors: black (dark surroundings) and white and brightly illuminated by an 80 W light source. The light was placed in the centre of the white compartment. The time spent in the light and dark compartment was recorded using a video camera (Geo Vision GV800-16, GeoVision Inc., Taiwan) for 5 min of the 6 min period, while the first min was for initial adjustment for the experiment. Throughout the study, the environment was kept dark (Bourin & Hascoët, 2003). The dosing schedule for each group of animals was described in Section 2.5.

2.10. Sedative activity

2.10.1. Open field test (OFT)

The open field apparatus was made of plywood consisting of 60 cm

× 60 cm × 60 cm white square box with 25 squares of equal dimensions (5 cm × 5 cm). The apparatus was used to study the locomotive and emotionally random activity in Swiss albino mice. The area of the open field was divided into two colored (black and white) square blocks. The experiment was performed in a silent room in the lighting condition. Mice were kept in the middle of the floor, and the number of square blocks crossed by each mouse was recorded using a video camera (Geo Vision GV800-16, GeoVision Inc., Taiwan) and after that calculated for 3 min on 0, 30, 60, 90 and 120 min intervals (Consolini et al., 2006; Herrera-Ruiz et al., 2006). Mice of all groups (control, standard, and two test groups) were treated as per the study plan mentioned in Section 2.5.

2.10.2. Hole cross test (HCT)

The hole cross cage was made up of stainless steel with an area of 30 cm × 20 cm × 14 cm. A partition was placed in the middle of the cage, having a hole of 3 cm in diameter with a height of 7.5 cm. The animals were placed into the centre of either side of the hole cross apparatus, and the number of holes crossed from one chamber to another was recorded using a video camera (Geo Vision GV800-16, GeoVision Inc., Taiwan) and then calculated for 3 min on 0, 30, 60, 90 and 120 min intervals (Hossain et al., 2016). The dosing schedule for each group of animals was described in Section 2.5.

2.11. In silico molecular docking

2.11.1. Ligand and protein preparation

Eight lead molecules of MEEG were selected from GC-MS data based on the prediction of activity spectra for components, namely squalene, lauric acid, phytol, palmitic acid, stearic acid, 9-octadecenoic acid, geranylgeraniol and glucal were retrieved from PubChem database as SDF format http://www.pubchem.mcbi.nlm.nih.gov. The 2D structures of the compounds were converted into 3D molecular structures for minimizing energy by using LigPrep module of Schrödinger suite 2017. The 3D structures of identified target proteins were retrieved from protein data bank as PDB format namely for anxiolytic (potassium channel; PDB ID: 4UUJ), antidepressant (5-HT1B-BRIL; PDB ID: 4IAQ) and sedative effects (human gamma-aminobutyric acid receptor; PDB ID: 4COF). Afterward, the protein files were prepared by removing all water molecules and hetero groups except metals (if any). Finally, Glide of Schrödinger Maestro (v11.1) was used for arrangement and refined using protein preparation wizard.

2.11.2. Grid generation and molecular docking analysis

The molecular docking study was performed to determine the possible mechanism of action of selected major compounds of MEEG against specific receptors for antidepressant, anxiolytic and sedative activity. Docking analysis between receptors and ligands were performed using Schrödinger Maestro (v11.1) as described previously (Khan et al., 2020). Afterward, ligand geometries were compared with those of a reference (standard drug) ligand and taking the scores with the different enzymes in XP mode, keeping all docking parameters as default. Each docking was run for three times in order to maintain accuracy. The best-docked poses with the lowest binding score were recorded for every ligand. Finally, resulted docked particles were saved as.sdf format for visualizing the docking picture using the Discovery Studio 3.0 Visualizer programming.

2.12. In silico ADME/T analysis

The Lipinski's rules of five (RO5) is simply used to determine the drug-like properties of a compound. According to the Lipinski's rules, a compound might have drug-likeness if it fulfils the major properties *i.e.*, molecular weight, H-bond acceptor, H-bond donor, TSPA and Log P value with specific ranges, but it should not violate more than one rule. Additionally, the ADME properties of the selected compounds were investigated by using QikProp tools of Schrödinger suite 2017 (Khan et al., 2020). In addition, the toxicological properties (ames and carcinogens) of these compounds were predicted using the admetSAR online tool (http://lmmd.ecust.edu.cn/admetsar2/) and to investigate whether the compound gave any adverse health effects or not.

2.13. Ethical considerations

All the experiments using animals were conducted in the Department of Pharmacy, International Islamic University Chittagong, Bangladesh. 'Principles of the Laboratory Animal Care' (NIH publication no. 85–23, revised 1985) and 'National Animal Care Laws' were strictly followed during handling of these animals for the study. The study protocol was approved by the Department of Pharmacy, International Islamic University Chittagong, Bangladesh (Ref.: IIUC/PHARM-AEC-74/10–19).

2.14. Statistical analysis

One-way analysis of variance (ANOVA) followed by Dunnett's test for antidepressant and anxiolytic activities and two-way ANOVA followed by Bonferroni post hoc tests were performed for sedative activity using GraphPad Prism Version 8.0 (GraphPad Software Inc., San Diego, CA). The obtained data were represented as Mean ± SEM, and all test groups were compared with control groups to investigate the statistical differences for this study. P values less than 0.05 were considered statistically significant.

3. Results

3.1. Acute toxicity test

The acute toxicity results revealed that the oral administration of MEEG at the different doses (200–4000 mg/kg, b.w.) in experimental mice was found safe and devoid of any signs of toxicity within 72 h and up to the 14 consecutive days of the close observation period. And so, dose levels of 200 and 400 mg/kg, b.w. were selected for the current study.

3.2. Qualitative phytochemical analysis

The qualitative phytochemical profiling of MEEG revealed the presence of steroids, glycosides, flavonoids, terpenoids, and phenols (Table 1).

3.3. GC-MS analysis

Around forty bioactive compounds were identified from the GC-MS analysis (Fig. 1) of the MEEG with different retention times (Table 2). The identified bioactive compounds with excellent retention time were noted as: 5-methylheptan-2-amine; levonordefrin; folic acid; bioallethrin; nonanaldehyde; stearic acid; lauric acid; palmitic acid; D-alanine; phytol; glutaraldehyde; glucal; 9-octadecenoic acid; squalene; geranylgeraniol.

Table 1
Qualitative phytochemical profiling of MEEG.

Phytochemicals	Name of the tests	Observation
Flavonoids	Alkaline reagent test	+
Alkaloids	Wagner's reagent test	–
Quinones	Sulphuric acid test	–
Glycosides	Keller-killiani test	+
Steroids	Salkowski test	+
Tannins	Acetic anhydride test	–
Phenols	Ferric chloride test	+
Terpenoids	Salkowski test	+

Signs (+) indicates the presence and (−) indicates the absence of phytochemical class.

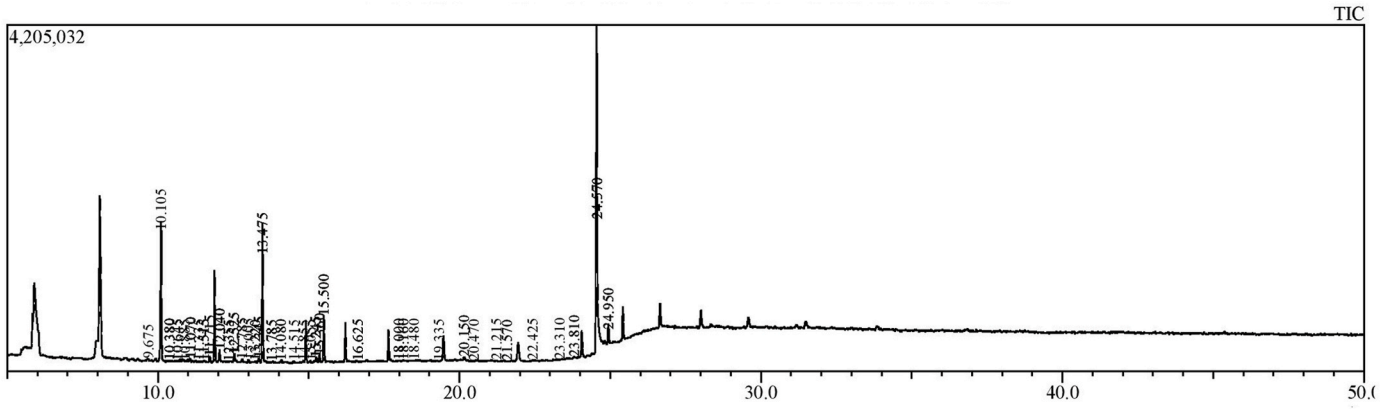

Fig. 1. Total ionic chromatogram (TIC) of the methanol extract of *E. guineensis* leaves (MEEG) using GC-MS analysis.

Table 2
Compounds identified in MEEG by GC-MS analysis.

Sl.	RT (min)	Compounds	Molecular Formula	MW (g/mol)	*m/z*	Area	Nature
1.	9.791	5-Methylheptan-2-amine	$C_8H_{19}N$	129.24	44.00	19231	Organic compound
2.	10.101	Benzoic acid, 2,6-dihydroxy, tri-TMS	$C_{16}H_{30}O_4Si_3$	370.66	73.00	853754	Ester
3.	10.105	2-Methylaminomethyl-1,3-dioxolane	$C_5H_{11}NO_2$	117.15	44.00	17929	Organic compound
4.	10.105	Octodrine	$C_8H_{19}N$	129.24	44.00	17929	Amino acid
5.	10.105	Azetidin-2-one 3,3-dimethyl-4-(1-aminoethyl)	$C_7H_{14}N_2O$	142.20	44.00	16107	Organic compound
6.	10.735	Levonordefrin	$C_9H_{13}NO_3$	183.2	44.00	16559	Phenylpropanes
7.	10.735	Folic acid	$C_{19}H_{19}N_7O_6$	441.4	44.00	16559	Organic compound
8.	11.532	alpha-Alanylnorleucine (DL)	$C_9H_{18}N_2O_3$	202.25	44.00	15182	Amino acid
9.	12.037	Bioallethrin	$C_{19}H_{26}O_3$	302.4	124.00	64140	Ester
10.	12.037	Dimethylmuconic acid	$C_8H_{10}O_4$	170.16	124.00	64140	Ester
11.	12.037	trans-Chrysanthemic acid	$C_{10}H_{16}O_2$	168.23	124.00	64140	Organic compound
12.	12.105	N-Butylurea	$C_5H_{12}N_2O$	116.16	44.00	14006	Organic compound
13.	12.785	*trans*-2-Undecen-1-ol	$C_{11}H_{22}O$	170.29	44.00	18909	Fatty alcohol
14.	12.785	Nonanaldehyde	$C_9H_{18}O$	142.24	44.00	18909	Aldehyde
15.	12.785	Heptyl aldehyde	$C_7H_{14}O$	114.19	44.00	18909	Aldehyde
16.	12.785	Stearic acid	$C_{18}H_{36}O_2$	284.5	44.00	18909	Fatty acid
17.	12.785	2-Nonen-1-ol	$C_9H_{18}O$	142.24	44.00	18909	Fatty alcohol
18.	12.785	Decahydroiso-quinoline	$C_9H_{17}N$	139.24	44.00	18909	Quinoline
19.	12.785	N-Methyloctadecylamine	$C_{19}H_{41}N$	283.5	44.00	18909	Organic compound
20.	13.620	Lauric acid	$C_{12}H_{24}O_2$	200.32	44.00	20166	Fatty acid
21.	13.620	2-Propyl-tetrahydropyran-3-ol	$C_8H_{16}O_2$	144.21	44.00	20166	Organic compound
22.	13.620	Dimethyl formamide	C_3H_7NO	73.09	44.00	20166	Organic compound
23.	13.469	Palmitic acid	$C_{16}H_{32}O_2$	256.42	74.00	432277	Fatty acid
24.	13.469	Methyl pentadecanoate	$C_{16}H_{32}O_2$	256.42	74.00	432277	Fatty acid
25.	13.620	D-Alanine	$C_3H_7NO_2$	89.09	44.00	20166	Amino acid
26.	14.646	Propanamide	C_3H_7NO	73.09	44.00	14884	Amide
27.	15.569	6,9,12-Octadecatrienoic acid, phenylmethyl ester, (Z,Z,Z)-	$C_{25}H_{36}O_2$	368.6	44.00	26724	Linolenic acid ester
28.	15.569	Phytol	$C_{20}H_{40}O$	296.5	44.00	26724	Diterpene alcohol
29.	15.569	Levomenthol	$C_{10}H_{20}O$	156.26	44.00	26724	Diterpene alcohol
30.	15.500	Methyl isomyristate	$C_{15}H_{30}O_2$	242.4	74.00	217226	Ester
31.	15.500	Methyl behenate	$C_{23}H_{46}O_2$	354.6	74.00	217226	Fatty acid
32.	15.500	Methyl heneicosanoate	$C_{22}H_{44}O_2$	340.6	74.00	217226	Ester
33.	17.997	Glutaraldehyde	$C_5H_8O_2$	100.12	44.00	16580	Dialdehyde
34.	19.694	2-Propylmalonic acid	$C_6H_{10}O_4$	146.14	44.00	4793	Organic compound
35.	20.012	4-Guanidinobutyric acid	$C_5H_{11}N_3O_2$	145.16	44.00	9814	Amino acid
36.	23.461	Glucal	$C_6H_{10}O_4$	146.14	44.00	10932	Glycoside
37.	24.077	9-Octadecenoic acid	$C_{28}H_{44}O_4$	282.5	44.00	13956	Fatty acid
38.	24.548	Erucamide	$C_{22}H_{43}NO$	337.6	59.00	1111508	Fatty amide
39.	24.548	Squalene	$C_{30}H_{50}$	410.7	69.00	404434	Triterpene
40.	24.548	Geranylgeraniol	$C_{20}H_{34}O$	290.5	69.00	404434	Terpenoid

3.4. Effects of MEEG on antidepressant activity test

The outcomes of treatment with MEEG on the duration of immobility time for FST and TST were depicted in Fig. 2A and B, respectively. The figure showed that the oral administration of MEEG (200 and 400 mg/kg, b.w.) and positive control fluoxetine HCl (20 mg/kg, b.w.) significantly ($p < 0.05$; $p < 0.001$) decreased the immobility time in both FST and TST when compared to the negative control.

3.5. Effects of MEEG on anxiolytic activity test

3.5.1. Elevated plus maze test

The EPM test showed that MEEG at different doses (200 & 400 mg/kg) resulted in an increase in both times spent in open arms and the number of entries in open arms in a dose-dependent manner (Fig. 3A & B). Meanwhile, among the doses, MEEG at 400 mg/kg, b.w. and positive control diazepam (1 mg/kg, i.p.) showed the most significant activity ($p < 0.001$) as compared to the control group.

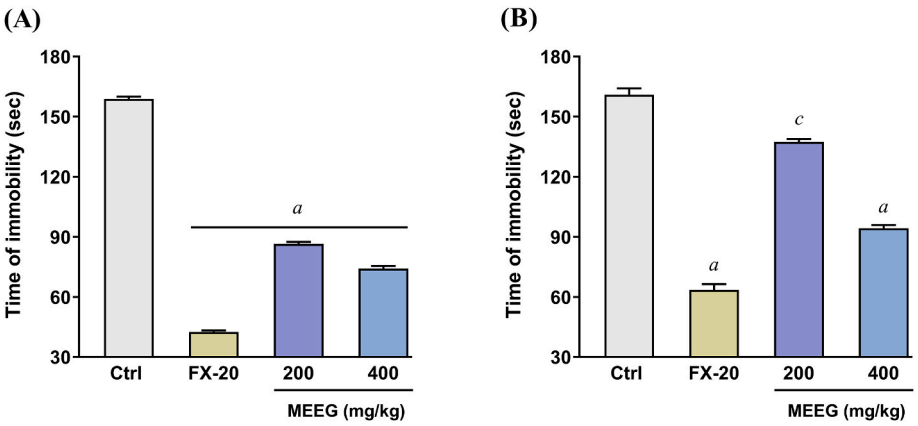

Fig. 2. Effects of MEEG on the immobility time of forced swimming test (A) and tail suspension test (B) in mice. Results were expressed as mean ± SEM, and $^{c}p < 0.05$, $^{b}p < 0.01$ and $^{a}p < 0.001$ were considered statistically significant compared to the control group. Ctrl = control; FX-20 = fluoxetine HCl (20 mg/kg, p.o.); MEEG = methanol extract of *E. guineensis* leaves.

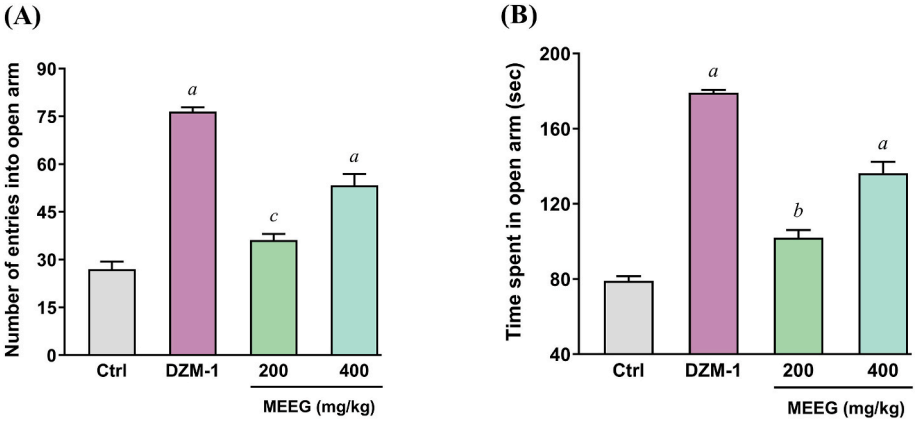

Fig. 3. Effects of MEEG on the number of entries into the open arm (A) and time spent in open arm (B) in the EPM test. Results were expressed as mean ± SEM, and $^{c}p < 0.05$, $^{b}p < 0.01$ and $^{a}p < 0.001$ were considered statistically significant compared to the control group. Ctrl = control; DZM-1 = Diazepam (1 mg/kg, i.p.); MEEG = methanol extract of *E. guineensis* leaves.

3.5.2. Hole board test

In HBT, the treatment with MEEG in experimental animals at the lower dose showed moderate activity compared to the control group. On the other hand, the oral administration of MEEG at higher dose (400 mg/kg, b.w.) significantly ($p < 0.001$) increased the number of head dipping in comparison with the control group (Fig. 4). A similar result was revealed with the treatment of standard drug diazepam (1 mg/kg, i.p.).

3.5.3. Light-dark box test

The time spent in both compartments on the light-dark box of MEEG was shown in Fig. 5A & B. As depicted in the figure, MEEG showed a significant ($p < 0.001$) increase in the time spent in the light compartment at all the experimental doses as compared to control, and similar results were found for the reference drug-treated group. On the other hand, treatment with MEEG at 400 mg/kg and diazepam (1 mg/kg, i.p.) showed significant ($p < 0.001$) decrease in the time spent on the dark compartment while compared with control was observed.

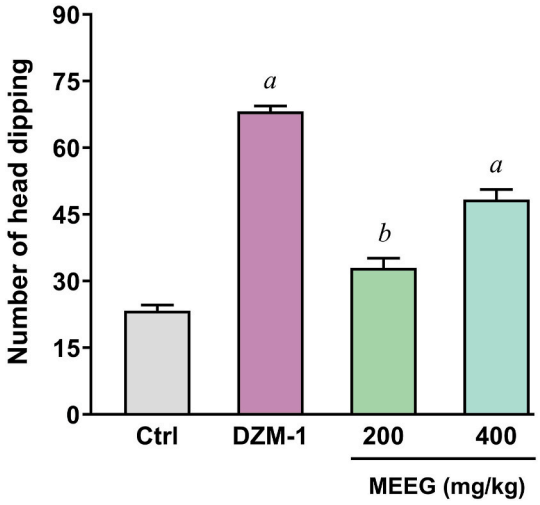

Fig. 4. Effects of MEEG on the hole board test in mice. Results were expressed as mean ± SEM, and $^{c}p < 0.05$, $^{b}p < 0.01$ and $^{a}p < 0.001$ were considered statistically significant compared to the control group. Ctrl = control; DZM-1 = Diazepam (1 mg/kg, i.p.); MEEG = methanol extract of *E. guineensis* leaves.

3.6. Effects of MEEG on sedative activity test

3.6.1. Open field test (OFT)

In OFT, the locomotion activity of experimental mice was apparent owing to the diminution in the crossing of square blocks from the first monitoring period (0 min) to the final monitoring period (120 min). The

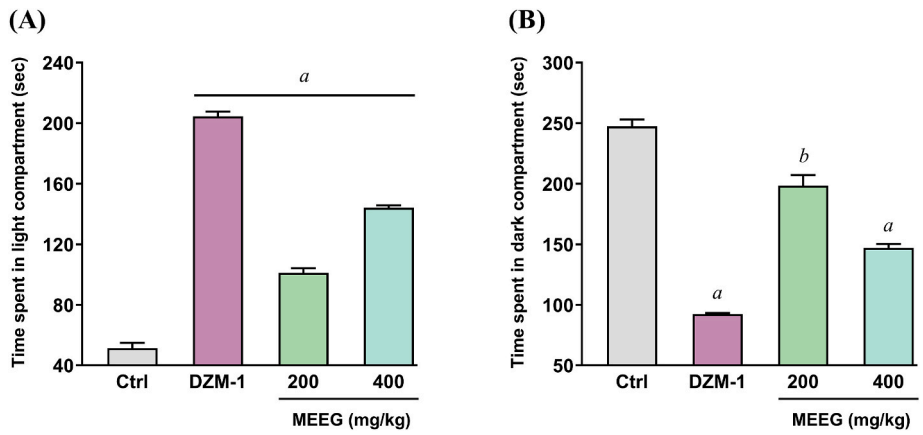

Fig. 5. Effects of MEEG on time spent in the light compartment (A) and time spent in the dark compartment (B) in the light-dark test. Results were expressed as mean ± SEM, and $^{c}p < 0.05$, $^{b}p < 0.01$ and $^{a}p < 0.001$ were considered statistically significant compared to the control group. Ctrl = control; DZM-1 = Diazepam (1 mg/kg, i.p.); MEEG = methanol extract of *E. guineensis* leaves.

total motion of the experimental mice was diminished significantly ($p < 0.001$) during the last four scrutinization periods (30, 60, 90, and 120 min) at all tested doses (200 & 400 mg/kg) of MEEG including the reference drug diazepam (1 mg/kg, i.p.) as compared to control group (Fig. 6A).

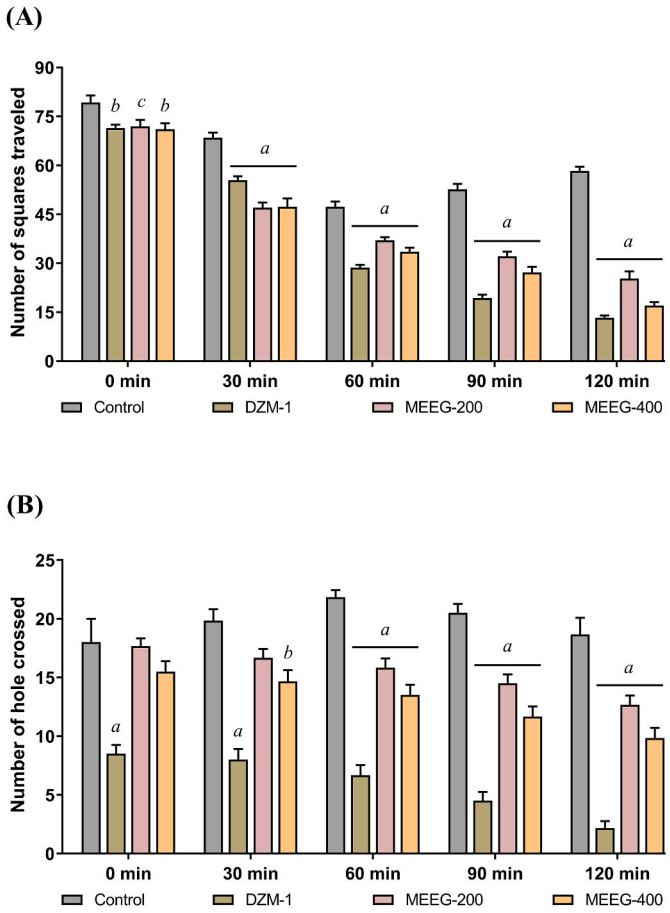

Fig. 6. Effects of MEEG on the open field test and hole cross test; the number of squares travelled (A) and the number of holes crossed (B) at the different interval (0 min, 30 min, 60 min, 90 min and 120 min). Results were expressed as mean ± SEM, and $^{c}p < 0.05$, $^{b}p < 0.01$ and $^{a}p < 0.001$ were considered statistically significant compared to the control group. DZM-1 = Diazepam (1 mg/kg, i.p.); MEEG = methanol extract of *E. guineensis* leaves.

3.6.2. Hole cross test (HCT)

The record of spontaneous locomotion activity of MEEG at different dose levels is presented in Fig. 6B. After oral administration of MEEG, the numbers of holes crossed were significantly ($p < 0.001$) reduced at almost all the tested doses; such inhibition was began from 60 min and continued till 120 min of closed surveillance period when compared with control. In the meantime, similar effects were noted for the reference drug diazepam (1 mg/kg, i.p.) treated group.

3.7. Molecular docking analysis of neuropharmacological activity

In the present investigation, eight major compounds (Fig. 7) from the forty compounds identified by GC-MS analysis were docked with different neuroprotective receptors, namely for anxiolytic (potassium channel; PDB ID: 4UUJ), antidepressant (5-HT1B-BRIL; PDB ID: 4IAQ) and sedative effects (human gamma-aminobutyric acid receptor; PDB ID: 4COF), respectively. However, from the docking results, squalene displayed highest binding scores (−3.570 & −6.885 Kcal/mol^{-1}) interacting with 4UUJ & 4IAQ receptors, respectively, which are comparable to the binding scores of standard drugs diazepam and fluoxetine HCl (−4.377 & −6.721 Kcal/mol^{-1}, respectively). In the case of antidepressant activity, squalene displayed better results than standard drug fluoxetine HCl. Furthermore, in the case of sedative activity, among the eight docked compounds, stearic acid exhibited a better docking score (−5.332 Kcal/mol^{-1}) while the standard drug diazepam showed topmost binding score (−7.081 Kcal/mol^{-1}). Finally, it could be inferred from these outcomes that among all the compounds squalene exhibited a potential docking score for both antidepressant and anxiolytic activities and stearic acid for sedative activity. The result of the docking analysis is stated in Table 3 and interactions were depicted in Fig. 8.

3.8. ADME/T analysis for drug-likeness

The absorption, distribution, metabolism and excretion properties of the major compounds of MEEG were explicated using the QikProp module of Schrödinger suite and results are demonstrated in Table 4. For this purpose, certain parameters (Lipinski's rules of five) were considered for all these compounds to justify their potentiality as a drug candidate. Among the eight major compounds, only glucal violated one rule (AMR), whether rest of the compounds did not violate any rule. All the selected compounds satisfy the Lipinski's rules of five for drug-likeness. Additionally, toxicological properties (ames and carcinogens) were also determined using admerSAR online tools. All compounds revealed non-ames toxic and non-carcinogens except for two compounds *i.e.*, palmitic acid and glucal (Table 5).

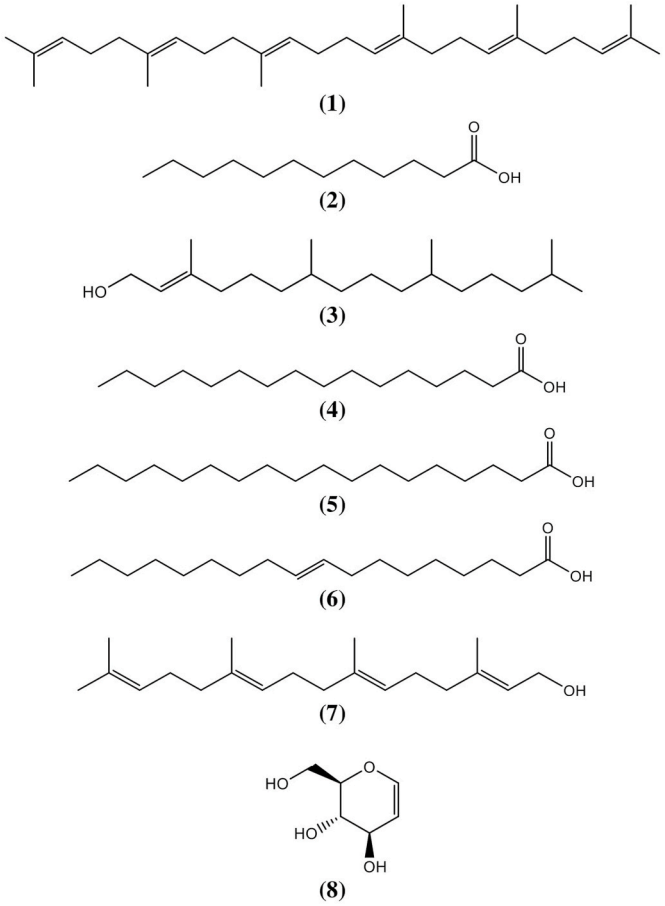

Fig. 7. Structures of eight major bioactive compounds identified in methanol extract of *E. guineensis* leaves (MEEG); (1) Squalene, (2) Lauric acid, (3) Phytol, (4) Palmitic acid, (5) Stearic acid, (6) 9-Octadecenoic acid, (7) Geranylgeraniol, and (8) Glucal.

Table 3
Docking scores (kcal/mol) of the major compounds of MEEG for antidepressant, anxiolytic and sedative activity.

Proteins	PDB ID: 4IAQ (Antidepressant)	PDB ID: 4UUJ (Anxiolytic)	PDB ID: 4COF (Sedative)
Ligands	Docking Score	Docking Score	Docking Score
Fluoxetine HCl	−6.721	–	–
Diazepam	–	***−4.377***	***−7.081***
Squalene	***−6.885***	***−3.570***	−2.939
Lauric acid	−0.264	−1.222	−1.970
Phytol	−2.247	−1.291	−1.452
Palmitic acid	−0.358	−0.934	−1.109
Stearic acid	−6.550	−0.672	***−5.332***
9-Octadecenoic acid	−1.613	−0.060	−0.917
Geranylgeraniol	−2.674	−2.573	−1.266
Glucal	−5.083	−3.024	−5.323

Values in bold italic indicate the best binding scores.

4. Discussion

The discovery of natural products based on traditional medicinal plants has been used for their remedial values since primitive times. The pharmaceutical, nutraceutical and food supplement industries widely use natural products to prepare different herbal medicines, nutrients, dietary supplements and medication of various diseases (Haque et al., 2017). Though African oil palm (*E. guineensis*) is well-known for its traditional uses and African herbal medicine to treat various ailments, it has not yet been investigated for its pharmacological activity on the central nervous system. To the best of our knowledge, no study has been reported on the neuropharmacological effects of African oil palm leaves and therefore, the present study was designed to explore the effective connotation of MEEG on the CNS and also find out the most bioactive leads through computer-aided approaches to justify the findings from animal neurobehavioral model comprehensively.

The use of medicinal plants/herbs relies upon certain pharmacological activities depending on their bioactive secondary metabolites. The qualitative phytochemical profiling of the present study revealed the existence of major phytoconstituent types, including steroids, glycosides, flavonoids, terpenoids and phenols. As well, the GC-MS analysis of MEEG affirmed around forty bioactive isolates and the majority of the isolates were found as organic compounds, fatty acids, aldehydes, glycosides, esters, amino acids, fatty alcohol, phenylpropanes, quinoline, amide, linolenic acid ester, diterpene alcohol, terpenoids, and terpenes. The prospective neuropharmacological activities of MEEG might be responsible for these diverse bioactive isolates.

Depression and anxiety, among other mood disorders worldwide, are the most important health concerns nowadays. The present experimental design provides corroboration on the antidepressant and anxiolytic-like effects of MEEG. The forced swimming test (FST) and tail suspension test (TST) were used to evaluate the depressive-like condition in Swiss albino mice (Ishola et al., 2012). Immobility or desperation behavior produced in both FST and TST has been reconstructed to demonstrate the animal's behavioral desperation as seen in human depression. The outcomes of the present experiment exposed the significant antidepressant and anxiolytic potentials of MEEG. The immobility time of FST and TST was noticeably short as compared to control at lower and higher doses. In the meantime, a similar immobility time was recorded in standard antidepressant drug fluoxetine HCl. Interestingly, fluoxetine HCl works by serotonin reuptake inhibition and a similar mechanism of action can be predicted for MEEG. In addition, antidepressant studies indicated that normal antidepressant function is regulated by increasing the degree of noradrenaline and serotonergic transmission in the brain that supports the apoptogenic effect of the plant, minimizing different stress parameters and the monoaminergic levels (Kawaura et al., 2009). However, this investigation does not conclude the exact mechanism, and hence, extentive mechanistic studies are needed to clarify the issue.

Correspondingly, the present study evaluated anxiolytic activity with the elevated plus maze (EPM), hole board test (HBT) and light-dark test (LDT). In this research, during EPM, mice were treated with different doses of MEEG (200 & 400 mg/kg, p.o.) and results showed a significant increase in both times spent in open arms and the number of entries into open arms, indicating potential decrease in anxiety-like behavior. Similar observations were found in case of standard drug (diazepam) treatment. Subsequently, the hole board test was used to measure rodents' reaction to an unfamiliar environment that can detect the anxiolytic-like behavior. However, some studies reported that animals head dipping behavior is directly related to their mind-set state (Ebert et al., 2006). Based on this finding, the anxiolytic state was found to correlate with mice anxiolytic effects that increase head poking. In this model, MEEG instigated a greater propensity of head dipping at higher doses (400 mg/kg, p.o.). Alternatively, the light-dark test is the most common method for evaluating anxiolytic activity and it has been developed to forecast the potency of the clinically used compounds. Previous studies reported that time spent in illuminated areas indicates a coherent parameter to connoting anxiety (Arrant et al., 2013). Specifically, an imbalance of neurotransmitters or disruption of GABA-ergic pathways may raise anxiety. The anxiolytic-like effects were found due to the opening of chloride channels activated by GABA which amplify the reaction of GABA receptors (Herrera-Ruiz et al., 2006). The present experimental findings showed that MEEG increased the time spent in an illuminated compartment suggesting anxiolytic effects at both test doses by changing the function of neurotransmitter or the

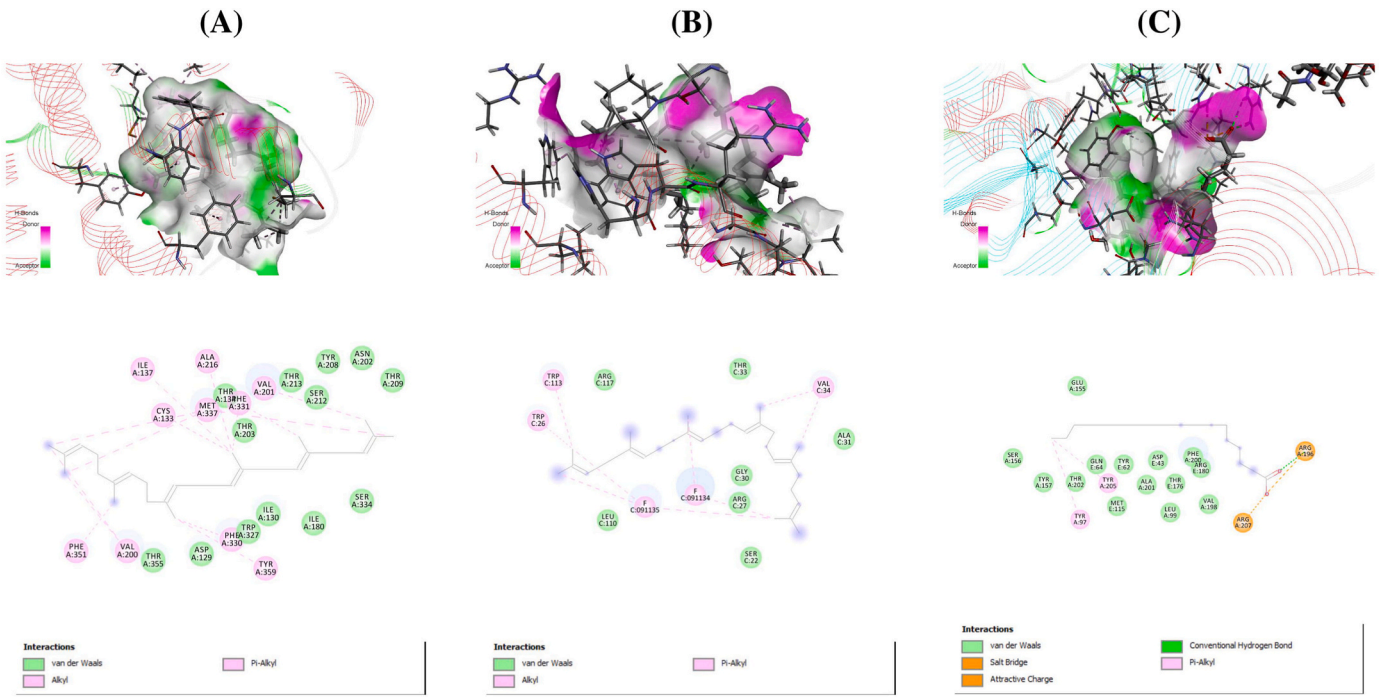

Fig. 8. 3D and 2D molecular interaction of best ranked poses of squalene with active site residues of 4IAQ (A), 4UUJ (B) and stearic acid with active site residues of 4COF (C), respectively for the neuropharmacological effects.

Table 4
ADME properties of the major compounds of MEEG for good oral bioavailability.

Compounds	MW	HBA	HBD	Log P	AMR	TPSA	Lipinski's Violations
Rule	<500	≤10	≤5	≤5	40–130	≤140 (Å^2)	≤1
Squalene	410.72	0	0	4.37	123.28	19.26	0
Lauric acid	200.32	2	1	2.70	61.57	37.30	0
Phytol	296.53	1	1	4.71	98.94	20.23	0
Palmitic acid	228.37	2	1	3.32	71.18	37.30	0
Stearic acid	284.48	2	1	4.30	90.41	37.30	0
9-Octadecenoic acid	282.46	2	1	4.27	89.94	37.30	0
Geranylgeraniol	290.48	1	1	4.75	97.52	20.23	0
Glucal	146.14	4	3	1.08	32.94	69.92	1

MW, Molecular weight; HBA, Hydrogen bond acceptor; HBD, Hydrogen bond donor; Log P, Lipophilicity; AMR, Molar refractivity; TPSA, Tropological surface area.

Table 5
Toxicological properties predictions for the major compounds of MEEG.

Compounds	Ames Toxicity	Carcinogenicity
Squalene	Non-Ames toxic	Non-carcinogenic
Lauric acid	Non-Ames toxic	Non-carcinogenic
Phytol	Non-Ames toxic	Non-carcinogenic
Palmitic acid	*Ames toxic*	Non-carcinogenic
Stearic acid	Non-Ames toxic	Non-carcinogenic
9-Octadecenoic acid	Non-Ames toxic	Non-carcinogenic
Geranylgeraniol	Non-Ames toxic	Non-carcinogenic
Glucal	*Ames toxic*	Non-carcinogenic

Findings in italic indicate compound shows toxicity.

reconciliation of GABA-ergic pathways.

The sedative effects of MEEG were evaluated using the most common animal model of open field test (OFT) and hole cross test (HCT) by distinguishing unconstrained locomotion activity. Diazepam, which belongs to the class of benzodiazepines, is a CNS depressant used for the treatment of sleeping disorders like insomnia. Benzodiazepines have a binding site on the GABA receptor complex. These drugs minimize activity, moderate the excitement and calm down the receiver. As well, benzodiazepines minimize the onset and increase the length of barbiturate sleep and eliminate sedative exploratory behavior (Hossain et al., 2016). The experimental data exhibited that the sedative activity of MEEG comes up with satisfactory behavioral changes in both test models. Notably, both animal models significantly reduced the number of movements in one chamber to another and hole cross, respectively, signifying the decrease in mice's locomotion activity. In the present study, treatment with MEEG began to reduce the movements of experimental mice significantly at 30 min and 60 min (for OFT and HCT, respectively) and persisted for up to 120 min, which may be due to decrease in the CNS excitability of experimental mice and thus revealed potential sedative effects. This exploratory behavior and locomotion were almost identical to the control group animals at all the intervals over a 120 min period. Furthermore, similar effects were observed in the diazepam-treated mice.

Besides experimental approaches, computer-aided drug design was elucidated to predict the neurobiological properties of the major isolates/compounds of MEEG. The purpose of this computer-aided approach was to understand the ligand-receptor complexes and to confirm whether the experimental data is in line with the *in silico* results. Therefore, before initiating the experiment, PASS software was used to verify whether the phytocompounds based on structure-activity relationship is in accordance with the PASS database training set SAR. Analogously, *in silico* molecular docking, the most constructive computational strategy in structural molecular biology was used to anticipate

ligand-receptor interaction and to find out the information about biological responses of the natural phytocompounds (Khan et al., 2019). In this experiment, molecular docking analysis was investigated with target receptors (4UUJ, 4IAQ and 4COF) for anxiolytic, antidepressant and sedative activities of eight major isolates of MEEG. Interestingly, among the eight isolates, squalene showed promising binding affinity in both antidepressant and anxiolytic activities. This compound also provided a better glide score in antidepressant activity as compared to the standard drug fluoxetine HCl. Additionally, in sedative activity, stearic acid showed better binding affinity which is comparable to the binding affinity of standard drug diazepam. This study inferred that in some way, squalene might be a potential bioactive natural compound for anxiolytic and antidepressant activities and stearic acid for locomotion activity, hence, suggested for further QSAR and homology modelling studies.

The bioavailability of these major compounds was investigated based on the Lipinski's 'rule of five' parameters. Results demonstrated that the studied compounds follow this rule and do not violate more than one parameter. Theoretically, investigated outcomes showed that eight compounds maintain Lipinski's rule, hence, orally bioavailable for the drug candidate. In addition, the toxicological study using admetSAR revealed that all compounds manifested non-ames toxic and non-carcinogens except palmitic acid and glucal. However, extensive preclinical toxicological investigations and pharmacokinetic studies considering various *in vivo* and *in vitro* models are recommended before the clinical stage investigations.

However, the leaves of African oil palm have gathered a great interest to the traditional West African societies due to their potential ethnomedicinal uses. And, the ethnomedicinal claims for managing mental disorders have also been proved by our present investigation. In addition, the leaves of African oil palm are a rich source of bioactive phytochemicals having various positive impacts on health. Therefore, the leaves could be used to produce added-value products in the food or nutraceutical industries, and may have strong prospect of being used as a functional foods/complementary source of drug candidate to manage anxiety, depression and related disorders.

5. Conclusion

The present investigation revealed very auspicious neuropharmacological properties of the African oil palm (*E. guineensis*) leaves ascribed for the presence of numerous bioactive metabolites present in the plant and therefore supports its ethnomedicinal uses for neurodegenerative disorders. In the computer-aided investigation, squalene showed promising binding energy higher than the reference drug for antidepressant activity. Besides, stearic acid showed a better glide score for the locomotion activity. Therefore, the present study recommends that the leaves of the plant may serve as a potential source of drug candidates for the treatment of insomnia, depression, and related neurological disorders. However, an extensive mechanistic investigation followed by isolating the bioactive leads is crucial to justify the exact mechanism of this promising plant's neuropharmacological insights.

Contributions of authors

N.I., S.N., N.B.H., M.F.K. and C.L. conducted the investigation. N.I., L.A., U.K., M.F.K., and M.A.H. contributed to analyzing and interpreting data and drafting the manuscript. M.R.K., L.A., N.A.C., R.C. and M.A.H. contributed to the conceptualization, visualization and editing of the draft. M.R.K., R.C. and M.A.H. coordinated the research, revised the manuscript and approved the final version for publication. All authors have read and agreed to the published version of the manuscript.

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CRediT authorship contribution statement

Nadia Islam: Investigation, Formal analysis, Data curation, Writing - original draft, conducted the investigation, contributed to analyzing and interpreting data and drafting the manuscript, All authors have read and agreed to the published version of the manuscript. **Mohammad Forhad Khan:** Investigation, Formal analysis, Data curation, Writing - original draft, conducted the investigation, contributed to analyzing and interpreting data and drafting the manuscript, All authors have read and agreed to the published version of the manuscript. **Mst. Riniara Khatun:** Conceptualization, Visualization, Writing - review & editing, contributed to the conceptualization, visualization and editing of the draft, coordinated the research, revised the manuscript and approved the final version for publication, All authors have read and agreed to the published version of the manuscript. **Shafinaz Nur:** Investigation, conducted the investigation, All authors have read and agreed to the published version of the manuscript. **Nujhat Binte Hanif:** Investigation, conducted the investigation, All authors have read and agreed to the published version of the manuscript. **Ummay Kulsum:** Formal analysis, Data curation, Writing - original draft, contributed to analyzing and interpreting data and drafting the manuscript, All authors have read and agreed to the published version of the manuscript. **Laiba Arshad:** Formal analysis, Data curation, Writing - original draft, Conceptualization, Visualization, Writing - review & editing, contributed to analyzing and interpreting data and drafting the manuscript, contributed to the conceptualization, visualization and editing of the draft, All authors have read and agreed to the published version of the manuscript. **Chadni Lyzu:** Investigation, conducted the investigation, All authors have read and agreed to the published version of the manuscript. **Nunzio Antonio Cacciola:** Conceptualization, Visualization, Writing - review & editing, contributed to the conceptualization, visualization and editing of the draft, All authors have read and agreed to the published version of the manuscript. **Raffaele Capasso:** Conceptualization, Visualization, Writing - review & editing, contributed to the conceptualization, visualization and editing of the draft, coordinated the research, revised the manuscript and approved the final version for publication, All authors have read and agreed to the published version of the manuscript. **Md. Areeful Haque:** Formal analysis, Data curation, Writing - original draftWriting – original draft, Conceptualization, Visualization, Writing - review & editing, contributed to analyzing and interpreting data and drafting the manuscript, contributed to the conceptualization, visualization and editing of the draft, coordinated the research, revised the manuscript and approved the final version for publication, All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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