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Preclinical Evaluation Of Indian Medicinal Plants Ficus Mysorensis And Atlantia Monophylla For Its Effect In Cns Disorders

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Abstract:
Central Nervous System (CNS) diseases are a variety of disorders affecting the brain and spinal cord, including neurodegenerative diseases like Alzheimer's, psychiatric disorders like depression, anxiety, autoimmune diseases like multiple sclerosis, infections like meningitis, and neurodevelopmental disorders like ADHD and autism spectrum disorder. In the present study the hydroalcoholic extracts of leaves of Ficus Mysorensis and Atlantia Monophylla at the doses of 100, 200 and 400 mg/kg were evaluated for its efficacy in CNS disorders. Further fractionation of prepared extract was done which was further evaluated for its effect in CNS disorders at the doses of 20 and 40 mg/kg using similar in-vivo animal models. The results of extracts and fractions were compared and.

INTRODUCTION:

Global healthcare systems are widely affected by substantial issues due to neurological illnesses. These ailments can have a serious negative effect on a person's quality of life and cause mental, emotional, and physical disabilities (Thakur et al., 2016). According to the World Health Organization (WHO), depression is one of the most impairing illnesses in the world. According to the global burden of disease, depression will rank as the second most common cause of disability in 2020 (Bohra et al., 2015). Various mental illnesses become chronic or recurrent, which basically impairs a person's ability to manage day-to-day tasks. According to predictions, up to 20% of people worldwide suffer from depression (Chuang et al., 2011) Depression can result from neuroendocrine and serotonergic dysfunctions in response to long-term stress.(Pan, L.T. Yi et al 2008)

Neurological diseases, such as depression, are influenced by a variety of genetic, environmental, and biological factors (Hasler et al., 2010). Depression is an emotional disorder characterized by severe melancholy and loss of interest in activities. Neurotransmitters, such as dopamine, serotonin, and noradrenaline, play a crucial role in mood regulation.(Dwyer et al., 2020) Imbalances in these neurotransmitters can lead to feelings of fatigue and low motivation, contributing to depression. (Arnone et al., 2024)

All demographics are impacted by the widespread neurological condition known as epilepsy, with at least 80% of those affected residing in developing or resource-poor nations. (Beghi et al., 2020). The neurological mechanisms underlying epilepsy are reflected in the recurring paroxysmal episodes that are characterized by stereotyped behavioral alterations (Fisher et al., 2017). Epilepsy is a long-term neurological condition characterized by frequent, spontaneous seizures resulting from abnormal electrical disruptions in the brain. Symptoms include muscle spasms, unusual sensations, unusual behaviors, and loss of consciousness . Between 8 and 10% of people may experience epileptic seizures, with 1-2%

resulting in an emergency room visit (Manole et al., 2023). The pathophysiology of convulsions and epilepsy involves disturbances in brain electrical activity, leading to excessive and unusual electrical discharges, which can result in convulsions. Convulsions are a common type of seizure, but not all involve them (Huff et al., 2024).

MATERIALS AND METHODS:

The plant materials were collected from local vendor. All the drugs and chemicals of analytical grade were procured from local vendor.

Animals

Swiss albino mice (20-40gm) and Wistar albino rats (180-220 gm) of either sex was procured from Local vendor and were maintained at 25 ± 2° C and relative humidity of 45 to 55% and under standard environmental conditions (12 h light: 12 h dark cycle) The animals had free access to food and water throughout study. Institutional Animal Ethical Committee approved the protocol. All the experiments were carried out between 9:00- 16:00 hour.

Preparation of hydroalcoholic extracts of selected plant materials:

Hydroalcoholic extracts of leaves of ficus mysorensis and atlantia monophylla were prepared by using soxhlet extraction method. Leaves of both the plants were dried and finely powdered followed by extraction using a soxhlet extractor with hydroalcoholic solvent system which is used in the ratio 1:1 and the temperature was set at 60-70 º C. Extracts were filtered and concentrated by solvent evaporation and were labelled as HFM & HAM respectively, each of these solvent extracts was weighed and preserved at 5°C in an airtight bottle until further use. (Garmus et al., 2019)

Preliminary phytochemical analysis of extracts:

The prepared extracts of leaves of ficus mysorensis and atlantia monophylla were subjected to preliminary phytochemical analysis using standard procedures to reveal the presence of different phytochemicals such as alkaloids, steroids, glycosides, saponins, tannins, triterpenoids, carbohydrates, proteins etc. using various tests. (Khandelwal, 2006; Kokate, 1997).

ANIMAL EXPERIMENTAL DESIGN:

Acute oral toxicity studies of hydralcoholic extracts of hydroalcoholic extracts of leaves of ficus mysorensis (HFM) and atlantia monophylla (HAM)

Acute toxicity study was performed in healthy adult male albino mice (18-22 gm) as per guidelines (AOT 425) suggested by the Organization for Economical Co-operation and Development (OECD). Hydroalcoholic extract of leaves of ficus mysorensis (HFM) and atlantia monophylla (HAM) were administered were separately administered orally at the doses of 175, 550 and 2000 mg/kg to the mice. Mice were then observed for incidence of mortality or any sign of toxicity up to 24 hours after oral administration.

PRECLINICAL EVALUATION OF ANTIDEPRESSANT ACTIVITY:

1. Forced Swim Test:

48 mice of either sex were divided into following 08 normal control, test, standard groups and given the respective treatments for 14 days as follows:
Group-1: Animals of this group received distilled water (1 ml/kg, p.o.)
Group-2: Animals of this group received HFM (100 mg/kg, p.o.)
Group-3: Animals of this group received HFM (200 mg/kg, p.o.)
Group-4: Animals of this group received HFM (400 mg/kg, p.o.)
Group-5: Animals of this group received HAM (100 mg/kg, p.o.)

Group-6: Animals of this group received HAM (200 mg/kg, p.o.)
Group-7: Animals of this group received HAM (400 mg/kg, p.o.)
Group-8: Animals of this group received Imipramine (5 mg/kg, p.o.)
On 14th day all mice were subjected to assessment of antidepressant activity using forced swim test. Each mice was individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm) containing 15 cm of water at 25±1°C. for the period of 05 minutes and the duration of immobility (ie when mice ceased struggling and remained floating motionless in the water, making only those movements to keep its head above water.) is noted down. An antidepressant-like effect is indicated by a reduction in the length of immobility. (Porsolt et al.. 1977)

2. Tail Suspension test
48 Mice of either sex are divided into normal control, test, standard groups and given the respective treatments for 14 days as follows:
Group-1: Animals of this group received distilled water (1 ml/kg, p.o.)
Group-2: Animals of this group received HFM (100 mg/kg, p.o.)
Group-3: Animals of this group received HFM (200 mg/kg, p.o.)
Group-4: Animals of this group received HFM (400 mg/kg, p.o.)
Group-5: Animals of this group received HAM (100 mg/kg, p.o.)
Group-6: Animals of this group received HAM (200 mg/kg, p.o.)
Group-7: Animals of this group received HAM (400 mg/kg, p.o.)
Group-8: Animals of this group received Imipramine (5 mg/kg, p.o.)
Using sticky tape positioned about 1 cm from the tip of the tail, mice were individually suspended on the edge of the table, 50 cm from the floor, for 10 minutes on 14th day, one hour after the last dosage. Six minutes of the ten-minute interval were used to record the overall amount of time that tail suspension caused immobility. A mouse was deemed immobile if it hung passively, showed no signs of movement, and remained still. (Steru et al., 1985).

3. Spontaneous Locomotor Activity Test:
48 mice of either sex are divided into normal control, test, standard groups and given the respective treatments for 14 days as follows:
Group-1: Animals of this group received distilled water (1 ml/kg, p.o.)
Group-2: Animals of this group received HFM (100 mg/kg, p.o.)
Group-3: Animals of this group received HFM (200 mg/kg, p.o.)
Group-4: Animals of this group received HFM (400 mg/kg, p.o.)
Group-5: Animals of this group received HAM (100 mg/kg, p.o.)
Group-6: Animals of this group received HAM (200 mg/kg, p.o.)
Group-7: Animals of this group received HAM (400 mg/kg, p.o.)
Group-8: Animals of this group received Imipramine (5 mg/kg, p.o.)
On 14th day all the animals were subjected to assessment of locomotor activity using digital actophotometer. Then animals were placed in the digital actophotometer for 5 minutes and the locomotor activity counts displayed by interception of photobeams by movement of animals were be recorded and compare against control mice. Imipramine (5 mg/kg i.p.) was used as reference standard.

PRECLINCAL EVALUATION OF ANTIANXIETY ACTIVITY

1. Elevated plus maze test
48 mice of either sex weighing 22-25 gm were divided into following 08 groups each group consisting of 06 rats. The control, test, standard groups received the respective treatments. Diazepam (1 mg/kg, i.p.) was used as a reference standard. After respective treatment mice were placed individually in the centre of the maze, head facing toward open arm and the number of entries in open and closed arms and time

spent in open and closed arms, respectively, was recorded for a period of 5 min. Entry into an arm can be defined as the point when the animal places all four paws onto the arm.
Group-1: Animals of this group received distilled water (1 ml/kg, p.o.)
Group-2: Animals of this group received HFM (100 mg/kg, p.o.)
Group-3: Animals of this group received HFM (200 mg/kg, p.o.)
Group-4: Animals of this group received HFM (400 mg/kg, p.o.)
Group-5: Animals of this group received HAM (100 mg/kg, p.o.)
Group-6: Animals of this group received HAM (200 mg/kg, p.o.)
Group-7: Animals of this group received HAM (400 mg/kg, p.o.)
Group-8: Animals of this group received Diazepam (1 mg/kg, i.p.)

2. Mirrored chamber test:
48 mice (22-25 gm) of either sex were randomly divided in 08 groups mentioned below each consisting of 06 mice and were treated with respective doses for the period of 14 days (this duration was selected based on literature survey). On 14th day one hour after the administration of respective treatment, each mouse was individually placed at the back side of mirrored cube and the latency to enter the mirror chamber and time spent in mirror chamber during 5 min observation period shall be recorded 60 min after the drug administration. Diazepam (1 mg/kg, i.p.) will be used as a reference standard. The following 03 parameters were noted down for the period of next 05 minutes.

a. Latency to first entry into the mirror chamber.
b. Number of entries made in the mirror chamber.
c. Total time spent in the mirror chamber.

Note: This experiment was carried out by visual observation, as equipment was not equipped with video tracking system. The variation in result if any has to be cover in the discussion
Group-1: Animals of this group received distilled water (1 ml/kg, p.o.)
Group-2: Animals of this group received HFM (100 mg/kg, p.o.)
Group-3: Animals of this group received HFM (200 mg/kg, p.o.)
Group-4: Animals of this group received HFM (400 mg/kg, p.o.)
Group-5: Animals of this group received HAM (100 mg/kg, p.o.)
Group-6: Animals of this group received HAM (200 mg/kg, p.o.)
Group-7: Animals of this group received HAM (400 mg/kg, p.o.)
Group-8: Animals of this group received Diazepam (1 mg/kg, i.p.)

RESULTS:

1. Forced Swim Test:
Table No: 1 Evaluation of anti-depressant activity of hydroalcoholic extracts of ficus mysorensis and atlantia monophylla using forced swim test model

Sr. No.	Treatment	Immobility time (secs)
1	Normal control	72.49 ± 01.65
2	HFM (100 mg/kg, p.o.)	71.35 ± 00.91
3	HFM (200 mg/kg, p.o.)	66.553 ± 00.99*
4	HFM (400 mg/kg, p.o.)	61.04 ± 01.34**
5	HAM (100 mg/kg, p.o.)	69.97 ± 00.95
6	HAM (200 mg/kg, p.o.)	68.87 ± 01.03
7	HAM (400 mg/kg, p.o.)	65.11 ± 00.85**
8	Imipramine (5 mg/kg, p.o.)	53.835 ± 01.31**

Values are mean ± S.E.M., n=6; Statistical analysis by one-way ANOVA followed by Dunnett's test using Graph pad Instat software; $p<0.05$*, $p<0.01$**and $p<0.001$*** compared to normal control group.

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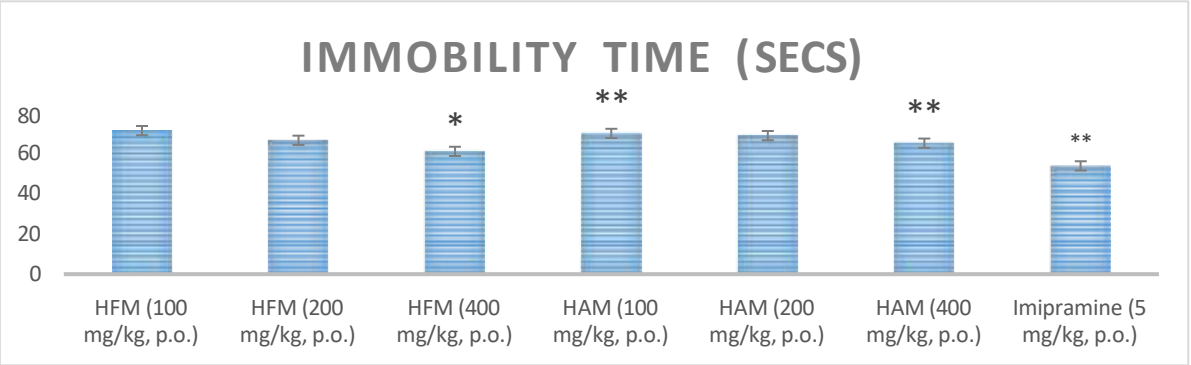


HFM i.e., hydroalcoholic extract ficus mysorensis on doses 200 and 400 mg/kg exhibited dose dependent reduction in immobility duration, which is an indication of antidepressant activity (Porsolt et al.. 1977) whereas, hydroalcoholic exract of atlantia monophylla HAM 400 mg/kg alone showed similar significant. To put it briefly, the maximum doses of both extracts that were administered were found to be both equipotent and efficacious, as compared to the reference standard drug.

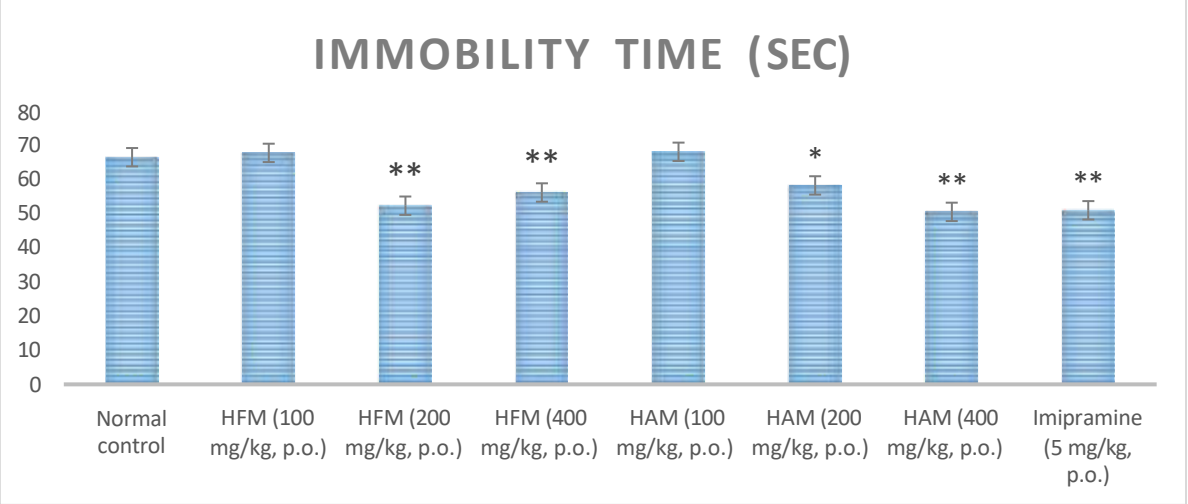
From the above results it can be concluded that HFM is more significant than HAM as HFM showed decrease in immobility of rats at both doses i.e., 200 and 400 mg/kg and HAM exhibited antidepressant activity at only higher dose of 400 mg/kg.

2. Tail Suspension test

Table No: 2 Evaluation of anti-depressant activity of hydroalcoholic extracts of ficus mysorensis and atlantia monophylla using Tail Suspension test

Sr. No.	Treatment	Immobility time (secs)
1	Normal control	66.25 ± 02.38
2	HFM (100 mg/kg, p.o.)	67.51 ±01.13
3	HFM (200 mg/kg, p.o.)	52.11 ± 02.70**
4	HFM (400 mg/kg, p.o.)	55.96 ± 01.97**
5	HAM (100 mg/kg, p.o.)	67.83 ± 01.42
6	HAM (200 mg/kg, p.o.)	58.02 ± 01.52*
7	HAM (400 mg/kg, p.o.)	50.31 ± 02.34**
8	Imipramine (5 mg/kg, p.o.)	50.77 ± 01.87**

Values are mean ± S.E.M., n=6; Statistical analysis by one-way ANOVA followed by Dunnett's test using Graph pad Instat software; $p<0.05$*, $p<0.01$**and $p<0.001$*** compared to normal control group.



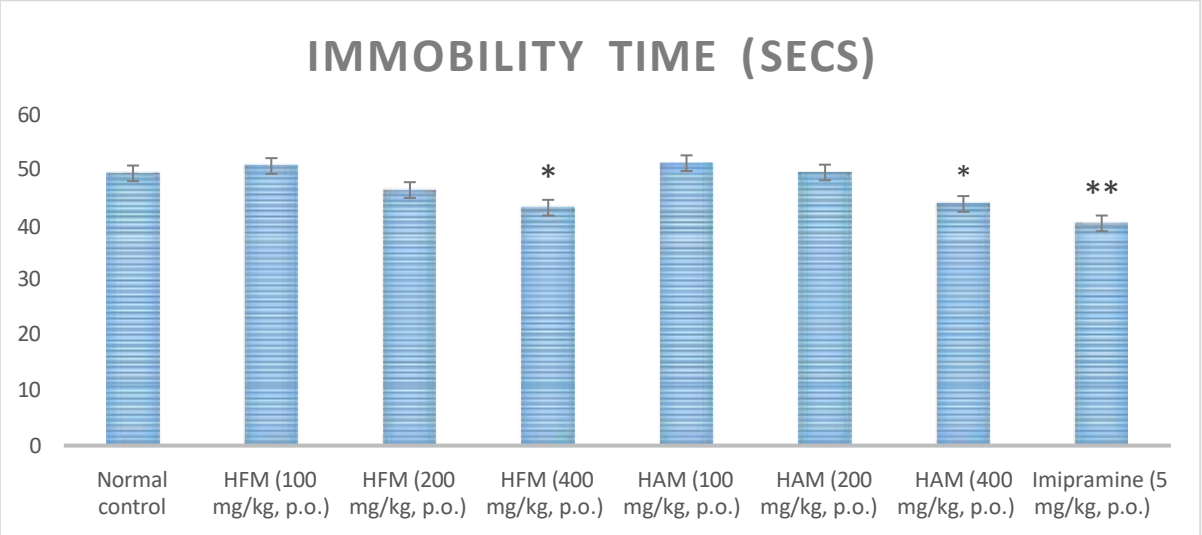
Lower dose of 100 mg/kg HFM & HAM did not show any significant decrease in immobility time. Both the extracts have shown significant reduction in immobility time which is an indication of antidepressant activity. 200 mg/kg and 400 mg/kg of HFM & HAM reduced the immobility time as compared to that of normal control group, thus recorded to possess antidepressant activity.

3. Spontaneous Locomotor Activity Test:

Table No: 3 Evaluation of anti-depressant activity of hydroalcoholic extracts of ficus mysorensis and atlantia monophylla using actophotometer.

Sr. No.	Treatment	Immobility time (secs)
1	Normal control	49.00 ± 01.41
2	HFM (100 mg/kg, p.o.)	50.33 ± 02.09
3	HFM (200 mg/kg, p.o.)	46.00 ± 01.23
4	HFM (400 mg/kg, p.o.)	42.83 ± 01.60*
5	HAM (100 mg/kg, p.o.)	50.83 ± 01.16
6	HAM (200 mg/kg, p.o.)	49.16 ± 01.01
7	HAM (400 mg/kg, p.o.)	43.50 ± 00.76*
8	Imipramine (5 mg/kg, p.o.)	40.00 ± 01.23**

Values are mean ± S.E.M., n=6; Statistical analysis by one-way ANOVA followed by Dunnett's test using Graph pad Instat software; $p<0.05$*, $p<0.01$**and $p<0.001$*** compared to normal control group.



Hydroalocoholic extracts of both the plants showed significant reduction in locomotor activity of rats only on administration of high dose of 400 mg/kg. HFM 400 mg/kg and HAM 400 mg/kg showed significant reduction in the locomotor activity, which may be the indication of antidepressant activity subjected to the results of other models.

Reference standard Imipramne showed similar reduction in the core and was found to be more potent compared to above mentioned test drug doses.

4. Elevated plus maze test

Treatment	Total time spent on open Arm	Total time spent on Closed Arm	Number of entries in Open Arm	Number of entries in Closed Arm
Normal control	70.83 ± 04.6	141.66± 04.90	6.16±0.47	5.66 ± 0.49

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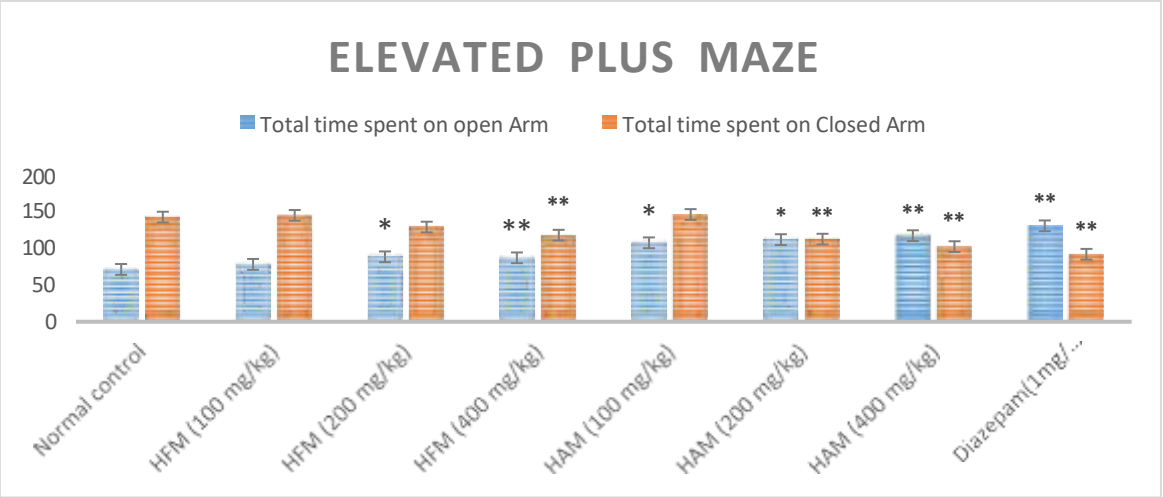
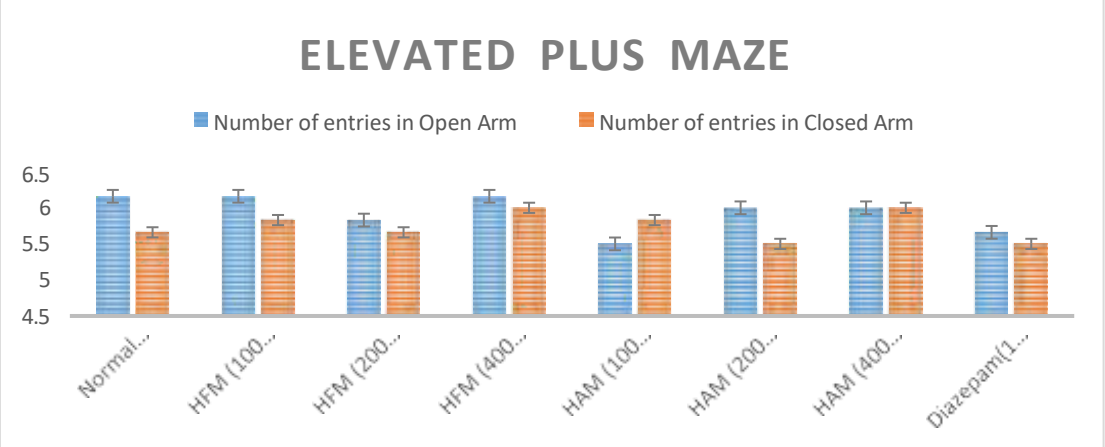
HFM (100 mg/kg, p.o.)	77.66 ± 03.90	144.00 ± 06.26	6.16± 0.47	5.83 ± 0.47
HFM (200 mg/kg, p.o.)	87.83 ± 03.43*	128.16 ± 05.19	5.83± 0.43	5.66 ± 0.33
HFM (400 mg/kg, p.o.)	86.50 ±04.70**	117.16 ± 04.3**	6.16±0.46	6.00 ± 0.57
HAM (100 mg/kg, p.o.)	106.83±03.49*	145.16 ± 02.65	5.50 ±0.42	5.83 ± 0.47
HAM (200 mg/kg, p.o.)	111.1± 03.21*	111.83 ± 02.81**	6.00± 0.36	5.50 ± 0.42
HAM (400 mg/kg, p.o.)	116.50±03.99**	101.66± 02.52**	6.00± 0.36	6.00 ± 0.36
Diazepam(1mg/kg,i.p)	129.83 ± 03.85**	91.33 ± 02.37**	5.66 ± 0.33	5.50 ± 0.42



The result suggests that, both the extracts have shown significant anti-anxiety activity. HAM was found to be more potent than HFM in this regard. The above graph represents the amount of time in seconds spent in open and close arm of elevated plus maze. The results suggests that, both the extracts have shown significant reduction in time spent by animal in close arm and significantly increased the time in open arm. HFM was more effective at dose 400 mg/kg but HAM was seen to be more effective at both lower and higher dose i.e., 200 and 400 mg/kg. Therefore, HAM was found to be more potent than HFM in this regard.



According to the results, neither extract had any effect. Both extracts shown an equivalent enhancement in the duration spent in the open arm, a primary parameter, indicating their anti-anxiety effectiveness. Nevertheless, there was no discernible shift in the quantity of entries in the open and closed arms. Since

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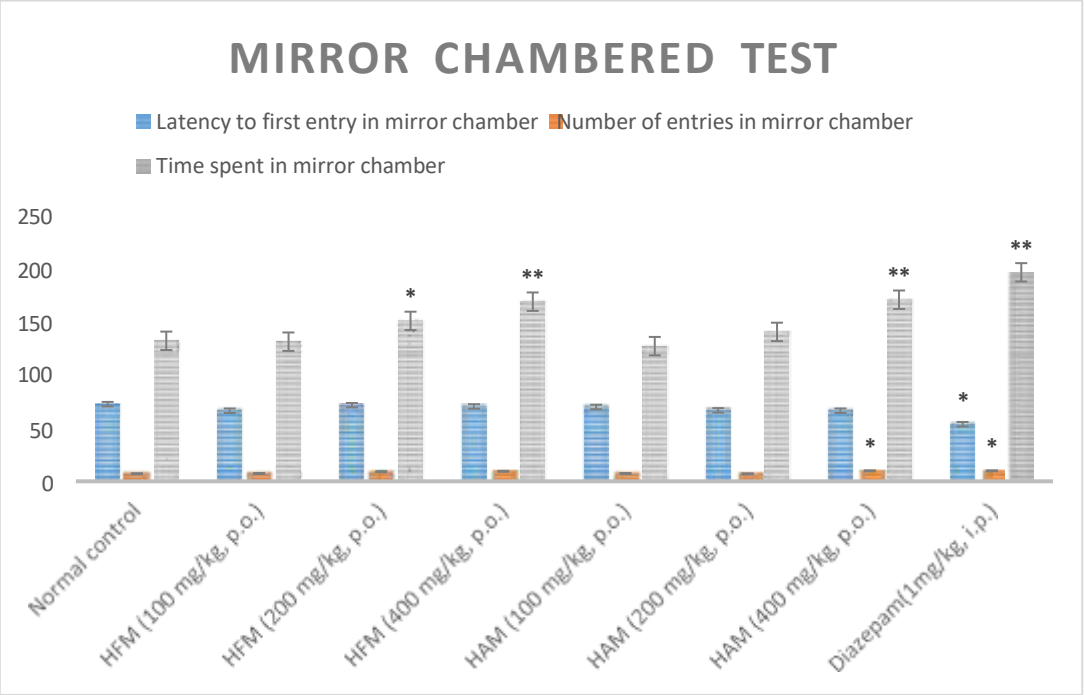
Vol. 11 No. 3, 2025
https://www.theaspd.com/ijes.php

the animal's anxiety, exploration, and behavior patterns all influence the entry pattern, even if there isn't any discernible change, the extract's ability to reduce anxiety is still open.

5. . Mirrored chamber test:

Treatment	Latency to first entry in mirror chamber	Number of entries in mirror chamber	Time spent in mirror chamber
Normal control	72.33 ± 4.185	7.16 ± 0.792	131.66 ± 6.825
HFM (100 mg/kg, p.o.)	66.16 ± 4.729	7.33 ± 0.666	130.83 ± 5.570
HFM (200 mg/kg, p.o.)	71.33 ± 4.828	9.00 ± 0.577	150.33 ± 3.232*
HFM (400 mg/kg, p.o.)	70.16 ± 4.012	9.33 ± 0.881	168.33 ± 3.602**
HAM (100 mg/kg, p.o.)	69.66 ± 4.014	7.33 ± 0.494	126.66 ± 3.242
HAM (200 mg/kg, p.o.)	66.50 ± 4.965	7.00 ± 0.577	140.00 ± 3.873
HAM (400 mg/kg, p.o.)	66.16 ± 4.347	9.83 ± 0.477*	170.16 ± 3.701**
Diazepam(1mg/kg, i.p.)	53.50 ± 4.748*	9.83 ± 0.654*	195.83 ± 4.983**



None of the doses of both the extracts was found to be effective to alter the latency for first entry stating that it does not have any impact as per this parameter. Even reference standard diazepam showed only mild action in this regard.

Similar result were recorded for the number of entries in the mirror chamber however HAM 400 was the only dose from the extracts was significant to show mild anti-anxiety action similar to that of ref. standard diazepam. As far as time spent in mirror chamber is considered, both the extract have exhibited the action. Here HFM showed dose dependent action while only highest dose of HAM i.e., 400 mg/kg was found to be effective. From the above parameters it can be concluded that both the extracts have shown weak antianxiety activity.

DISCUSSION & CONCLUSION:

CNS disorders comprise a wide range of complaints,. The major complaints includes depression, anxiety, epilepsy, psychosis etc causing significant impairment in quality of life. (Naz and Siddique et al., 2020) Rather, most pharmacotherapeutic approaches for these disorders focus on alleviating the symptoms, restoring functional balance, and promoting well-being of the patient. (Thau et al., 2024). The extent of occurance, relapse and severity of these disorders is increasing day by day with the advancement of life style. The modern lifestyle has become an unavoidable factor and hence these disorders have become a point of concern. The complex nature most of these complaints is another determinant that does not allow the modern medicine to provide ideal outcome. Thus, in most of the cases, either therapy leads to limited outcome or polypharmacy may become point of concern rather than therapy.

Amongst all key CNS disorders, psychosis is considered to be most important due to its wider impact on individual's life and rapid conversion from disorder to syndrome; hence exploring the new treatment option with special emphasis on psychosis was the objective of this study. With such widespread conditions of disorders coupled with the limitations of existing pharmacotherapies, it becomes essential to explore for better alternative.

The mental illness known as psychosis is characterized by a detachment from reality, which results in prominent symptoms like delusions, hallucinations, disordered thinking, and diminished insight. People who suffer from psychosis may experience delusions, see things that aren't there (hallucinations), and struggle to organize their thoughts, which can lead to nonsensical words or actions. Medical conditions including brain injuries, infections, or substance abuse can cause psychosis, representing in the form of variety of psychiatric disorders like schizophrenia, bipolar disorder, severe depression etc. As per current clinical practice, need based blend of antipsychotic therapy counseling, and close support are mainstay to control symptoms and restore impaired functioning.

Depression is another common complaint after psychosis which when gets associated with the psychosis, the deterioration can be by multiple folds. It is observed that the co-existence can be both ways, like patient with depression is suceptible for psychosis and vice a versa. On similar line, role of anxiety and convulsions have also been reported towards progress of pathogenesis of psychosis. Because of the numerous connections between these disorders, it is essential to take anxiety, depression, convulsions into account when researching psychosis. Better diagnosis, more effective treatment plans, and improved patient care can result from an understanding of the connection between psychosis and other mentioned disorders. Hence in this study psychosis have been studied along with these disorders.

The two main classes of anti-psychotics that are now on the market for treating psychosis are first- and second-generation anti-psychotics. First-generation anti-psychotics' (FGAs) main drawbacks include an increased incidence of extrapyramidal symptoms, such as rigidity, tardive dyskinesia, and tremors, drowsiness etc. These medications have also been reported to may produce cardiovascular problems like QT prolongation and hypotension, as well as anticholinergic side effects such dry mouth, constipation, and urine retention. The negative symptoms of schizophrenia are less well addressed by FGAs, and they are more likely to affect emotional and cognitive functioning. Conversely, second-generation antipsychotics have been associated with metabolic adverse effects, such as dyslipidemia, aggrevation of diabetes mellitus, substantial weight gain, agranulocytosis etc. These limitations not only affect the therapeutic outcome but sometime force to stop the therapy and switch to other therapy. The switching can be associated with withdrawal symptoms, non-compliance of patient, disturbed financial implications which make the outcome quite uncertain.

The gross impact of all these changes is continuous search for more effective, patient friendly and sustained therapy. On the other hand, central nervous system disorders have long been managed and treated with plants and plant material in its crude forms. Many of these traditional medicines that are being used as traditional medicine have been scientifically documented and thus gaining attention as lucrative alternative treatments options. Since these medicine are derived from natural source they are usually more patient friendly which is added advantage for long term therapy.

As per our literature survey atlantia monophylla and ficus mysorensis are mentioned in Ayurvedic text as a remedy for various CNS disorders were selected for the present study. On this background, the present

investigation titled “Phytochemical and Biological Evaluation of some Indian Medicinal Plants for their Antipsychotic Activities” was carried out.

In case of herbal therapy, the extent of therapeutic action, possible limitations and the mechanisms of actions largely depends on the prominent presence of particular class of phytoconstituent. The actual therapeutic results and untoward effects are usually governed by the phytochemical presence. Preliminary phytochemical analysis, followed by a comparison of the results with existing published literature is most trustworthy way to determine probable role of phytoconstituents.

The solubility of phytoconstituents is critical step and hence to get complete profile, the three different extracts of both the plants were prepared using 03 solvents with different polarity and subjected to preliminary phytochemical analysis. According to the results hydroalcoholic extracts of both the plants showed presence of biologically active phytoconstituents like alkaloids, flavonoids, sterols, terpenoids etc. Once the extracts were shortlisted after preliminary phytochemical evaluation, toxicology profile testing becomes extremely important to ensure its safety before moving forward with the actual exploration of its pharmacological activity. Accordingly, the acute toxicity study of both the hydroalcoholic extracts was carried out as per OECD guideline 425. The results of acute oral toxicity studies revealed that the extract is safe with no signs of morbidity nor mortality and any type of adverse effects up to 2000 mg/kg which is highest prescribed limit as per this test. Based upon these findings and available literature, the three proposed doses of each extract i.e., 100, 200 & 400 mg/kg were finalized for further study.

Animal models of psychosis generated by apomorphine, ketamine and haloperidol are appropriate for assessing psychosis because they can replicate important aspects of the illness, such as dopaminergic dysregulation. Hyperdopaminergic states are induced by the dopamine agonist apomorphine and reversed by the dopamine antagonist haloperidol. By evaluating the impact of antipsychotic medications on behavior and neurochemistry, these models aid in testing them.

Apomorphine (a non-selective dopamine agonist) induced stereotype behaviour prominently exhibited by the positive symptom i.e., climbing behaviour has been used to screen the activity. In this test, both HFM & HAM have significantly attenued the climbing behaviour. Overall, HFM was slightly more effective than HAM which may be attributed to the experimental design and subclass of phytoconstituent measured as climbing index and total duration of climbing. The results suggests that both the extract have qualified the basic requirement and thus documented that the positive symptoms in psychosis is a major hurdle for patient to execute day to day activity and hence these results are quite encouraging.

The results demonstrate that treatments with HFM, HAM, and imipramine all lead to significant reductions in climbing time compared to the normal control group, particularly at higher doses. Apomorphine, on the other hand, significantly increases climbing time, indicating a stimulatory effect likely due to dopaminergic activation. Specifically, higher doses of HFM (400 mg/kg) and HAM (400 mg/kg) significantly reduced climbing time, with imipramine (5 mg/kg) showing similar effects.

The management of negative symptoms of psychosis are equally important as that of positive symptoms to obtain desired therapeutic outcome. As per reports 50-70% of patients exhibit social deficit which has significant impact on patients life. This social withdrawal is also responsible to develop depression in long run. In this study, Ketamine induced social interaction period was significantly improved with HFM & HAM - 200 mg/kg. In the entire study, this parameter has shown specific result with respect to middle dose of the extract only, which suggest dose specificity to control this prominent negative symptoms of the psychosis.

One of the critical challenges in developing effective antipsychotic treatments is minimizing the motor side effects, such as catalepsy, which are often induced by conventional drugs like haloperidol. Catalepsy, characterized by muscle rigidity and impaired motor coordination, serves as a widely accepted model to assess the extrapyramidal side effects of antipsychotic medications. In this context, the ability of Atlantia monophylla and Ficus mysorensis to reduce haloperidol-induced catalepsy indicates their potential as novel agents with antipsychotic properties. The observed reduction in catalepsy suggests that both plant extracts at higher doses of 400 mg/kg is indicative of role of bioactive compounds like flavonoids, triterpenoids and phenolic content (Rao, V. S., et al. 2005) that are already documented for the motor impairments associated with traditional antipsychotic drugs.

As per scientific records 50% (Nevena et al., 2014)of patients experience extrapyramidal side effects with prominent exhibition of muscular rigidity and poor muscular co-ordination out of which 20-30% of patient (Schizophrenia Research (2009)) has to switch to other drug which is a major challenge for clinicians. Hence antipsychotic action with reduced extrapyramidal side effects is the one of the prime objectives and both these extracts being studied have focused to be fruitful in this regard.

These extracts have been already reported for its antioxidant potential which may be the reason for minimal side effects and reduced extrapyramidal symptoms. (Gupta et al., 2020) This finding is perhaps the best outcome of the study and can ensure long term treatment. The similar results have been reproduced with the fractions suggesting role of alkaloids, phenolic compounds, flavonoids, sterols, terpenoids, proteins etc. The presence of multiple phytoconstituent leading to complementary action which is a core advance of use of medicinal plant derived product is visible in this study. Thus overall pharmacological activity with reduced side effects can be the game changer action in psychosis.

Furthermore, the results suggest that Atlantia monophylla and Ficus mysorensis could potentially offer therapeutic benefits without typical side effects of current pharmacological treatments for catalepsy, highlighting the need for further investigation into their molecular mechanisms and potential to complement or replace existing treatments. In CNS disorders, the addition of one or other disorder is observed more frequently as compared to disease and disorder related to other organs. It may be due to complex nature of CNS and close neuronal networking. Hence, while developing drug for particular conditions (like psychosis), the other pathological state which can easily developed and their co-existence effect must be studied. On this background, anxiety, depression and convulsions have been reported as top possibilities and hence study of effect of the extracts and fractions have also been extended.

According to a study published in Schizophrenia Bulletin (2014), approximately 40-60% of individuals with psychosis also experience significant symptoms of anxiety. This co-occurrence of anxiety in psychosis patients is notably prevalent, highlighting the importance of addressing both conditions simultaneously in clinical treatment. The exact percentage of co-existence can vary depending on factors such as the specific diagnosis within the spectrum of psychotic disorders and the methods of assessment used in studies. However, it is widely accepted that anxiety is a common comorbidity in psychotic disorders globally. Evaluating the anti-anxiety effects of Atlantia monophylla and Ficus mysorensis alongside their anti-psychotic effects is important because many individuals with psychotic disorders also experience comorbid anxiety, which can exacerbate their overall condition. Hence, addressing both symptoms simultaneously may enhance the therapeutic potential of these plants, offering a more comprehensive treatment approach for psychotic disorders.

Anxiety is an outcome of variety of responses. There may be different triggers to develop anxiety and hence the ideal antianxiety agent is expected to be effective irrespective of triggers. This is possible when the screening is done using multiple experimental models with different mechanisms of inductions and/ inducers.

Accordingly, we assessed the anti-anxiety potential of both the extracts in further detail. The Elevated Plus Maze Test, Mirrored Chamber Test, Hole Board Test, and Light and Dark Test were the animal models utilized for the same because they utilize natural rodent behaviors linked to fear and exploration. The Elevated Plus Maze measures open arm exploration (anxious rodents avoid open arms), the Hole Board test measures neophobia (fear of new environments) by measuring the frequency of head dips, the Mirrored Chamber Test assesses avoidance of a perceived threat (the reflection), and the Light and Dark test determines preference for enclosed, dark areas. Anxiolytic substances encourage behaviors that are suggestive of less anxiety in each of these tests, including head-dipping, mirrored chamber exploration, higher open arm duration, and light compartment exploration, respectively. We used the aforementioned main indicators as measures to assess the anti-anxiety activity of HAM & HFM extracts.

In EPM the time spent in open arm was significantly increased by both the extracts at the dose of 200 and 400 mg/kg and thus qualified primary parameter to validate antianxiety action. However, there was no change in the number of entries in open and close arms, which is secondary parameter. The study already showed antipsychotic effects of these extracts which is attributed to modulation recorded of

dopaminergic neurotransmission. The same modulation might be responsible for no change in entries and thus rule out possibility of false positive result of time spent in open and close arm.

A different well-known experimental animal model was employed to assess the anxiolytic effects of both hyroalcoholic extracts. Important metrics such as the number of entries, the delay to initial entry, and the amount of time spent in the mirrored chamber were used to determine the outcomes of the animal models. While the majority of treatments showed no significant change in delay to first entry, HFM (200 and 400 mg/kg) (*) and HAM (400 mg/kg**) both markedly extended the amount of time spent in the mirrored chamber. The quantity of entry into the mirrored chamber was likewise markedly boosted by HAM at 400 mg/kg. The latency to initial entry was reduced by diazepam (positive control), which also significantly enhanced the frequency of entries and time spent in the mirrored chamber. According to these findings, HAM at 400 mg/kg has a more strong effect by increasing the number of entries, while HFM and HAM, especially at higher doses, appear to have anxiolytic-like effects by promoting exploration of the aversive reflected environment.

From the present research work we can conclude that, hydroalcoholic extracts of the leaves of Atlantia monophylla and Ficus mysorensis have shown significant multitarget activity in the management of psychosis, as well as co-existing depression, anxiety, and convulsions. These extracts exhibit a broad spectrum of pharmacological effects, addressing multiple aspects of neuropsychiatric disorders simultaneously. They have demonstrated potential in modulating neurotransmitter systems, reducing oxidative stress, and enhancing neuroprotective mechanisms, which may contribute to their efficacy in treating complex conditions such as psychosis accompanied by mood disorders and seizure activity. Their multitarget action makes them promising candidates for developing holistic therapies for individuals suffering from these interconnected mental health conditions.

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