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Angelica glauca oil exhibits antidepressant-like effect in experimental animals: An *in silico*, ADMET and *in vivo* investigation

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Abstract

Angelica glauca is an aromatic plant of the Apiaceae family. Traditionally *A. glauca* is used to cure several diseases including anxiety and depression. The present investigation is focused on studying the *in silico* and *in-vivo* antidepressant potential of *A. glauca* essential oil (AGEO). The GC-MS analysis was performed on *A. glauca* root oil to confirm the genuineness of the drug. Compounds viz. alpha phellandrene, limonene, and z-ligustilide obtained through GC-MS analysis were screened for Monoamine oxidase from *Aspergillus niger* (MAO-N) (PDB: 2vvl) binding through molecular docking studies by using autoDock/Mcule tool. Prediction of ADME and physicochemical properties of above-detected compounds was done by using preADMET tool version 2.0. The antidepressant activity was investigated by the forced swimming method and tail suspension method. The docking studies exhibits that limonene has a maximum affinity for MAO-N, followed by alpha phellandrene and z-ligustilide. It has been observed that upon oral administration of *A. glauca* oil (250 & 500 µl/kg b.w.) and reference drug selegiline at the dose of (0.2 mg/kg) shows significant ($p<0.01$) reduction in immobility in rats in both the behavioral models. All the results were compared with the control group and justified by histopathological analysis of the brain. The data obtained from the study suggests the antidepressant-like action of *A. glauca* root oil and its phytocompounds in the behavioral models of FST and TST in a dose-dependent manner.

Keywords

Angelica glauca; Antidepressant; ADMET; Molecular docking; Behavioral models; Histopathology.

Introduction

World Health Organization stated that depression has the largest burden of disability among mental disorders. Globally, approximately fifty percent of all patients suffer from some kind of depression and the prevalence are 5.9% in females and 3.8% in males (1). Depression is a psychiatric disorder linked with serious negative consequences and characterized by depressed mood accompanied by sleep and food deregulation, psychomotor changes, guilt and, in more rigorous cases, suicidal thoughts (2). Depression causes symptoms that affect populations of all ages, affecting quality of life and everything from work to social relationships. Moreover, depression is the source of many somatic disorders, sexual disorders, and biological rhythms disorders (3). Therefore, it is essential to seek the best, most effective, and least hazardous medications and strategies for coping the depression.

It is well known that essential oils are loaded with bioactive compounds. Recent studies have shown that essential oil enters in the bloodstream either by inhalation or oral administration and exerts psychological effects that complement pharmacological interventions viz. decreases the symptoms of dementia (4); improves sleep quality, reduces anxiety, and improves vibes (4-5). Several wild Angelica species are used for similar purposes around the world including the wild American *Angelica atropurpurea* L., and the Indian *A. glauca*, used in Ayurvedic ethnomedicine. The plant *A. glauca* (smooth angelica), commonly known as Gandhrayan or Choru belongs to the family Apiaceae, is a herb indigenous to high-altitude Himalayan regions of Jammu and Kashmir, Uttarakhand, and Himachal Pradesh. Traditionally, the rhizomatous roots of *A. glauca* are used as a stimulant, carminative, cardioactive, expectorant and diaphoretic and produce a pale-yellow essential oil (0.4-1.3% dry basis) (6). The composition of essential oil of *A. glauca* revealed the presence of α-phellandrene, β-phellandrene, (Z)-ligustilide, β-pinene, limonene, methyl octane, thujene, β-bisabolene, β-caryophyllene, β-caryophyllene oxide, trans-carveol (7-8); as the chief constituents. Various preclinical pharmacological activities, namely, antimicrobial, antioxidant, antifungal (8-9); memory enhancer, bronchial relaxant, phytotoxic, insecticidal and anxiolytic (10) have been stated in the literature. The essential oil of *A. glauca* has not been scientifically explored for its antidepressant action to date though there are evidences that isolated compounds of these essential oils have antidepressant effect. Hence this study was conducted to explore the *Angelica glauca* essential oil (AGEO) and their constituents for the treatment of depression with the help of *in silico* approach and behavioral status in experimental animals.

Materials and Methods

Drugs and Reagents

AGEO was procured from Organikos Velly, Kanpur, India. Standard drug selegiline were obtained as a gift sample from Sun Pharmaceuticals Industries Ltd. Ahmedabad, India. Several other reagents and solvents used were of analytical grade. Distilled deionized water was utilized throughout research work.

Authentication of AGEO by GC-MS

AGEO was authenticated using Gas Chromatography-Mass Spectrometry (GC-MS) analysis to ascertain the presence of bioactive components present in AGEO. The essential oil was examined using a Perkin Elmer Clarus 680 gas chromatograph with Sq 8 mass Spectrometer. The following instrumental conditions were utilized to test GC-MS: A PE Elite-5 column (30 m X 0.25mm X 0.25µm) was taken and and helium gas was injected at a constant flow rate of 1 ml/min for approximately 99% of the gas used is carrier gas. The ion-source temperature was 220°C with split 1:100 while the injector temperature was 290°C. The temperature of the oven was set to 60°C (isothermal for approximately 2 min), and then increased to 240 °C at a rate of 3 °C/min for approximately 10 minutes. For fragments varying from 40 to 500 amu, and the mass spectra were obtained at 70 eV by a scan interval of 0.8 seconds with an interscan delay of 0.01 sec. The identity of the active components' identities was determined by comparing their mass spectra.

In silico studies

For the *in silico* analysis of the antidepressant action of AGEO, a structural archive of the leading isolated compounds (from GC-MS analysis) was prepared. The crystal structure coordinates of monoamine oxidase N (MAO -N-D3) (PDB entry: 2vvl; resolution, 2.45 Å) were obtained from Protein Data Bank. The compounds were prepared for docking by removing all nonreceptor atoms, water, heteroatoms, and other ions, etc. Molecular docking was accomplished for selected compounds alpha phellandrene, Limonene, z-lingustilide, and selegeline as potential antidepressant agents. All the selected compounds were simulated by applying Chem Draw Ultra 8.0 software and prepared into suitable model structures. The energy-minimized structures are expected for molecular docking and designing corresponding PDB files. Docking studies were carried out on the designed ligands to predict the binding energy and find the proper docking position. Validation of docking was done using the Mcule platform.

Prediction of ADME & Physicochemical Properties

The Swiss ADME tool of the Swiss Institute of Bioinformatics was used to compute the physicochemical descriptions of three major compounds detected in GC-MS along with the standard drug selegiline. The blood-brain barrier penetration described as (Conc.(brain)/Conc.(blood)) was calculated using the preADMET tool version 2.0 (https://preadmet.webservice.bmdrc.org/adme/).

Experimental animals

The protocol for the research work was approved by the Institutional Animal Ethics Committee of United Institute of Pharmacy, Prayagraj with approval no. UIP/IAEC/March-2023/02 and all experiments were carried out in accordance with the guidelines of the committee for the control and supervision of experiments on animals (CCSEA) New Delhi. Male wistar albino rats weighing 200 ± 10g and 2-3 months of age procured from the CCSEA registered animal breeder Chakraborty Enterprises Kolkata West Bengal, India were used for the study. Rats were retained in an air-conditioned room at 25°C ± 2°C with a 12h light/dark cycle with lights off at 19:00 h and given free access to food (Amrut pellet diet, Pranav Agro Industries Ltd., Pune, India) and tap water *ad libitum*. The entire animal experiment was carried out under hygienic conditions.

Toxicity study and selection of dose

Acute toxicity of this plant was reported to be - 2.2 g/kg for mice and 11.2 g/kg for rats [11]. In accordance with the IAEC recommendation to avoid duplication of studies, acute toxicity studies were not performed, and two doses of 250 and 500 µL/kg were used in the present study.

Antidepressant Activity

Experimental protocol and treatment schedule

All animals were divided into four groups, each group

containing 6 animals. The vehicles and drugs were administered one hour prior to the experiment.

Group I - serving as the normal control group which received saline solution 10 ml/kg b.w.

Group II - serving as the standard group received selegiline 0.2 mg/kg b.w.

Group III - received AGEO 250 µl/kg b.w.

Group IV - received AGEO 500 µl/kg b.w.

Behavioral Tests

The Tail Suspension Test (TST) and the Forced Swimming Test (FST), were performed to assess depressive-like behaviors for 2 days.

Forced swimming test (FST)

For the execution of forced swimming test (FST), Animals were forced to swim in an open cylindrical acrylic glass container (diameter 20 cm, height 30 cm) containing 22 cm of water at 27±2°C. Treatment was given one hour prior to the investigation as reported in the experimental design. All animals were forced to swim for 10 minutes and the duration of immobility was noticed and measured during the final 5 minutes interval of the test. Each animal was considered immobile when it stopped struggling and swam motionless in the water, only making the movements to keep its head above water. A decline in the duration of immobility indicates an antidepressant-like effect. (12).

Tail Suspension Test (TST)

The TST used in this experiment was performed as per the procedure of Mannan et al. 2015 (12); with slight modification. Treatment was given one hour before the study as described by experimental design. The rats were suspended from the edge of the table, about 40 cm above the floor by means of an adhesive tape placed around 1 cm from the tip of the tail. The entire duration of immobility induced by tail suspension was recorded during 10 minutes of the 15 minutes period. The animal was considered to be immobile when it showed no movement of the body, hanged passively and completely motionless.

Histopathological analysis

After the behavioral test, the animals were fasted overnight for about 12 hours on the last day of experimental model before the induction of anaesthesia. The rats were sacrificed under anaesthetic condition and the whole brains were quickly collected and the cerebral cortex was isolated from the whole brain then post-fixed with 10% formalin for 7 days, cleared, dehydrated, and fixed in paraffin following routine histological practices. The test samples were sliced in the frontal plane in 5 µM consecutive sections and the cortex region was subjected to histopathological studies.

Statistical analysis

Graph pad prism version 9.5.1 was used to conduct the statistical analysis. Data has been presented as Mean±SD. The two-way ANOVA model with Tukey's multiple comparisons test was used to examine the data of FST and TST models.

Results

GC-MS Analysis of the Essential Oil

The GC-MS investigation of AGEO revealed that the main compounds were identified as alpha phellandrene (RT: 5.03 min; MW: 136), α-pinene (RT: 5.22min; MW: 136), camphene (RT: 5.63 min; MW: 136), sabinene (RT: 6.20 min; MW: 136), beta phellandrene (RT: 6.36 min; MW: 136), d-limonene (RT: 7.89 min; MW: 136), p cymene (RT: 7.74 min; MW: 134), 1,8 cineole (RT: 8.0 min; MW: 154), beta.-Selinene (RT: 24.53 min; MW: 204), and z-ligustilide (RT: 31.29 min; MW: 190). (Fig. 1).

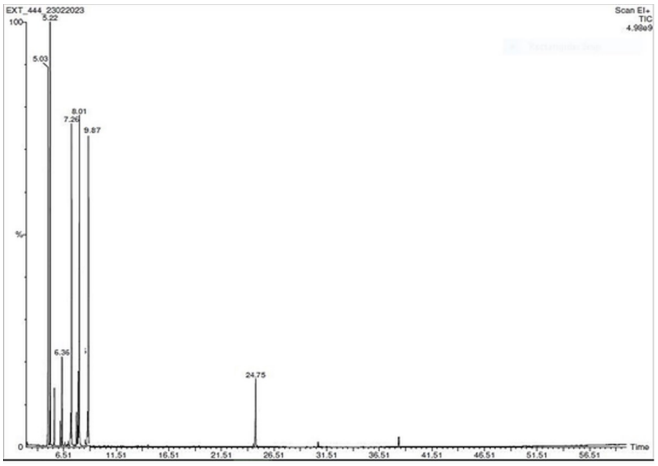

Fig. 1. GC-MS graph of AGEO

In silico studies

Using an automated and virtual screening programme called AutoDock, the full intermolecular interactions between the ligand and the target protein (Fig, 2) were determined.

Figure 3A shows that alpha phellandrene can interact with ALA03, VAL305, ASN204, PRO302, LEU61 residues, limonene can interact with ALA63, PHE268, GLY462, GLY269, ILE301, LEU306, PRO271, CYS270, and

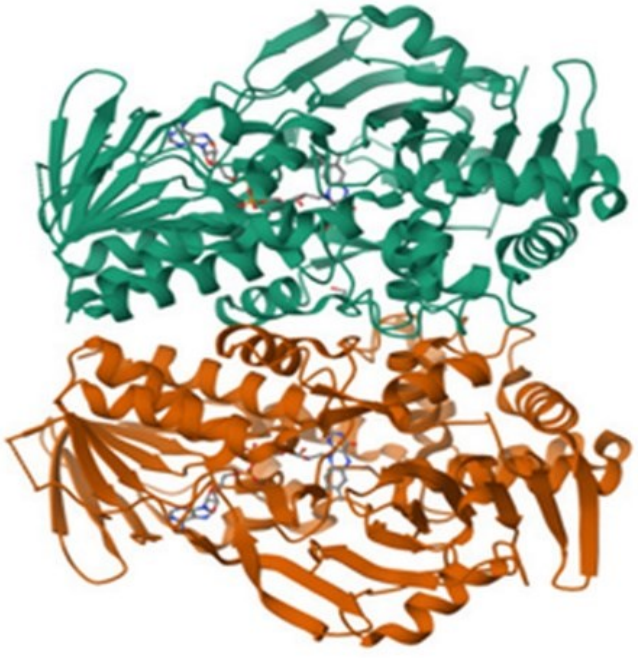

Fig. 2. 3D structure of MAO-N-D3 (PDB: 2vvl)

VAL305 (Fig. 3B) and z-ligustilide can interact with VAL305, PRO11, CYS 270, GLY269, GLU62, PHE268, ALA54 (Fig.3C) whereas standard drug selegiline can form hydrogen bonding with ARG57, SER458, ER450, PHE409, ILL46, and ALA463 (Fig. 3D) residues in the active site of monoaminoxidase inhibitor. The binding affinity of alpha phellandrene, limonene, z-ligustilide and selegiline was found to be -6.6 kcal/mol, -6.9 kcal/mol, -6.5 kcal/mol and -7.0 kcal/mol respectively.

Prediction of ADME & Physicochemical Properties: Swiss ADME tool 2.0 was applied to predict the physicochemical properties of the alpha phellandrene, limonene, z-ligustilide as well as standard drug selegiline. All four compounds pass Lipinski's law of five with zero violation. The radius of various physicochemical parameters (solubility: log S<6; lipophilicity: XLOGP3 between -0.7 and +5.0; polarity: TPSA 20-130 Å2; size: MW 150-500 g/mol; flexibility: rotatable bonds >9; saturation: fraction of sp3-hybridized carbons in sp3>0.25) focusing oral bioavailability which was represented by the pink-coloured area in bioavailability radar (Figure 4). The radar plot shows that all compounds display a bioavailability score of around 0.55 and fall within an optimal range of the above physicochemical properties which is indicative of the drug like behaviour of these compounds. Prediction for the ADME/pharmacokinetic properties of all the compounds has been carried out which shows that all the molecules were able to pass the blood-brain barrier (BBB). The predictions for the passive BBB permeation and GIT absorption are displayed together in the BOILED-Egg diagram. Among these four molecules, only z-ligustilide and selegiline are able to inhibit the cytochrome P450 (CYP1A2) while inhibition of cytochrome P450 (CYP2C19) was not shown by any molecule.

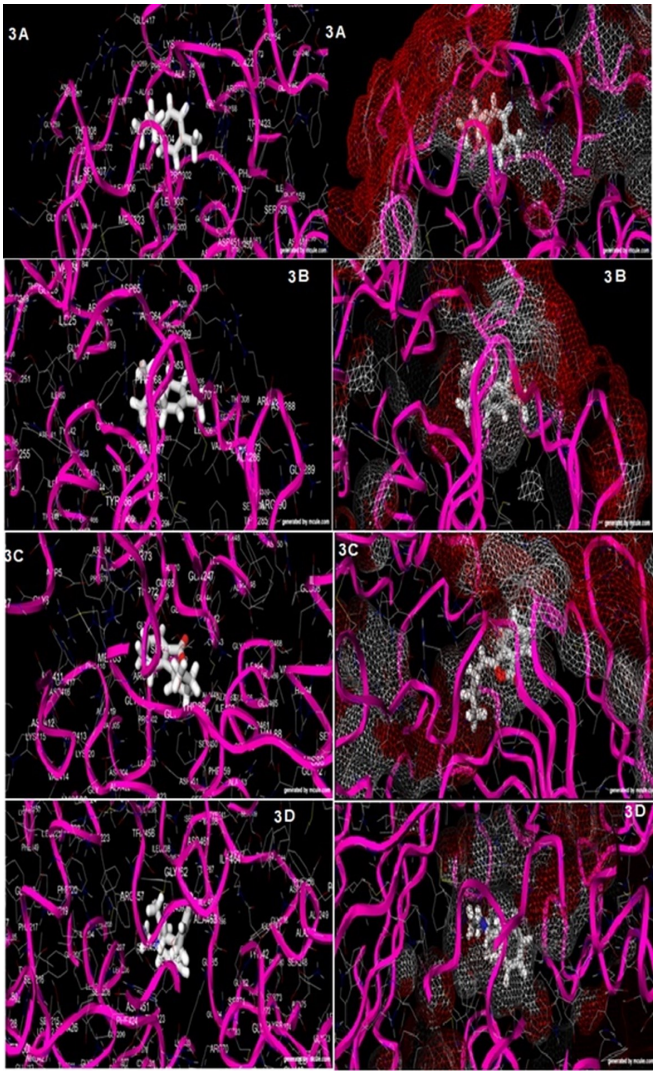

Fig. 3. Interaction & superimposed structure of (3A) alpha phellandrene, (3B) limonene, (3C) z-ligustilide, (3D) selegiline

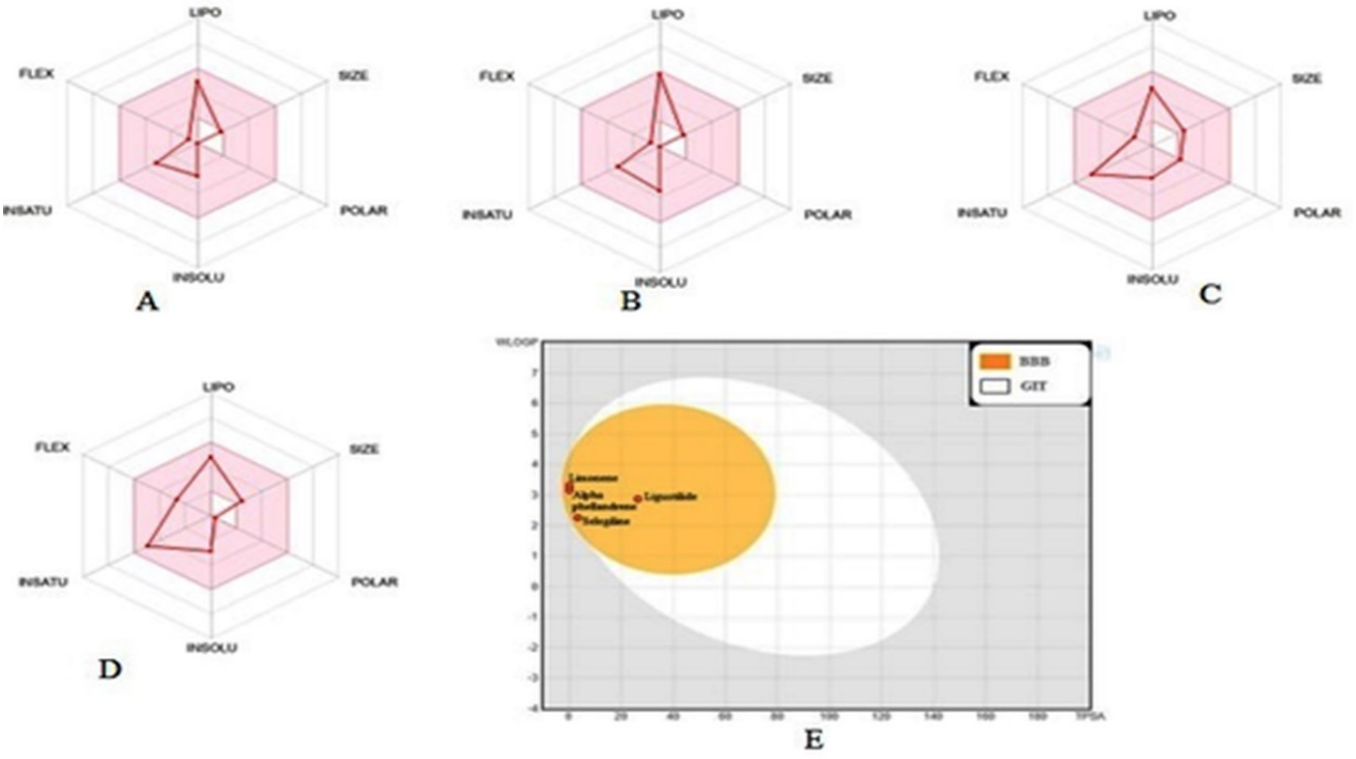

Fig. 4. Bioavailability radar plots for prediction of physiochemical parameters of (A) alpha-phellandrene, (B) limonene, (C) z- ligustilide and (D) selegiline. The boiled egg plot displays comparative indication of BBB permeation ability and absorption of above compounds

Antidepressant activity: The antidepressant effects of AGEO (250 and 500 µl/kg) and selegiline (0.2 mg/kg) were examined by observing the variations in the duration of immobility in the two models: FST and TST. Both, in the TST and FST, AGEO 250 and 500 µl/kg, p.o. shows a significant reduction ($p<0.01$) in the immobility period when compared to control group animals that received only the saline solution. The results are depicted in Table 1.

Table 1. Effect of AGEO on immobility time in FST and TST

Treatment/ Group	Dose	FST immobility time (sec)	TST immobility time (sec)
Control	-	231.4±0.55	323.8±0.38
Selegiline	0.2 mg/kg	213.6±0.65*	249±0.28*
AGEO	250µl/kg	153.6±0.31*	173.4±0.16*
AGEO	500µl/kg	192±0.49*	213±0.90*

Values are expressed as mean ±SD; (n=6), *$p<0.01$ compared with the control group.

Histopathological analysis: Fig.5 shows photomicrographs of the section of the brain of control and treated groups animals. In the control group rat's brain section, normal closely packed pyramidal cells were noticed with natural architecture (5A). Animal groups treated with the standard drug Selegiline (0.2mg/kg) show dentate gyrus composed of granular cells with high neuronal density (5B) whereas animals treated with AGEO 500 µl/kg (5D) exhibit significant neuroprotection as confirmed by an increase in the number of viable pyramidal cells with high neuronal density while in case of the animal group treated with AGEO 250 µl/kg, few shrunken deeply stained pyramidal cells with mild infiltration of basophilic cytoplasm have been observed (5C).

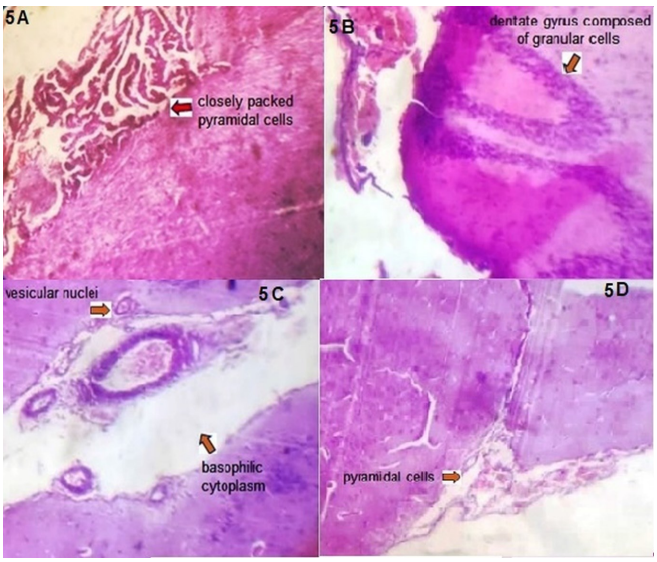

Fig. 5. Photomicrographs of histopathology of the brain

Discussion

Depression is a crucial psychiatric disorder that directly influences the quality of life and social relationships of the individual. When the signs and symptoms are very severe, major depression is suspected (13). The main problem in the screening for novel antidepressant effect is establishing a valid animal model capable of sufficiently and accurately identifying various depressive treatments without committing errors or omissions. In that instance, the forced swimming and tail suspension tests are generally adopted behavioural models for assessing antidepressant activity. The distinctive behaviour evaluated in these tests, termed immobility, is deemed to imitate behavioural despair similar to that observed in human depression. Antidepressants are known to be able to lessen immobility time in rodents (14).

In the present study, the antidepressant-like effect of *A. glauca* essential oil was investigated in the stressed rats via behavioural and histological approach. To demonstrate behavioural approach, we adopted two reference models, TST and FST. Both models are widely adopted behavioural models for evaluating antidepressant activity. During these behavioural models, recent studies found that there is decreased glucose metabolism in the orbital and insular cortices, hippocampus and inferior colliculi while an increased tracer uptake was observed in the cerebellum and striatum (15-16). Moreover, it is well established that several antidepressant medicines can reduce immobility period in rodents. AGEO caused a significant decrease in immobility period at doses of 250 and 500 µl/kg in the rats.

Studies on molecular docking are frequently used to predict ligand-target interactions and to better understand targets-specific ailments and biological actions of natural products. Additionally, it provides more light on probable modes of action and binding tactics inside the binding pockets of various proteins. Therefore, docking studies were performed with major bioactive molecules present in AGEO against the molecular target (MAO-N-D3). The best docking pose exhibited by limonene as it can form hydrogen bonds with ALA63, PHE268, GLY462, GLY269, ILE301, LEU306, PRO271, CYS270, and VAL305 residues in the active site with docking energy of -6.9 kcal/mol. Contemporary research focuses on drugs that targets-specific ailments. Though the antidepressant competence of AGEO is renown there is a need to identify the phytocompounds that can fortify it as a brain drug to compete with blood brain barrier. In ADMET analysis, the radar diagram shows that all compounds display bioavailability scores and indicates pharmacokinetic properties of compounds which shows that all the molecules were able to pass the blood-brain barrier (BBB).

Several studies have endorsed Angelica plant as a potential neuroprotectant through various *in vivo* models (17); but the present work proves its dual role in active against depression and bypasses the blood brain barrier. Conversely, the effectiveness of specific phytocompounds have been validated in this work with both *in silico* and ADMET analysis.

The *A. glauca* plant contains various categories of phytochemicals and its oil is rich in effective components like alpha phellandrene, z-ligustilide, limonene, beta phellandrene, α-pinene, β-pinene, Carene, Cineole, α-humulene and these compounds contribute positively to the antidepressant activity through neuroprotective, anti-neuronal apoptosis, anti-inflammatory, improving mitochondrial dysfunction, having anti-oxidant effects,

regulating autophagy, regulating gut flora and strengthening the central cholinergic system (18-20) showing the multicomponent and multi-target effect of AGEO.

Conclusion

In the present study, we have reported evidence indicating an antidepressant-like effect of AGEO in classic FST and TST models of depression that showed significant antidepressant-like activity comparable to the standard drug Selegiline. *In silico* and ADMET analysis provides predicted biological targets viz. MOA-N-D3 and pharmacokinetic parameters responsible for amelioration of depression. Further exhaustive investigation is needed for the identification of the active compounds in *A. glauca* oil with antidepressant-like effects clinically.

Authors' contributions

All the experiments were carried out by PM and SBM. NG carried out *in silico* and ADME analysis, Manuscript is drafted by SBM. PM performed the statistical analysis. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: "None".

References

1. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med. 2013;43(3):471-481. https://doi:10.1017/S0033291712001511
2. Nemeroff CB, Owens MJ. Treatment of mood disorders. Nat Neurosci. 2002;5 Suppl:1068-1070. https://doi:10.1038/nn943
3. Chisholm D, Sweeny K, Sheehan P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. Lancet Psychiatry. 2016;3(5):415-424. https://doi:10.1016/S2215-0366(16)30024-4
4. Björkholm C, Monteggia LM. BDNF - a key transducer of antidepressant effects. Neuropharmacol. 2016;102:72-79. https://doi:10.1016/j.neuropharm.2015.10.034
5. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci. 2006;7(2):137-151. https://doi:10.1038/nrn1846
6. Kaul PN, Mallavarapu GR, Chamoli RP. The essential oil composition of *Angelica glauca* roots. Planta Med. 1996;62(1):80-81. https://doi:10.1055/s-2006-957812
7. Agnihotri VK, Thappa RK, Meena B, et al. Essential oil composition of aerial parts of *Angelica glauca* growing wild in North-West Himalaya (India). Phytochemistry. 2004;65(16):2411-2413. https://doi:10.1016/j.phytochem.2004.07.004
8. Irshad M, Aziz S, Rehman H, Hussain H. GC-MS analysis and antifungal activity of essential oil of *Angelica glauca*, *Plectranthus rugosus* and *Valeriana wallichii*. J Essent Oil Bear Plants. 2012;15:15–21.
9. Irshad M, Rehman HU, Shahid M, Aziz S, Ghous T. Antioxidant, antimicrobial and phytotoxic activities of essential oil of *Angelica glauca*. Asian J Chem. 2011;23:1947–51.
10. Pillai SG, Yadav Y, Sharma K. A Review on an endangered himalayan medicinal aromatic plant - Choraka (*Angelica glauca* Edgew). Int Ayur Med J. 2020; Available from: http://www.iamj.in/posts/images/upload/4508_4515.pdf
11. Sharma S, Rasal VP, Patil PA, Joshi RK. Effect of *Angelica glauca* essential oil on allergic airway changes induced by histamine and ovalbumin in experimental animals. Indian J Pharmacol. 2017;49(1):55-59. https://doi:10.4103/0253-7613.201019
12. Mannan A, Abir AB, Rahman R. Antidepressant-like effects of methanolic extract of *Bacopa monniera* in mice. BMC Complement Altern Med. 2015; 15:337 https://doi.org/10.1186/s12906-015-0866-2
13. Long Y, Li D, Yu S, et al. Medicine-food herb: Angelica sinensis, a potential therapeutic hope for Alzheimer's disease and related complications. Food & Function. 2022;13(17):8783-8803. https://doi:10.1039/d2fo01287a.
14. Ma JC, Zhang HL, Huang HP, et al. Antidepressant-like effects of Z-ligustilide on chronic unpredictable mild stress-induced depression in rats. Exp Ther Med. 2021;22(1):677. https://doi:10.3892/etm.2021.10109
15. Jang DP, Lee SH, Lee SY, Park CW, Cho ZH, Kim YB. Neural responses of rats in the forced swimming test: [F-18] FDG micro PET study. Behav Brain Res. 2009;203(1):43-47. https://doi:10.1016/j.bbr.2009.04.020
16. Vazquez-Matias DA, de Vries EFJ, Dierckx RAJO, et al. PET imaging of animal models with depressive-like phenotypes. Eur J Nucl Med Mol Imaging. 2023; 50, 1564–1584 https://doi.org/10.1007/s00259-022-06073-4
17. Boiangiu RS, Bagci E, Dumitru G, Hritcu L, Todirascu-Ciornea E. *Angelica purpurascens* (Avé-Lall.) Gilli. Essential oil improved brain function via cholinergic modulation and antioxidant effects in the Scopolamine-induced Zebrafish (Danio rerio) model. Plants (Basel). 2022;11(8):1096. https://doi:10.3390/plants11081096
18. Liu Y, Li Y, Xie J. Traditional chinese medicine strategy for treating major depressive disorder based on a famous formulation-Baweixiaoyaosan. An. Acad. Bras. Cienc. 2023; 95 (suppl 1): e20220676. https://doi:10.1590/0001-3765202320220676.
19. Winiarska-Mieczan A, Kwiecień M, Jachimowicz-Rogowska K, Donaldson J, Tomaszewska E, Baranowska-Wójcik E. Anti-Inflammatory, Antioxidant, and Neuroprotective effects of polyphenols-polyphenols as an element of diet therapy in depressive disorders. Int J Mol Sci. 2023;24(3):2258. https://doi:10.3390/ijms24032258
20. Hassan SSU, Samanta S, Dash R, et al. The neuroprotective effects of fisetin, a natural flavonoid in neurodegenerative diseases: Focus on the role of oxidative stress. Front Pharmacol. 2022;13:1015835. https://doi:10.3389/fphar.2022.1015835