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Antidepressant activity of *Spathodea campanulata* in mice and predictive affinity of spatheosides towards type A monoamine oxidase

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Abstract: The antidepressant activity *of Spathodea campanulata* flowers was evaluated in mice and *in silico*. When tested at doses of 200 and 400 mg/kg, the methanol extract of *S. campanulata* (MESC) showed dose-dependent antidepressant activity in the force swim test (FST), tail suspension test (TST), lithium chloride-induced twitches test and the open field test. In FST and TST, animals treated with MESC demonstrated a significant decrease in the immobility period compared to the control group. The lithium chloride-induced head twitches were significantly reduced following administration of MESC. The latter, at the dose of 400 mg/kg, also significantly reduced locomotor activity. Following administration of MESC, changes in the levels of serum corticosterone, and of norepinephrine, dopamine, serotonin, 4-hydroxy-3-methoxyphenylglycol (MHPG), 4-dihydroxyphenylacetic acid (DOPAC), and 5-hydroxyindoleacetic acid (5-HIAA) were measured in different brain regions using HPLC. The presence of spatheoside A (*m/z* 541) and spatheoside B (*m/z* 559) in MESC was detected using HPLC/ESI-MS. These two iridoids demonstrated a high predictive binding affinity for the active site of the type A monoamine oxidase (MAO-A) enzyme with scores of 99.40 and 93.54, respectively. These data suggest that *S. campanulata* flowers warrants further investigation as a source of novel templates for antidepressive drugs.

Key words: Antidepressant activity; Depression; Monoamines; Molecular docking; *Spathodea campanulata.*

Introduction

Depression is a common and serious psychiatric disorder that is a major contributor to the global burden of disease. According to the World Health Organisation, an estimated 322 million people worldwide suffer from depression (1). It has been reported that reactive oxygen species (ROS) and nitrogen species play an important part in the pathogenesis of depression by regulating the levels and activity of noradrenaline (norepinephrine), serotonin, dopamine and glutamate, the principal neurotransmitters involved in the neurobiology of depression (2). Several classes of antidepressant drugs (i.e. tricyclic antidepressants, selective serotonin reuptake inhibitors, selective reversible inhibitors of monoamine oxidase A, and specific serotonin–norepinephrine reuptake inhibitors) are used currently to treat depression However, a high number of side effects (e.g. sexual dysfunction) have been reported with these drugs and there is a need to discover an effective alternative treatment for depression that is better tolerated (3).

A variety of medicinal plants are used as antidepressants in traditional medicine (4) and/or contain some chemical constituents that have already demonstrated antidepressant activity (5). *Spathodea campanulata* Beauv. (Bignoniaceae), known as the African tulip tree, is native to Africa but commonly distributed throughout South America, the Caribbean and the Pacific Isles (6). Traditionally, *S. campanulata* is useful for the treatment of fever, dysentery, constipation, malaria, diabetes and skin diseases (7). The species is reported to contain some iridoids, flavonoids, tannins, saponins, alkaloids, terpenoids and steroids (8-10). Previous reports have suggested that phytochemicals like iridoids, flavonoids, alkaloids and tannins have antidepressant activity (11,12). To the best of our knowledge, the antidepressant activity of *S. campanulata* and its constituents are yet to be evaluated. The present study was performed to evaluate the antidepressant activity of *S. campanulata* flowers in different mice models. Further alteration in the levels of monoamines such as norepinephrine (NE), dopamine (DA), serotonin (5-HT), and their respective metabolites 4-hydroxy-3-methoxyphenylglycol (MHPG), 4-dihydroxy-phenylacetic acid (DOPAC), and 5-hydroxyindoleacetic acid (5-HIAA) was recorded in different regions of mice brains following administration of *S. campanulata* extracts. The role of corticosterone in anxiety/depression was also investigated by measuring its serum levels in treated *versus* untreated animals. A molecular docking study was performed to investigate

the predictive binding affinity of two iridoids identified within *S. campanulata*, spatheoside A and spatheoside B, towards the type A monoamine oxidase enzyme.

Materials and Methods

Plant collection and identification

Spathodea campanulata flowers were collected in Mannargudi and around Thiruvarur (Dt), Tamil Nadu, India in the month of July and August 2012. The plant was identified and authenticated by Dr. Soosairaj, Department of Botany, St. Joseph's College, Trichirappalli, Tamil Nadu, India, where a voucher specimen number (SJCBOT 1563/2013) has been deposited.

Extraction of plant material

The flowers were air dried in the shade for 10-15 days and the dried material (246 g) was grounded to a fine powder and stored in air tight bottles. Extraction was performed by maceration at room temperature with ethyl acetate and then methanol (10% w/v) for 72 h with intermittent shaking to afford EAESC and MESC, respectively. Following filtration, the extracts were concentrated under reduced pressure at < 40 °C and were stored in desiccators. The yields obtained were 5.03 and 6.37 % DW for EAESC and MESC, respectively.

Preliminary phytochemical investigation

Extracts were screened for presence of flavonoids, tannins, saponins, alkaloids, terpenoids and steroids using standard methods (8, 13,14).

Experimental animals

Male Swiss albino mice (25-40 g) were used for all experiments. The animals (four per cage) were sheltered under conventional laboratory conditions of temperature (25 ± 2 °C) with a 45-55% relative humidity and a 12/12 h light/dark cycle (15). Sterile husk paddy was used as bedding material. Standard pellets (Golden feeds, New Delhi) were used as the standard diet with the availability of water *ad libitum*. Pellets were withdrawn (but not water) 4 h prior to the administration of extracts and/or drug until completion of all experiments on the day. Animals were transferred 1 h prior to an experiment to an experimental room for adaptation purposes. Ethical approval was obtained from the Institutional Animal Ethical Committee (Ref no PBRI/IAEC/PN-15014). All experimental studies were carried out according to the guidelines from the Committee for the Purpose of Control and Supervision of Experiment on Animals.

Acute toxicity

This study was performed according to Annex 2a of the OECD guidelines (16). The animals were divided into groups ($n = 3$) which received increasing oral doses (5, 50, 300 and 2000 mg/kg) of MESC. The control group received sterile distilled water (SDW). After 24 h, the general signs and symptoms of toxicity and mortality rates in each group were recorded.

Antidepressant activity

Antidepressant activity was studied by observing the behaviour of individual mice in response to a stressful stimulus which it cannot escape from in the force swim test and the tail suspension test. The animals ($n = 6$) were divided in groups I–VI, where group I received SDW (negative control), group II-VI were treated orally with 20 mg/kg amitriptyline, 200 and 400 mg/kg EAESC, and 200 and 400 mg/kg MESC, respectively.

Forced Swim Test (FST)

In this test, after treatment, each animal from group I-VI was positioned gently into water (up to 20 cm) in transparent cylindrical polyethylene tanks (25 cm high, 10 cm internal diameter) for 6 min. When an animal stopped swimming - swimming being a normal escape response mechanism - and floated on the surface of the water, it was considered it had "given up" (a characteristic reported to be similar to depression in humans). The duration of immobility (in seconds) was assessed during the last 4 minutes of the test (17).

Tail Suspension Test (TST)

In this test, after treatment, the mice were hanged, with the help of adhesive tape placed approximately 1 cm from the tip of their tails, 58 cm above the floor for a period of 6 minutes. The duration of immobility (in seconds) produced by the tail suspension was recorded during the last 4 minutes of the test (18).

Lithium chloride-induced head twitches

The mice were randomly divided in five groups ($n = 6$), where group I received the vehicle (SDW), group II received lithium chloride (100 mg/kg, intraperitoneally), group III-V were treated with amitriptyline (20 mg/kg, p.o), 200 and 400 mg/kg MESC, respectively. Lithium chloride was administered intraperitoneally to groups III-V and the number of head twitches was counted for 1 h for each group of mice (19).

Open field test

The mice ($n = 6$) were distributed in four groups, where group I received SDW (negative control), group II-IV were orally administered 20 mg/kg amitriptyline (positive control), 200 and 400 mg/kg MESC, respectively. The mice were individually placed in a wooden box (40 × 60 × 50 cm) with the floor divided into 12 squares. The number of crossed lines passed with the four paws by each animal was registered during a period of 6 min (20).

Determination of the levels of monoamines and of their metabolites in the mice frontal cortex, striatum, hippocampus, and hypothalamus

Instrumentation

High-performance liquid chromatography (HPLC) was performed with a quaternary pump HPLC-DST curie (SHIMADZU Corporation, Kyoto, Japan), equipped with a 25 cm length × 4.6 mm internal diameter Cosmosil C_{18} Column (particle size 5 µm) and a rheodyne syringe injector (25 µL). Acetic acid (0.01–0.1%) methanol, phosphoric acid (0.01–0.1%): methanol and formic acid (0.01–0.1%):acetonitrile was used as mobile phase. The wavelength was selected as 280 nm according to the previous literature (21) and the injection volume was 20 µL.

Quantification of monoamines and metabolites

Immediately after the FST and TST assays were carried out, the mice (Group I, II, V and VI) were anaesthetized and their brains were removed to isolate the frontal cortex, striatum, hippocampus and hypothalamus tissues. Each tissue was weighed and placed separately in 5 mL of ice-cold homogenizing solution (8.8 mg of ascorbic acid and 122 mg of EDTA in 1 L of perchloric acid 0.1 M). After homogenization, the solution was centrifuged at 10,000 × g for 10 min at 4 °C. Twenty microliters of the resultant supernatant were injected in the HPLC system. The levels of monoamines (NE, DA and 5-HT) and of their metabolites (MHPG, DOPAC, 5-HIAA) were measured using electrochemical detection in each of the four brain tissues (22). Blood samples were further collected into 1.5 mL ethylenediaminetetraacetic acid (EDTA)- coated microcentrifuge vials. The tubes were centrifuged at 10,000 rpm for 4 min, the serum was obtained and stored at – 20 °C until further analyses. Serum corticosterone levels were measured using a DRG EIA-5186 ELISA kit (DRG diagnostic, Marburg, Germany) (23,24).

HPLC/ESI-MS profiling of MESC

The methanol extract of *S. campanulata* was analysed by LC/MS. Analysis was performed using the Acquity UPLC- I Class system and a Xevo G2-XS QTof spectrometer, with the Unifi software (Waters®). Separation was carried out using an Acquity UPLC HSS-T3 column (100 x 2.1 mm, 1.7 µm). The column was maintained at 40 °C throughout the analysis and sample temperature was kept at 20 °C. The elution was carried out at a flow rate of 0.4 mL/min using a gradient elution with a mobile phase of 0.1 % formic acid in water (mobile phase A) and 0.1 % formic acid in acetonitrile (mobile phase B) and recorded for 30 min. 1 µL of test solution was injected during the analysis in positive mode and 0.5 µL in negative mode (25). Structure assignments were made based on a systematic search for molecular ions using the extracted ion mass chromatograms and comparing them with literature data.

Statistical analyses

Two-way and one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons were used to compare differences among groups. Data are presented as mean± standard deviation, where $P < 0.05$ was considered as significant. The Graph Pad prism software (v.8.0.2) was used for the data analysis.

Molecular docking

Ligand and protein preparation

The structures of two iridoids, namely spatheoside A and spatheoside B, and of chlorgyline (a known monoamine oxidase type A inhibitor) were drawn using Chem3D Ultra and then exported to the Accelery's Drug Discovery Studio (version 2) software. The crystal structure of the monoamine oxidase type A (MAO-A) enzyme was downloaded from the protein data bank in PDB format (PDB ID: 2BXS) (https://www.rcsb.org/). All water molecules were removed from the protein structure, valency was monitored and hydrogen atoms were added. The active site was defined for the prepared protein within a radius of 9 Å, so as to include the key protein residues involved in binding interactions with the ligands.

Docking

The LibDock module of Accelery's Drug Discovery Studio was used for the docking study. The prepared structures of spatheoside A, spatheoside B and chlorgyline were docked into the defined active site of the prepared MAO A protein. Different poses for spatheoside A, spatheoside B and chlorgyline were generated and analysed on the basis of their docking scores (13).

Results

Preliminary phytochemical investigation

Phytochemical investigation of MESC revealed some alkaloids, tannins, glycosides, terpenoids, polyphenols, flavonoids and steroids, whereas EAESC showed the presence of some flavonoids, glycosides, saponins, alkaloids, steroids, fats and oils (data not shown).

Acute oral toxicity

Following the administration of EAESC and MESC, we observed no lethal effects even at the highest dose of 2000 mg/kg. Therefore, the doses of 200 and 400 mg/kg were selected for further pharmacological work (data not shown).

Antidepressant activity

Forced swim test (FST) and tail suspension test (TST)

In both of these behavioural models of depression, *S. campanulata* extracts at doses of 200 and 400 mg/kg decreased significantly the immobility period of the mice when compared to the control group. Amitriptyline at a dose of 20 mg/kg also decreased the immobility period when compared to the control group in both tests. As MESC exhibited a highly significant ($p<0.0001$) effect compared to the control group in both tests, this extract was selected for further studies (Table 1).

Effect on lithium chloride-induced head twitches

The results indicated that lithium chloride produced 26.66 ± 2.16 head twitches in mice. Animals treated with MESC at doses of 200 and 400 mg/kg had a significant ($P < 0.0001$) reduction in the number of head twitches when compared to the lithium chloride-treated control group. Treatment with amitriptyline (20mg/kg) also led to a significant reduction in the number of head twitches (Table 2).

Open field test

A significant ($p<0.0001$) reduction in locomotor activity was observed after the administration of MESC at 400 mg/kg when compared to the control group. The amitriptyline-treated group also revealed a significant reduction in locomotor activity compared to the control group (Figure 1).

Determination of the levels of monoamines and of their metabolites in the mice frontal cortex, striatum, hippocampus, and hypothalamus

All brain regions of mice treated with MESC (400

Table 1. Effect of *S. campanulata* extracts on the duration of the immobility period in the force swim and the tail suspension tests.

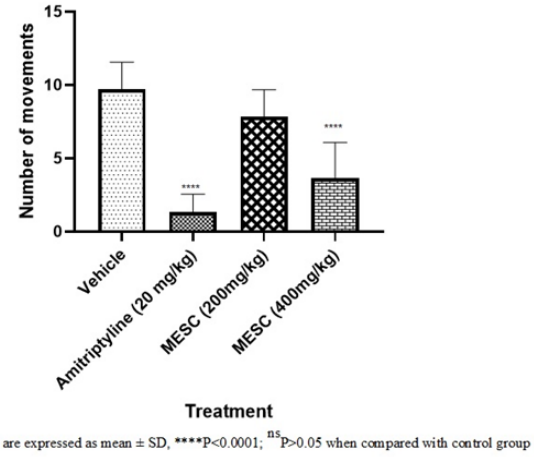
Treatment	Immobility (seconds)	
	FST	TST
Vehicle	204.66±7.04	231.33±11.44
Amitriptyline (20 mg/kg)	95.16±9.08****	109.83±10.94*
EAESC (200mg/kg)	187.33±8.28*	213.33±9.62*
EAESC (400mg/kg)	180.83±8.47**	201.66±11.82****
MESC (200mg/kg)	152.66±9.47****	168.66±16.39****
MESC (400mg/kg)	120.00±9.50****	132.00±15.03****

Values are expressed as mean ± SD, ****P<0.0001; ***P<0.001; **P<0.01; *P<0.1 when compared with vehicle group

Table 2. Effect of *S. campanulata* methanolic extract (MESC) on lithium chloride-induced head twitches in mice.

Treatment	Head twitches
Vehicle	3.93±1.31
Lithium chloride (100 mg/kg)	26.66±2.16
Amitriptyline (20 mg/kg)	4.66±1.21****
MESC (200mg/kg)	13.66±1.36****
MESC (400mg/kg)	8.83±1.47****

Values are expressed as mean ± SD, ****P<0.0001; when compared with lithium chloride group.



Values are expressed as mean ± SD, ****P<0.0001; ^{ns}P>0.05 when compared with control group

Figure 1. Effect of *S. campanulata* methanolic extract (MESC) on locomotor activity in mice.

mg/kg) showed significantly increased levels of 5-HT compared to the vehicle. Treatment with MESC (400 mg/kg) also showed significantly increased levels of NE (striatum and hypothalamus) and DA (hippocampus) compared to the vehicle. Treatment with MESC significantly reduced the levels of 5-HIAA (at 200 mg/kg in all regions and 400 mg/kg in the striatum, hippocampus, hypothalamus), MHPG (at both doses in all regions) and DOPAC (at 200 mg/kg in all regions and 400 mg/kg in the hypothalamus) when compared to the vehicle control (Figure 2a-d). In addition, oral administration of MESC (400 mg/kg) for one week caused a significant reduction in the serum levels of corticosterone when compared to the control group (Figure 3).

Metabolite profiling of MESC

Metabolites within MESC were analysed by HPLC/ESI-MS. The presence of spatheoside A and spatheoside B was detected with peaks at 16.04 min and 25.25 min showing molecular ions $[M-H]^-$ at *m/z* 541.1636 and *m/z* 559.1298, respectively (26) (Figure 4).

Molecular docking

Analysis of the docking poses of spatheoside A and spatheoside B, with the monoamine oxidase type A enzyme revealed that spatheoside A and spatheoside B (Libdock scores of 99.40 and 93.54, respectively) interacted with the active site of the target trough four H-bonds with Arg51, Gly49, Tyr444 and Ser24 residues. Both compounds showed four van der Waals interactions with Ile23, Ala448, Thr435 and Thr52 residues. Spatheoside A displayed hydrophobic interactions with Ala272, Gly434, Gly443, Met445, Gly67, Gly50 and Gly22. Spatheoside B displayed hydrophobic interactions with Gly434, Gly443, Met445, Gly67, Gly50 and Gly22. The standard antidepressant drug chlorgyline (Libdock score of 105.46) exhibited one hydrogen bond

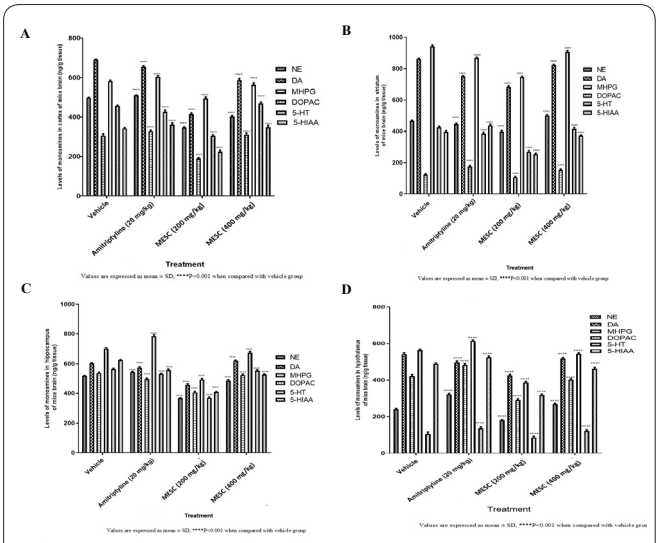


Figure 2. Effects of *S. campanulata* methanolic extract (MESC) on the levels of monoamines and their metabolites (ng/g tissue) in mice brain cortex (A), striatum (B), hippocampus (C), and hypothalamus (D). Norepinephrine (NE) and serotonin (5-HT), dopamine (DA), MHPG: 4-Hydroxy-3-methoxyphenylglycol, DOPAC: 4-dihydroxyphenylacetic acid, 5-HIAA: 5-hydroxyindoleacetic acid.

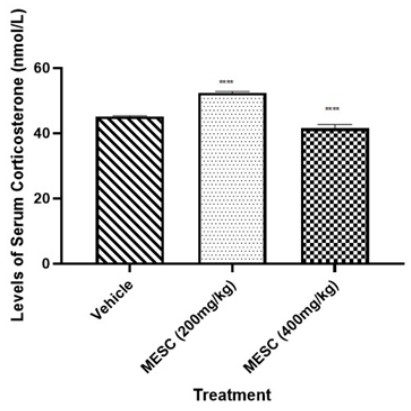


Figure 3. Effect of *S. campanulata* methanolic extract (MESC) on the levels of corticosterone in mice.

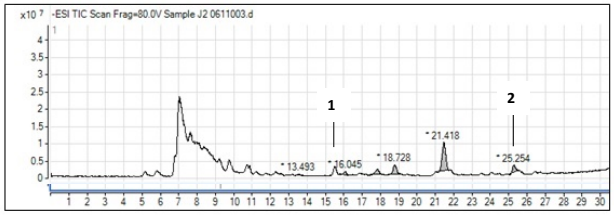


Figure 4. Detection of spatheoside A (1) and B (2) in *S. campanulata* methanolic extract (MESC) using LC/ESI-MS.

interaction with Arg51, five van der Waals interactions with Thr52, Gly66, Lys305, Thr435 and Ile23 and thirteen hydrophobic interactions. with Trp397, Tyr407, Ile304, Cys406, Phe352, Tyr69, Val303, Met445, Gly443, Ala448, Ala68, Val65 and Gly67 residues (Figure 5).

Discussion

In this study, we evaluated the antidepressant activity of an ethyl acetate (EAESC) and a methanolic (MESC) extract from *Spathodea campanulata* flowers using pharmacological and computational approaches. The antidepressant potential of EAESC and MESC was initially tested in two behavioural despair tests (FST and TST). Both tests are used to determine a characteristic response (duration of immobility), reflecting a typical state of despair or learned helplessness, which is common in depression (27, 28). The tests are based on an observation that after initial escape-oriented movements, rodents tend to develop an immobile posture when placed in a stressful condition (29). As our results indicated that MESC (at doses of 200 and 400 mg/kg) produced highly significant antidepressant-like activity in both tests, it was selected for further studies.

Numerous studies have revealed that monoaminergic neurotransmitters, including DA, NE and 5-HT are responsible in modulating brain circuits implicated in mood regulation (30,31). Depression is thought to result from an imbalance in the monoamine levels in regions of the brain (mainly frontal cortex, striatum, hippocampus and hypothalamus) that regulate behavioural functions, such as emotion, motivation, learning and memory. In particular, any dysfunctioning of the serotonergic neurotransmission system, leading to lower levels of

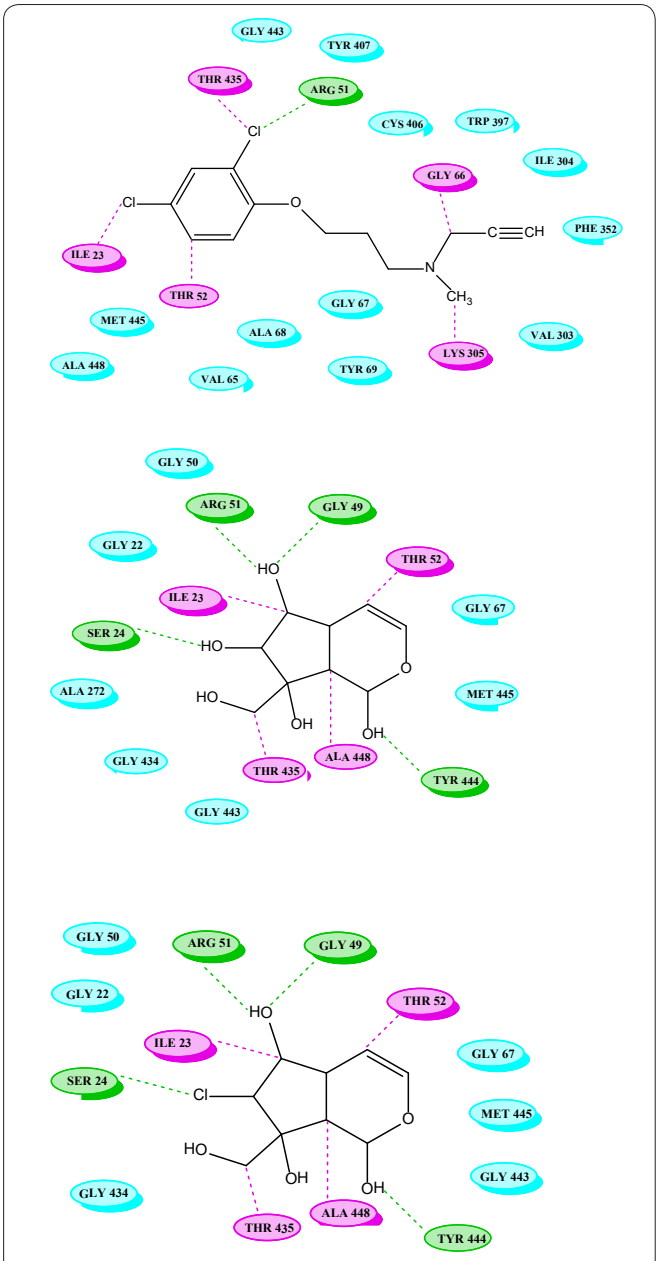


Figure 5. Docking pose of chlorgyline (a), spatheoside A (b) and spatheoside B (c) on the active site of MAO-A. The dotted green lines indicate hydrogen bondings whereas the pink lines indicate van der Waals interactions.

serotonin (5-HT) and 5- HIAA (the major metabolite of 5-HT) in the brain, contributes greatly to the pathogenesis of depression (32-34). Thus, the serotonergic system is considered to be the most promising target for the management of psychological disorders (35). MESC exhibited impressive antidepressant activity in FST and in TST possibly *via* modifying multifaceted serotonergic neurotransmission and reducing the levels of 5- HIAA (36).

Similarly, in the lithium chloride-induced head twitches assay, mice treated with MESC (200 and 400 mg/kg) demonstrated a significant reduction in head twitches when compared to the lithium chloride-treated group. Lithium is known to induce head twitches (37) as well as to alter the function of 5-HT_2 receptor *via* multiple pathways (38). These findings suggest that MESC possibly altered serotonergic transmission either by inhibiting the reuptake of serotonin in neuron or interfering with its metabolism at the nerve terminal *via*

inhibiting monoamine oxidases (39).

Administration of MESC (400 mg/kg) led to a dose-dependent significant reduction in locomotor activity in the open-field test, in agreement with previous studies that have showed that antidepressant-like effects can be linked with a decreased locomotor activity in open-field test in rodents (40).

Treatment with MESC (400 mg/kg) led to increased levels of NE (striatum and hypothalamus), DA (hippocampus), and 5-HT (cortex, striatum, hippocampus and hypothalamus). These are the major regions of the brain participating in important behavioural functions, such as emotion, motivation and learning and memory and it has been reported that depression develops as a result of an imbalance of the levels of monoamines in these regions (27). In various regions, MESC also significantly reduced the levels of the monoamine metabolites 5-HIAA, MHPG and DOPAC, suggesting that it may act by inhibiting the normal metabolism of monoamines in the brain (41).

Depression has been associated with a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which results in high levels of corticosterone (42). We observed that MESC (400 mg/kg) significantly decreased the levels of serum corticosterone in mice compared to untreated animals. This observation is in agreement with a previous study which has showed that plant-derived products with antidepressant-like activity could normalise the response of the HPA axis and reduce corticosterone serum levels in rodents (43-45).

S. campanulata is rich in iridoids and spatheoside A and spatheoside B are two iridoids which are known to be present in *S. campanulata* (26,46) and that were identified in MESC following LC-MS analysis. In an effort to understand the possible mechanism of action for antidepressant activity of MESC, we sought to predict the binding affinity of these iridoids towards the MAO-A enzyme using a molecular docking approach (47,48). The latter is a mitochondrial enzyme responsible for the oxidative deamination of monoamines, mainly 5-HT, NA, DA (49). An increase in the expression of MAO and a decrease in the brain levels of NE and 5-HT are considered as the major pathogenic factors in depressive disorders (11,50). When docked on the MAO-A, spatheoside A and spatheoside B showed a high Libdock score comparable to chlorgyline, an irreversible and selective inhibitor of this enzyme. This may explain their potential role in the antidepressant activity of MESC, in good correlation with previous studies which have reported the MAO inhibitory activity of iridoids (51).

In conclusion, the methanolic extract of *S. campanulata* (MESC) exhibited promising antidepressant activity in different behavioral models of depression in mice and was shown to reduce the serum levels of corticosterone and increase the levels of some monoamines, including serotonin, in specific regions of mice brains. LC-MS analysis revealed the presence of iridoids in this extract, including spatheoside A and spatheoside B which demonstrated good predictive affinity towards the type A monoamine oxidase. Further studies are required to establish if these compounds can act as new inhibitors of this enzyme and provide some templates for the development of new drugs to combat depression.

Author contributions

JB, RS, SJ: Methodology, Investigation, Validation. BS: Methodology, Investigation, Formal Analysis. JD, SS: Conceptualization, Project Administration, Funding Acquisition, Supervision. KV: Formal Analysis. VD, VS, APM: Visualization. SS: Writing Original Draft. VS: Writing – Review and Editing. All the authors reviewed the content of the manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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