RESEARCH PAPER

Pharmacological Investigation of Methanolic Extract of Gmelina arborea for Anxiolytic Activity and Neurotransmitter Modulation

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ABSTRACT

Introduction: Anxiety disorders are prevalent neuropsychiatric conditions associated with oxidative stress and neurotransmitter imbalance, particularly gamma-aminobutyric acid (GABA) and serotonin. Herbal medicines with antioxidant and neuroprotective properties may offer safer therapeutic alternatives. The present study investigated the anxiolytic potential of the methanolic extract of *Gmelina arborea* (MEGA) in stress-induced murine models.

Materials and Methodology: Acute oral toxicity was evaluated as per OECD guidelines. Swiss albino mice (25–35 g) were subjected to electric foot shock and restraint stress-induced anxiety models. Behavioral assessments were conducted using the Elevated Plus Maze (EPM) and Light–Dark Transition (LDT) tests. MEGA was administered orally at doses of 200 and 400 mg/kg, while Diazepam (1 mg/kg) served as the standard. In vitro antioxidant activity was assessed using DPPH, hydrogen peroxide, and nitric oxide scavenging assays. Neuroprotective activity was evaluated in SH-SY5Y neuroblastoma cells exposed to H_2O_2-induced oxidative stress. Brain GABA and serotonin levels were estimated post-treatment.

Results: MEGA was safe up to 2000 mg/kg with no mortality observed. The extract exhibited dose-dependent antioxidant activity and significant protection against oxidative stress in SH-SY5Y cells. In vivo studies demonstrated a significant increase ($p < 0.05$) in time spent in open arms (EPM) and light compartment (LDT) compared to disease control. Biochemical analysis revealed restoration of GABA and serotonin levels comparable to Diazepam-treated groups.

Conclusion: The findings confirm that *Gmelina arborea* possesses significant anxiolytic, antioxidant, and neuroprotective properties, supporting its potential as a natural therapeutic candidate for anxiety disorders..

Keywords: N\A

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INTRODUCTION

Anxiety disorders are a major global health concern, impacting millions of people across all age groups and countries. The symptoms which are characterized by excessive worry, fear and uneasiness, can negatively impact one's quality of life resulting in impairments in everyday functioning, decreased productivity and significant suffering [1]. Even though there is growing evidence in both preclinical and clinical settings suggesting Oxidative stress could potentially have a notable impact on the emergence of anxiety pathophysiology. Recent research indicates that increased oxidative harm to lipids, proteins and nucleic acids and antioxidant defenses may be characteristics of anxiety disorders [2]. Anxiety disorders can result from malfunctions in brain circuits responsible for regulating fear and other emotions [3]. In the face of challenging circumstances like pandemics, which can be distressing and cause profound emotional shifts in children as well as adults. According to the WHO, these conditions include OCD, phobias, panic disorder, social phobia, PTSD and GAD [4]. The majority of study on anxiety has been done on the regulatory systems, such as the serotoninergic and gamma-aminobutyricacidergic (GABAergic) systems [2]. The brain produces various neurotransmitters like DA, adrenaline, acetylcholine, NE, GABA and Serotonin each playing distinct roles in the neurophysiology of anxiety [4].

One of the significant and most extensively grown species of the Verbenaceae family of medicinal plants is *Gmelina arborea*, an essential component among Dashamula. This plant is used as a nervine tonic. It helps in neurological disorders. Gambhari is known to contain a wide range of phytochemicals, including alkaloids, flavanoids, glycosides, tannins, saponins and steroids.

MATERIALS AND METHODS

Animals

In the study, 25–35g Swiss albino mice of both sexes were used.

Plant Material

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The *Gmelina arborea* (Gambhari) leaves were obtained from KLE Ayurveda College, Belgaum (BMK/CRF/70/2024-25).

Preparation of Plant extract

% inhibition of DPPH radical = ([Abr – Aar]/Abr) X 100

After collecting, the leaves were dry in shade and crushed into a powder form using a grinder and Forty grams of leaves powder were extracted for 24 hours using 300 ml of methanol. Concentrating the extracts was done by evaporating them on a rotary evaporator, filtered with whatman filter paper and then refrigerated between 2 to 8^0C [5].

Drugs

Diazepam was used as a reference drug (1mg/kg). 200 and 400mg/kg Methanolic extract of *Gmelina arborea* made by adding 0.5% CMC as a suspending agent. All the solutions were prepared freshly on test days and administered orally.

% Scavenged (H2O2) = ([Ai – At]/Ai) X 100

2.5. *In Vitro* Cell viability Assay [6, 7]

MTT test cytotoxicity studies use the human neuroblastoma cell line SH-SY5Y. It is recognized as a useful cellular model for researching the biochemistry of Alzheimer's disease. SHSY5Y cells, commonly known as neurosteroid-producing cells, express the key steroidogenic enzymes.

Using DMEM media supplemented with 10% FBS, the neuroblastoma cell line SH-SY5Y's cell counts were modified to 1.0 × 105 cells per ml. A 96-well flat-bottom microtitre plate was prepared by adding 100µL of diluted cell solution (70–80% confluence) to each well. After a day, the cells were centrifuged once the population reached a sufficient size, and the pellets were suspended at varying levels: 25, 50, and 100 µg/mL. Following that, the plates were left to incubate for 24 hours at 37°C with 5% CO2 in order to facilitate microscopic examination. After then, observations were made every 24 hours. In order to cause oxidative stress, cells was subjected to different amounts of H2O2 for a duration of 90 minutes following a 24-hour period. After that, gently mixing MEM without phenol red, 20 µl of MTT (2 mg/mL) was added. Following that, the plates were maintained in a 37°C atmosphere with 5% CO2 for two hours. To dissolve the formazan that had formed, 100 µl of DMSO was gradually added to each plate and gently stirred. The sample's absorbance at 540 nm was measured using the microplate reader. The percent of viable cells and the extract concentration required to 50% limit cell growth were ascertained using the dose-response curve. Three measurements of each sample's absorbance were made utilizing an Elisa microplatereader (Benesphera E21) calibrated to 570 nm in wavelength.

2.6. Antioxidant Activity [8]

DPPH Scavenging Assay

The antioxidant potential of the test materials is determined by observing the variation in the optical density of DPPH radicals, which indicates their capacity to neutralize free radicals. Following a methanol dilution of the sample extract (0.2 ml), 3 ml of a 0.5 Mm DPPH solution, the absorbance was measured at 517 nm following a 30-minute interval. Use the following formula to get the percent of DPPH radical scavenging.

In this case, Abr represents absorbance prior to the reaction, while Aar represents absorbance after to the reaction.

Hydrogen Peroxide scavenging assay

The method can be applied to ascertain whether plant extracts have the ability to scavenge hydrogen peroxide. In 50Mm pH 7.4 phosphate buffer, a 4Mm hydrogen peroxide solution is made. To determine the quantity of hydrogen peroxide a spectrophotometer was utilized to determine the absorbance at 230 nm. An extract (20 µg/mL) in distilled water is then added to hydrogen peroxide after a 10-minute reaction with a blank solution that contains phosphate buffer but no hydrogen peroxide. This method is used to determine the proportion of hydrogen peroxide scavenging. In this case, Ai stands for the control absorbance and At for the test absorbance.

Nitric Oxide Scavenging Assay

0.5 ml of sample is combined with 2ml of 0.5 ml of PBS (pH 7.4) and 10 mm sodium nitroprusside is made at different quantities (200, 400, 600, 800, and 1000 µg/ml). After that, this combination is incubated at 25°C. After 150 minutes of incubation, 0.5 ml of the extracted solution is combined with 1 ml of naphthylethylenediamine dichloride (0.1% w/v) and 0.5 ml of Griess reagent (1.0 ml of sulfanilic acid reagent, diluted to 0.33% in 20% glacial acetic acid) at room temperature for five minutes. Pouring the liquid into a cuvette, the absorbance at 546 nm is measured after 30 minutes of room temperature incubation. The formula used to determine the degree of NO radical inhibition is as follows:

Where A0 and A1 denote the absorbance prior to and following the Griess reagent reaction, respectively.

% inhibition of NO radical = ([A0 – A1]/A0) X 100

2.7. Acute oral Toxicity [9, 10]

A group of 3 Mice will be orally administered with Methanolic extract of *Gmelina arborea* at a dose of 2000mg/kg body weight. Mice will be continuously observed for mortality and behavioral responses initially for 48 h and once daily for 14 days. If there is 0-1 death at a dose level of 2000 mg/kg administered to 3 animals during the first step, 2000 mg/kg will be administered to an additional 3 animals. If the test substance causes again 0-1 death after the second administration too, there is no need to administer doses exceeding 2000 mg/kg.

2.8. In Vivo Anti-anxiety models

Assessment of Anxiety

Elevated Plus Maze (EPM) [11]

The four arms of the EPM are placed so that the two arms of each type are opposed to one another: 30 × 5 cm^2 for two open arms and 30 × 5 cm^2 for two closed arms. The elevated maze is 30 cm above the floor. The closed arms have walls that are 17 cm high. Each animal faced one of the enclosing arms and was positioned in the center of the EPM, for the duration of the test. After that, the entire duration of both closed and open arms was measured during the course of a 5 minute test session.

Elevated Plus Maze

Light and Dark Transition Model (LDT) [12]

The LDT model is a commonly used for evaluating mice anxiety. The 42 × 20 × 35 cm^2 light/dark box was made up of two chambers joined by a floor-level aperture in the middle of the separating wall. One compartment measured 42 x 20 x 35 cm^2 painted black and the other measured 42 x 20 x 35^2 cm and was covered in white paint. The top was covered, the little chamber was completely black.

Light and Dark Transition model

2.9. Models for Anxiety

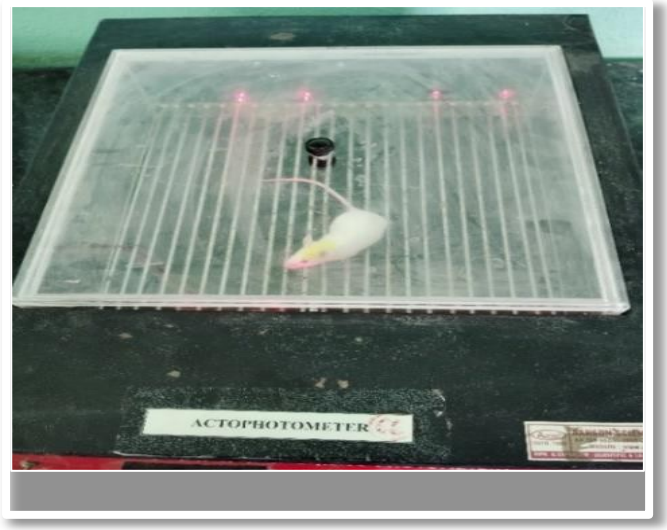
Electric Foot Shock Stress Induced Anxiety Model [13]

Every day, the mice received 3 minutes of electric foot shock (2 mA) using Actophotometer. Over the course of 7 days, the random programming of the shock intervals ranged from 2 to 3 seconds. The mice in Test I (200mg/kg) and Test II (400mg/kg) group received doses of the extracts and the Standard group received doses of diazepam (1mg/kg) orally from days 8 to 14. All mice were exposed to the EPM and LDT models on the 1^{st}, 7^{th} and 14^{th} day. It was done to evaluate each behavior. Another set of untreated mice (n = 6 per group), who were not given any medication and were not subjected to any form of electric foot shock, served as the control. Mice that weren't stressed were handled for two minutes every day before being put back in their own cage.

Electric foot shock Stress

Restraint or Immobilization Stress Induced Anxiety Model [14]

50 ml plastic falcon tubes were used to hold the mice and subjected to 2-3 hours of daily restraint stress for a period of seven days. To provide for adequate ventilation, a small hole was cut into the tube's base. The mice in Test I (200mg/kg) and Test II (400mg/kg) group received doses of the extracts and the Standard group received doses of diazepam (1mg/kg) orally from days 8 to 14. All mice were exposed to the EPM and LDT models on the first, seventh, and fourteenth day. It was done to evaluate each behavior. Another set of untreated mice (n = 6 per group), who were not given any medication and were not subjected to any form of electric foot shock, served as the control. Mice that weren't stressed were handled for two minutes every day before being put back in their own cage.



Restraint stress

2.10. Biochemical Studies [15, 16]

Removal of brain from Mice

The mice were immediately put to death by cervical dislocation following a behavioral examination. After the quick removal of the brain, 0.9% NaCl was added.

Estimation of Neurotransmitter:

GABA:

The pre-coated microplate wells were filled with 100 µL of dil. proBDNF standards, blank (assay diluent only), sample and QC sample. The assay protocol comprised sample for both positive & negative controls. After using plate sealer to seal the plate, it was incubated for 90 min. at 140 rpm and 0.351 G* on a shaker. The solution within the wells is disposed of and cleaned in manner previously mentioned. Each well receives 100 µL of 1x streptavidin-HRP conjugate. The plate is sealed with plate sealer and incubated for 30 min at 140 rpm and 0.351 G* on a shaker. After discarding the solution within the wells, repeat the washing. Each well received 100 µL of TMB & the plate was left to stand at normal room temperature for 10-15 min in the dark without being shaken. 100 µL of the stop solution was added in every well to halt the reaction. The colour visible blue turned to yellow. A plate reader was used to assess the absorbance at 450 nm.

Serotonin:

After preparing brain homogenate in cold acetyl acetate & centrifuging them for 30 min at 10000 RPM at below 4ºC. After preparing brain homogenate in cold acetyl acetate & centrifuging them for 30 min at 10000 RPM at below 4oC. 50 µL each of standard, acylated control and acylated sample were pipetted into designated wells of a microplate.

Subsequently, 50 µL of serotonin biotin & 50 µL of serotonin antiserum were added to each well. The plate was covered with a foil adhesive and incubated at room temperature (18- 25ºC) on an orbital shaker set at 500 rpm for 90 minutes. The incubation solution was discarded and the adhesive foil was removed. The plate was washed three times with 250 µL of diluted wash buffer, ensuring excess solution was removed by tapping the inverted plate on a paper towel. 150 µL of freshly prepared enzyme conjugate was added to each well. The plate was covered again with foil adhesive & incubated at room temperature (18- 25ºC) on an orbital shaker at 500 rpm for 60 minutes. After the second incubation solution was discarded & adhesive foil was removed. The plate was washed three times with 250 µL of diluted wash buffer, again tapping the inverted plate on a paper towel to remove excess solution. Each well received 200 µL of PNPP substrate solution and was incubated on an orbital shaker at 500 rpm for 60 min at room temperature (18-25ºC). To stop the substrate reaction, 50 µL PNPP stop solution was added to each well and the plate contents were gently mixed by shaking. The optical density was measured for 60 min after adding the stop solution at 405 nm using a photometer, with a reference wavelength set between 600-650 nm.

2.11. Statistical Analysis:

Using GraphPad Prism 9.0, the statistical evaluation was conducted using a one-way ANOVA and Dunnett's test, with the provided values marked as Mean±SEM in the context of *in vivo* experiments. The significant criteria for statistical analysis were set at $P<0.05$.

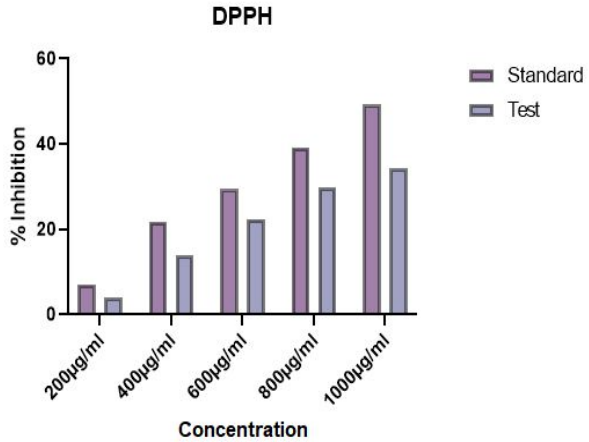
3. Results

3.1 Acute Oral Toxicity

The methanolic extract of *Gmelina arborea* is safe and non-toxic, even at doses as high as 2000 mg/kg p.o. The mice subjected to the tests showed no signs of developing abnormal behaviour or mortalities.

3.2 In vitro Antioxidant Assay

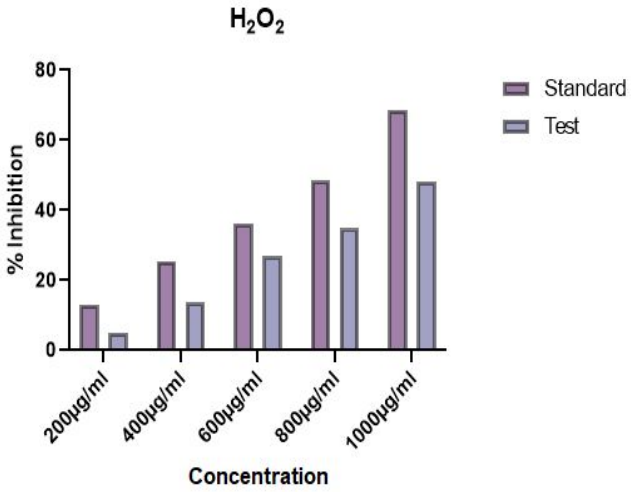
DPPH Scavenging Assay



% Inhibition of DPPH at different concentration (200-1000 µg/ml) of methanolic extract of *Gmelina arborea*.

The MEGA exhibited significant *In-vitro* DPPH radical scavenging activity. Notably, ascorbic acid displayed significantly greater DPPH radical scavenging activity than the methanolic extract of *Gmelina arborea*, with % inhibition at concentrations of 200 µg/ml and 1000 µg/ml, MEGA exhibited 35.321% and 72.612% inhibition of free radicals and Ascorbic acid exhibit 39.345% and 77.507% inhibition.

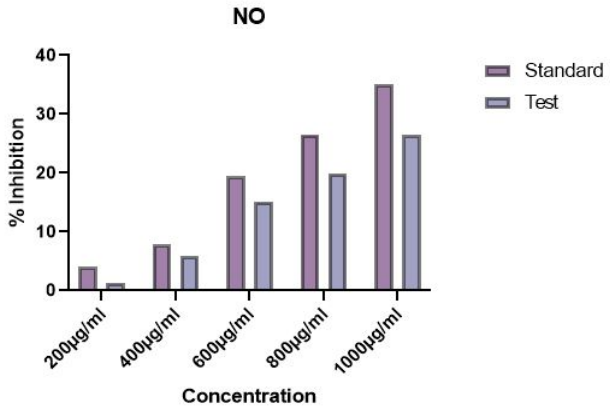
Hydrogen Peroxide (H_2O_2) Scavenging Assay



% Inhibition H_2O_2 at different concentration (200-1000 µg/ml) of methanolic extract of *Gmelina arborea*.

H2O2 scavenging assay of MEGA was found as mean % inhibition was compared with one another and with those of a standard solution. The % inhibition at concentrations of 200 µg/ml and 1000 µg/ml MEGA exhibited 5.076% and 48.223% inhibition of free radicals and Ascorbic acid exhibit 13.197% and 68.730% inhibition.

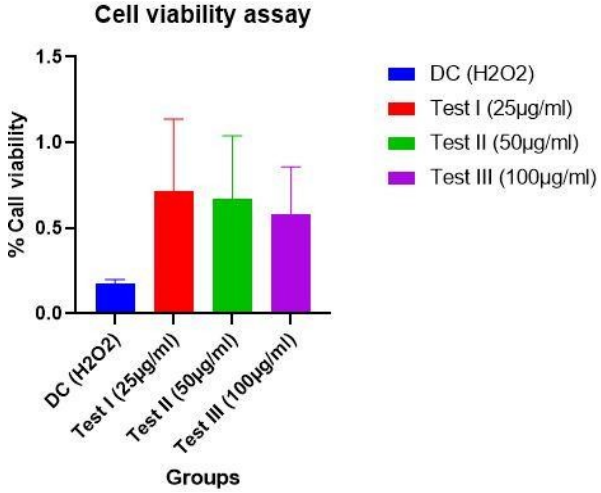
Nitric oxide (NO) scavenging assay



% Inhibition of NO at different concentration (200-1000 µg/ml) of methanolic extract of *Gmelina arborea*.

In this study, it was discovered that the NO scavenging activity of the MEGA, expressed as a percentage inhibition and calculated from the absorbance derived from the activity of samples at various concentrations, increased dose-dependently. The % inhibition at concentrations of 200 µg/ml and 1000 µg/ml MEGA exhibited 1.35% and 26.47% inhibition of free radicals and Ascorbic acid exhibit 4.02% and 35.07% inhibition.

3.3. Cell viability assay



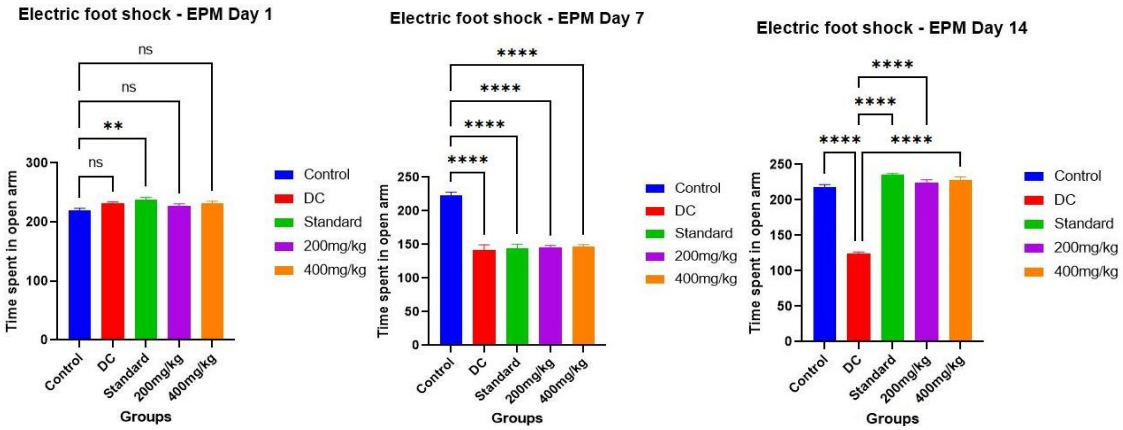
% Cell viability assay of Methanolic extract of *Gmelina arborea*.

Cell survival was measured after 90 minutes of exposure to H2O2 (100 µM) in SH-SY5Y cells. Significant dose-dependent inhibition of SHSY5Y cell growth is indicated by the results. Hence, the compounds of *Gmelina arborea* should possesses anti- anxiety components that inhibit the growth of SH-SY5Y cell lines. Compounds with protective properties are useful in treating CNS diseases associated with oxidative stress.

3.4. *In-vivo* Anxiolytic Activity of Extract

A) Electric Foot Shock Induced Anxiety Model

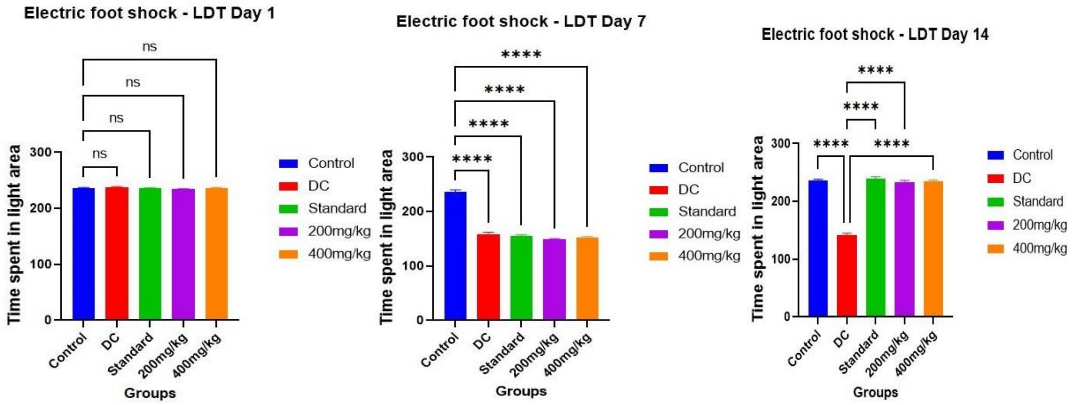
Elevated Plus Maze Model:



Assessment of behavioural changes by evaluation of Time spent in open arm on Day 1st, 7th & 14th.

In this investigation, the induction of electric foot shock stress significantly impacted behavioral parameters. The Diazepam-treated group and the group treated with the methanolic extract of *Gmelina arborea* both showed a marked increase in the time spent in the open arm and number of open arm entries compared to the disease control group.

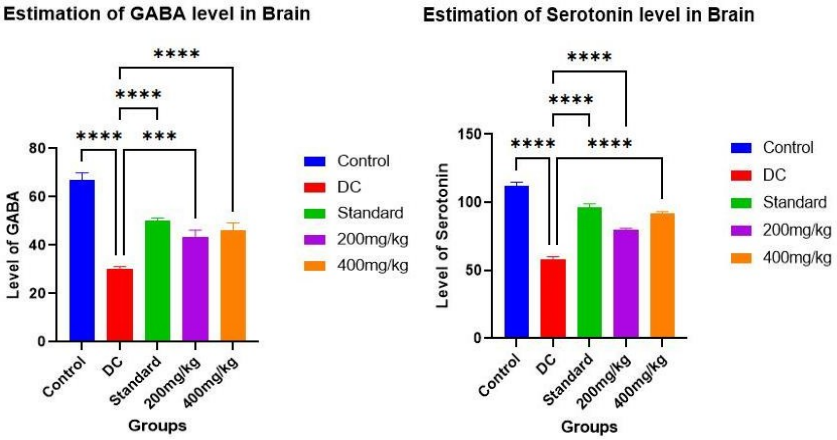
Light Dark Transition Model:



Assessment of behavioural changes by evaluation of time spent in lightbox on day 1st, 7th & 14th.

In the current in investigation, the behavioural parameters were dramatically affected as a result of the induction of stress. This was shown by a significantly increased time spent in lightbox in diazepam treated standard group and methanolic extract of *Gmelina arborea* treated test group when compared to disease control.

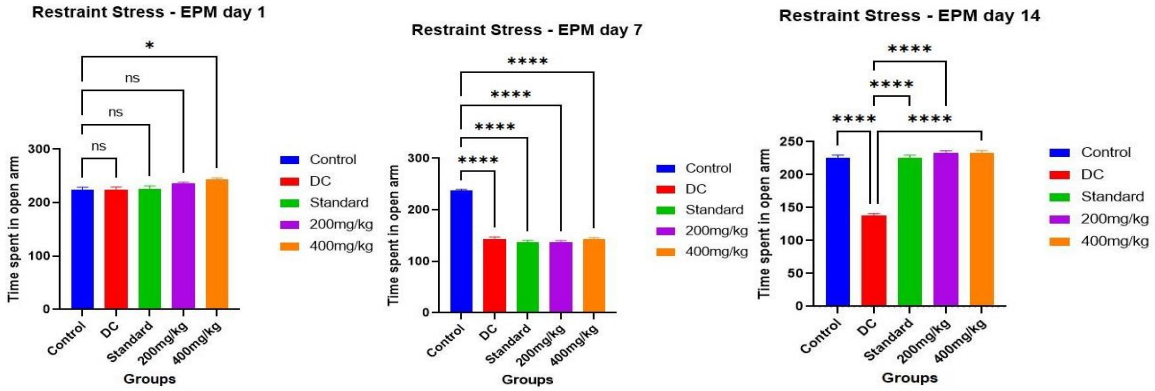
Estimation of Neurotransmitters



Electric foot shock stress induction significantly decreased the brain GABA and serotonin level in disease control group. Treatment with standard Diazepam and treatment with methanolic extract of *Gmelina arborea* showed significantly increase in level of both GABA and Serotonin in mice brain.

B) Restraint or Immobilization Stress-Induced Anxiety Model

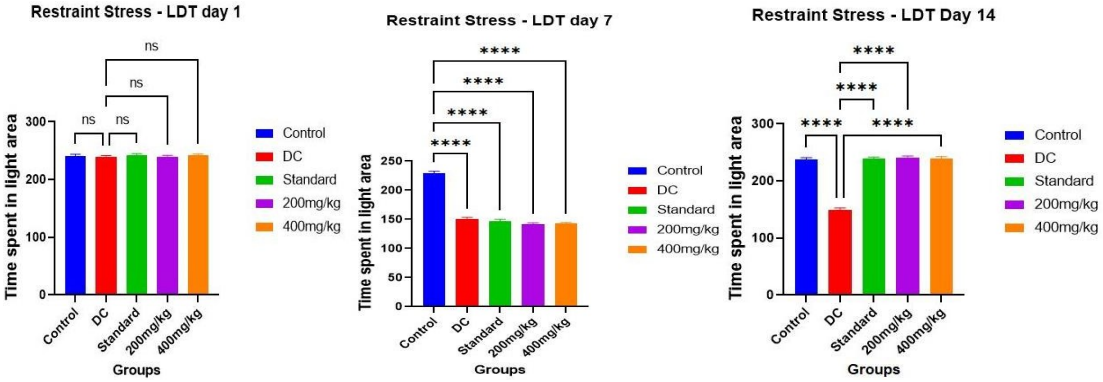
Elevated Plus Maze Model:



Assessment of behavioural changes by evaluation of time spent in open arm on Day 1st, 7th & 14th

In the present study, the behavioural parameters were dramatically affected as a result of the induction of restraint or immobilization stress. This was shown by a significantly increased number of open arm entries and time spent in open arm of Diazepam treated group and methanolic extract of *Gmelina arborea* treated group also showed similar result when compared to disease control.

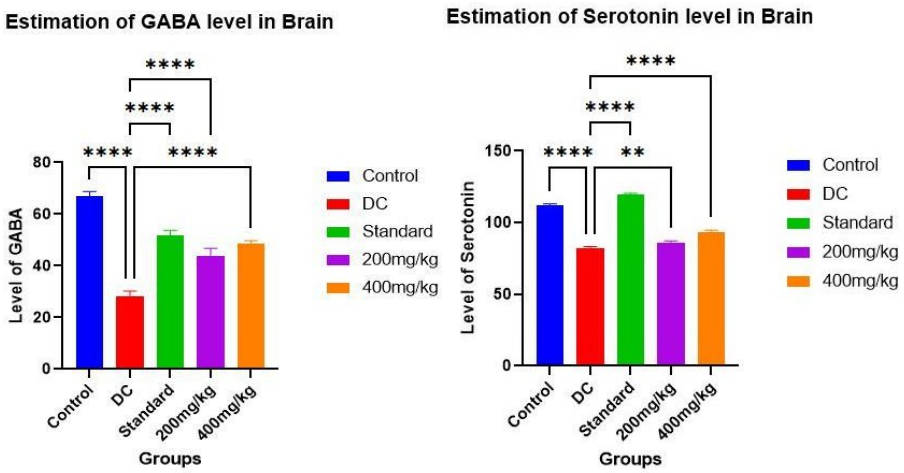
Light Dark Transition Model:



Assessment of behavioural changes by evaluation of time spent in lightbox on day 1st, 7th & 14th

In the current in investigation, the behavioural parameters were dramatically affected as a result of the induction of stress. This was shown by a significantly increased time spent in lightbox in diazepam treated standard group and methanolic extract of *Gmelina arborea* treated test group when compared to disease control.

Estimation of Neurotransmitters



Estimation of GABA and Serotonin level in brain

In the present investigation, Restraint or immobilization stress induction significantly decreased the brain GABA and serotonin level in the disease control group. Treatment with Diazepam and treatment with methanolic extract of *Gmelina arborea* in test group showed significantly increase in level of GABA as well as serotonin in mice brain.

CONCLUSION

The current investigation aimed to scrutinize methanolic extract of *Gmelina arborea* as an anxiolytic agent. The results of the toxicity testing showed that there is a large safety margin for *Gmelina arborea* when used at the recommended dosage levels.

Phytochemical analysis of *Gmelina arborea* methanolic extract was found to contain alkaloid, flavonoids, glycosides, tannins, phenols, saponins etc. In vitro cell viability assay of *Gmelina arborea* has shown highest cell death inhibition. MEGA produces Neuronal protection. It also shows the ability to act as an anti-oxidant.

The EPM and LDT were used as assessment models of the antianxiety activity. When the groups were subjected to stress-induced anxiety model, *Gmelina arborea* has demonstrated significant anti-anxiety effects in the LDT and EPM tests. *Gmelina arborea* effectively corrected the behavioral aberration caused by the stress when the extract was given by oral route. Two separate doses of 200 mg/kg and 400 mg/kg Diazepam were employed as the reference standard.

In the brain isolation normal & test goup had normal GABA and 5-HT levels, with the exception of the Disease control induced group, which had lower GABA and 5-HT levels. *Gmelina arborea* (MEGA) methanolic extract has neuroprotective properties that make it a viable treatment choice for diseases relating to the CNS.

The results obtained were compared to both the standard group and the normal group. Based on the findings, it was determined that *Gmelina arborea* methanolic extract had a remarkable anti-anxiety effect on the test subject..

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