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PHARMACOLOGICAL EVALUATION OF ANTIDEPRESSANT ACTIVITY OF MESUA FERREA IN RESERPINE-INDUCED DEPRESSION IN RATS

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ABSTRACT:

Depression is a common neuropsychiatric disorder associated with disturbances in monoaminergic neurotransmission. The present study aimed to evaluate the antidepressant potential of the ethanolic extract of Mesua ferrea using a reserpine-induced depression model in rats. Depression was induced by administering reserpine (5 mg/kg, i.p.) 18 hours prior to behavioral assessment. The animals were divided into six groups: normal control, reserpine control, standard drug (Fluoxetine 20 mg/kg, i.p.) with reserpine, and three test groups receiving the extract at doses of 100, 150, and 200 mg/kg (i.p.) along with reserpine. Antidepressant activity was assessed using the Forced Swim Test, Tail Suspension Test, and Open Field Test. Reserpine administration significantly increased immobility time and reduced locomotor activity, confirming induction of depressive-like behavior. Treatment with fluoxetine significantly reversed these changes. The ethanolic extract of Mesua ferrea produced a dose-dependent reduction in immobility time and improved locomotor and exploratory behavior, with the 200 mg/kg dose showing effects comparable to the standard drug. The Mesua ferrea possesses significant antidepressant-like activity in reserpine-induced depression, possibly mediated through modulation of monoaminergic pathways and the presence of bioactive phytoconstituents such as flavonoids and phenolics. Further studies are required to elucidate the exact mechanism of action.

Keywords: Mesua ferrea, Forced Swim Test, Tail Suspension Test, Open Field, Depression

INTRODUCTION

Mood disturbance is a common and important sequel of stroke, which may interfere with both recovery and outcome. Various neuropsychiatric disorders can be seen after stroke, most commonly depression, anxiety, irritability and agitation, emotional incontinence and apathy, catastrophic reactions and, less commonly, delusions and hallucinations [1-3] Depression is the most common neuropsychiatric sequel in the post stroke population, affecting nearly 30%–50% of patients within the first year. [2, 4, 5] Post stroke depression (PSD) is a significant source of burden for patients and caregivers. PSD is associated with attention deficits and impaired learning and executive and motor functions and has been linked to excess disability, cognitive impairment, poor response to rehabilitation, slow Physical recovery, impaired quality of life, and increased mortality.[6-8] Alexopoulos et al. proposed the concept of vascular depression (VaD) to describe depression associated with cerebrovascular Disease. VaD is thought to result from the disruption of prefrontal systems and lesions damaging the striato-pallido-thalamo-cortical pathways and other areas. [9, 10] The influence of depression on the long-term outcome of stroke patients has been studied extensively, and PSD has been thought to impede rehabilitation. Patients with major depression or with multiple stroke symptoms of depression

scales often had poor functional outcome at 3 months and 15 months follow-up post stroke [11]

Epidemiology

Depression is one of the most common mental disorders worldwide and represents a major public health concern due to its high prevalence, recurrent nature, and significant contribution to disability and mortality. According to the World Health Organization (WHO), more than 280 million people globally suffer from depression, accounting for approximately 3.8% of the world's population, making it one of the leading causes of disability worldwide [1]. Depression affects individuals of all ages, genders, ethnicities, and socioeconomic backgrounds, although its prevalence varies across different populations and geographic regions [2]. Epidemiological studies have reported a lifetime prevalence ranging from 10% to 20% in the general population, with women being nearly twice as likely as men to experience depressive disorders [3,4]. The higher prevalence among women has been attributed to biological factors such as hormonal fluctuations during menstruation, pregnancy, postpartum periods, and menopause, as well as psychosocial stressors including caregiving responsibilities, gender discrimination, and socioeconomic inequalities [5]. Depression can occur at any stage of life; however, its onset is most commonly observed during adolescence and early adulthood, although significant rates are also reported among elderly individuals [6]. In adolescents, factors such as academic pressure, social stress, peer relationships, family conflicts, and exposure to adverse childhood experiences contribute to increased vulnerability, whereas in older adults' depression is often associated with loneliness, chronic illnesses, cognitive decline, bereavement, and reduced social support [7]. Depression in older adults is frequently underdiagnosed because symptoms may manifest as fatigue, apathy, memory impairment, sleep disturbances, or loss of interest rather than persistent sadness [8]. The incidence of depression continues to rise globally due to urbanization, economic instability, social isolation, lifestyle changes, and increasing exposure to psychosocial stressors [9]. Numerous epidemiological investigations have demonstrated that socioeconomic status plays a critical role in the occurrence of depression, with higher rates observed among individuals experiencing poverty, unemployment, low educational attainment, financial insecurity, and poor living conditions [10]. Urban populations often exhibit a greater prevalence of depressive disorders compared with rural populations due to factors such as overcrowding, environmental stress, reduced social cohesion, and increased social isolation, although rural populations may face challenges related to limited access to mental healthcare services and underreporting of psychiatric symptoms [11]. Depression is considered a multifactorial disorder resulting from the complex interaction of genetic, biological, psychological, environmental, and social determinants [12]. Family and twin studies have consistently demonstrated a hereditary component, with individuals having a family history of depression being at increased risk of developing the disorder [13]. Neurobiological mechanisms implicated in depression include dysregulation of monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine, alterations in neuroplasticity, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, and increased inflammatory activity [14]. Stressful life events including bereavement, divorce, relationship problems, financial difficulties, trauma, abuse, and occupational stress have been identified as major psychosocial risk factors contributing to the development and recurrence of depression [15]. Chronic medical conditions such as diabetes mellitus, cardiovascular diseases, cancer, stroke, Parkinson's disease, chronic kidney disease, and chronic pain syndromes are also strongly associated with increased rates of depression, highlighting the bidirectional relationship between physical and mental health [16]. Depression frequently coexists with other psychiatric disorders including anxiety disorders, substance use disorders, and personality disorders, resulting in increased disease burden and poorer clinical outcomes [17]. Furthermore, depression is a significant risk factor for suicide, which remains a leading cause of death worldwide, particularly among adolescents and young adults [18]. The public health burden of depression extends beyond individual suffering and encompasses substantial social and economic consequences, including reduced work productivity, increased absenteeism, impaired interpersonal relationships, higher healthcare utilization, and increased healthcare costs [19]. The COVID-19 pandemic

further amplified the global burden of depression by increasing social isolation, fear, uncertainty, economic hardship, and psychological distress, resulting in a marked rise in depressive symptoms across many populations [20]. Despite the availability of effective pharmacological and psychological treatments, depression remains underdiagnosed and undertreated due to stigma, lack of awareness, inadequate mental health resources, and barriers to healthcare access [21]. Therefore, understanding the epidemiology of depression is essential for the development of effective prevention strategies, early detection programs, public health policies, and evidence-based interventions aimed at reducing the global burden of this debilitating disorder.

5. MATERIALS AND METHODS

Collection of Plant Materials:

Dried Mesua ferrea was purchased from an herbal Market of Hyderabad, Telangana, India, and authenticated by Dr. K. Madhava Chetty, Assistant Professor, Department of Botany, S.V University, and Tirupati.

Preparation of plant extract

Dried Leaves were extracted with ethanolic extract, using a Soxhlet extractor for 8 hrs. at 55-600C. The supernatant was filtered through Whatman filter paper No.1 and concentrated under reduced pressure using a vacuum at 44 ± 100C in a rotavapor (IKA ® RB 10 Rota Evaporator, India) The extract was stored at 220C in a seeded air-tight container.

The percentage yield of extract was calculated by using the formula.

$$\% \text{ yield of extract} = \frac{\text{weight in gm of extract obtained}}{\text{weight in gm of plant material taken}} \times 100$$

Oral toxicity study [22]

The up and down approach was used to test the acute oral toxicity of Mesua ferrea extracts (UDP). The main benefit of UDP is that it reduces the number of animals needed to assess the acute oral toxicity of a chemical and the median lethal dose. From Jeeva Life Sciences.

Procedure-

An individual animal was administered with 250mg/kg body weight dose one at a time orally. The animal was observed for 24 hours. The animal was survived; the 750mg/kg body weight dose one at a time orally was given to next animal. Again, animal was observed for 24 hours. The animal was survived; the 2000mg/kg body weight dose one at a time orally was given to next animal. Again, animal was observed for 24 hours. The animal was survived; four additional animals were dosed using the same dose. No deaths occurred; 3 animals of the other sex was tested at the same dose level. If mortality was not registered again, the test was terminated.

Antidepressant activity [23]

The trials were carried out on 36 adult Albino rats that weighed between 25 - 40 grams. Rats were housed in conventional laboratory settings with free access to water and standard laboratory food (12 h light/12 h dark cycle at 222 °C). The rats were put into six groups at random.

Table-5.1 Experimental Grouping and Treatment Protocol

Group	I	II	III	IV	V	VI
Treatment Group	Normal Control (Saline)	Reserpine Control	Standard + Reserpine	Mesua ferrea Ethanolic Extract (Low Dose) + Reserpine	Mesua ferrea Ethanolic Extract (Moderate Dose) + Reserpine	Mesua ferrea Ethanolic Extract (High Dose) + Reserpine
Treatment	Normal saline 1 ml/kg, o.p.	Reserpine 5 mg/kg, o.p. (18 h before test)	Fluoxetine 20 mg/kg, o.p. + Reserpine 5 mg/kg	Mesua ferrea Ethanolic Extract 100 mg/kg, o.p. + Reserpine 5 mg/kg	Mesua ferrea Ethanolic Extract 150 mg/kg, o.p. + Reserpine 5 mg/kg	Mesua ferrea Ethanolic Extract 200 mg/kg, o.p. + Reserpine 5 mg/kg

Behavioral test [24]

A. Forced swim test (FST):

Animals: Rats (25-40g)

Extract preparation: Suspension of all extracts was prepared in 1% acacia solution.

Standard Preparation: Suspension of powder fluoxetine tablet equivalent to 2mg/mL was prepared in 1% acacia solution.

Drug treatment: The rats were given oral doses of 100 and 200 mg/kg/day of a 1% acacia suspension of Mesua ferrea extracts for 7 days. All of the experimental procedures began one hour after the medication was administered on days 4 and 7. The control and standard groups were given vehicle (1 percent acacia solution) and fluoxetine (10 mg/kg body weight) orally, respectively.

Procedure: All of the experimental procedures began at 1 hr. on days 4 and 7. following the administration of the medication. Rats were made to swim in an open cylindrical container with a depth of 15cm of water at 251°C (diameter 14

cm, height 20 cm). After each trial, the water in the containers was changed.

Evaluation: The immobility period was measured in minutes and was defined as the lack of escape-oriented behaviors such as swimming. When a mouse stopped struggling and stayed motionless in the water, making just the motions required to maintain its head above water, it was deemed immobile.

B. Tail suspension test (TST) [25]

Extract preparation: Suspension of all extracts was prepared in 1% acacia solution.

Standard Preparation: Suspension of powder Fluoxetine tablet equivalent to 2mg/ml was prepared in 1% acacia solution.

Drug treatment: The rats were given oral doses of 100 and 200 mg/kg/day of a 1% acacia suspension of Mesua ferrea extract for 7 days. On days 4 and 7, all of the experimental procedures began at 1 hr. Once the drug has been administered, Fluoxetine (10mg/kg body weight) and vehicle (1 percent acacia solution) were supplied to the control and standard groups, respectively.

Procedure: The rats are suspended 50cm above the floor by adhesive tape inserted 1 centimeter from the tip of their tail.

Evaluation: During a 6-minute test session, the total immobility period was manually measured using a stopwatch. Immobility was defined as the lack of any limb or body movements other than those caused by breathing or when they were passively hung. The parameter gathered was the number of seconds spent immobile. As a metric, the number of seconds spent immobile was used.

C. Open-field Test (OFT) [26-27]

Animals: Albino Swiss rats (22-26g) male

Extract preparation: Suspension of all extracts was prepared in 1% acacia solution.

Standard Preparation: Suspension of powder fluoxetine tablet equivalent to 2mg/ml g was prepared in 1% acacia solution.

Drug treatment: The animals were given a 1 percent acacia suspension of Mesua ferrea extracts orally for 7 days at doses of 100 and 200 mg/kg/day. All of the experimental procedures began on the seventh day, one hour after the medication was administered. The control and standard groups received fluoxetine (10mg/kg body weight) and vehicle (1 percent acacia solution) correspondingly.

Procedure: Individual animals were placed in a box (303015cm) with a floor divided into nine identical squares. After each mouse presentation, the box was cleaned with 10% ethanol.

Evaluation: Following a 5-minute acclimatization period in the arena, ambulation/ locomotor (the number of squares crossed with all paws), grooming, and rearing events were observed for 5 minutes.

STATISTICAL ANALYSIS

The results of biochemical estimations were expressed as Mean ± S.E.M. Statistical analysis was performed using the Independent Samples t-test to compare the means between the control and treatment groups. A value of $p < 0.0001$ was considered statistically significant.

RESULTS

Table-1 Forced Swim Test

Group	Treatment	Immobility Time (s) (Mean ± SEM)
Group I	Normal Control (Saline)	78.4 ± 4.2***
Group II	Reserpine Control	182.6 ± 6.8***
Group III	Fluoxetine + Reserpine	92.3 ± 5.1***
Group IV	Mesua ferrea Extract 100 mg/kg + Reserpine	148.7 ± 5.9***
Group V	Mesua ferrea Extract 150 mg/kg + Reserpine	118.5 ± 4.7***
Group VI	Mesua ferrea Extract 200 mg/kg + Reserpine	96.2 ± 4.4***

Group 2 is Compare with Group 1;Group 3 to 6 are compared with Group 2 ***p <0.0001 [significant]

Reserpine administration significantly increased immobility time in rats, confirming induction of depressive-like behavior. Treatment with Fluoxetine markedly reduced immobility time. The ethanolic extract of Mesua ferrea produced a dose-dependent reduction in immobility time, with the 200 mg/kg dose showing effects comparable to the standard drug, indicating significant antidepressant potential in the Forced Swim Test

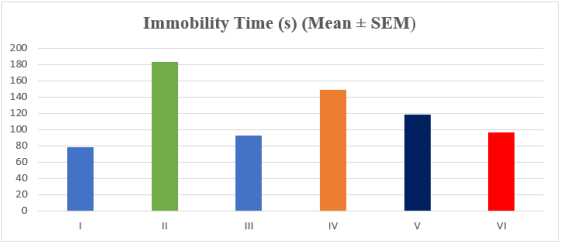

Fig-1:Effect of Mesua ferrea extract on immobility time in the Forced Swim Test

Table-2 Tail Suspension Test

Group	Treatment	Immobility Time (s) (Mean ± SEM)
Group I	Normal Control (Saline)	82.1 ± 3.9***
Group II	Reserpine Control	190.4 ± 7.2***
Group III	Fluoxetine + Reserpine	95.6 ± 4.8***
Group IV	Mesua ferrea Extract 100 mg/kg + Reserpine	156.3 ± 6.1***
Group V	Mesua ferrea Extract 150 mg/kg + Reserpine	124.8 ± 5.2***
Group VI	Mesua ferrea Extract 200 mg/kg + Reserpine	101.7 ± 4.6***

Group 2 is Compared with Group 1;Group 3 to 6 are compared with Group 2 *** p <0.0001 [significant]

Reserpine significantly increased immobility time, confirming depressive-like behavior. Treatment with Fluoxetine markedly reduced immobility. The ethanolic extract of Mesua ferrea produced a dose dependent reduction in immobility time, with the 200 mg/kg dose showing effects comparable to the standard drug, demonstrating notable antidepressant activity in the Tail Suspension Test.

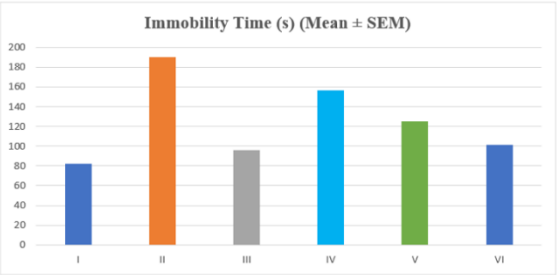

Fig- 2: Effect of Mesua ferrea extract on immobility time in the Tail Suspension Test

Table-3 Open-field Test

Groups	Treatment	Squares Crossed (Mean ± SEM)	Rearing (Mean ± SEM)	Grooming (Mean ± SEM)
Group I	Normal Control (Saline)	92.4 ± 5.1***	18.6 ± 1.8	6.2 ± 0.9
Group II	Reserpine Control	34.7 ± 3.9***	6.3 ± 1.1	2.1 ± 0.6
Group III	Fluoxetine + Reserpine	85.9 ± 4.6***	16.9 ± 1.6	5.8 ± 0.8
Group IV	Mesua ferrea Extract 100 mg/kg + Reserpine	52.8 ± 4.2***	9.4 ± 1.2	3.1 ± 0.7
Group V	Mesua ferrea Extract 150 mg/kg + Reserpine	68.3 ± 4.7***	12.7 ± 1.4	4.2 ± 0.8
Group VI	Mesua ferrea Extract 200 mg/kg + Reserpine	81.6 ± 4.9***	15.8 ± 1.5	5.3 ± 0.9

Group 2 is Compared with Group 1;Group 3 to 6 are compared with Group 2 *** p <0.0001 [significant]

Reserpine markedly suppressed locomotor and exploratory behaviors in rats. Treatment with Fluoxetine restored these parameters close to normal. The ethanolic extract of Mesua ferrea produced a dose-dependent improvement in squares crossed, rearing, and grooming, with the 200 mg/kg dose showing activity comparable to the standard drug, indicating significant recovery of psychomotor function in the Open-Field Test.

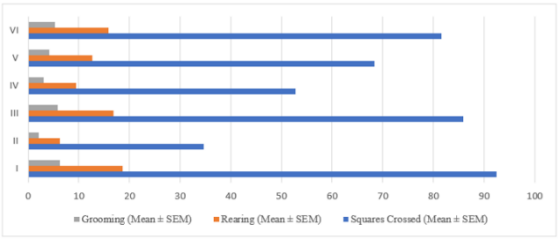

Fig-3 Effect of Mesua ferrea extract on immobility time in the Open-Field Test

DISCUSSION

Reserpine administration produced a marked increase in immobility time in both the Forced Swim Test and the Tail Suspension Test, along with a pronounced reduction in locomotor and exploratory activity in the Open Field Test. These behavioral alterations confirm successful induction of a depressive-like state, consistent with reserpine's monoamine-depleting action on central stores of serotonin, norepinephrine, and dopamine. Treatment with the standard antidepressant Fluoxetine significantly reduced immobility time and restored locomotor behavior toward normal, validating the sensitivity of the experimental model. Fluoxetine's effect is attributable to inhibition of serotonin reuptake, thereby enhancing synaptic availability of monoamines and reversing reserpine-induced behavioral deficits. Administration of the ethanolic extract of Mesua ferrea produced a dose-dependent reduction in immobility time in both despair-based tests and significantly improved ambulation, rearing, and grooming in the open field paradigm. The highest dose (200 mg/kg) demonstrated effects comparable to fluoxetine, indicating potent antidepressant-like activity. Improvement in open-field performance also suggests that the reduction in immobility was not due to nonspecific motor stimulation but reflected genuine antidepressant action.

The observed activity of Mesua ferrea may be attributed to its rich phytochemical profile, particularly the presence of flavonoids, phenolic compounds, and xanthones reported in the plant. These constituents are known to exert antioxidant and neuroprotective effects and may modulate monoaminergic neurotransmission. Flavonoids, in particular, have been documented to inhibit monoamine oxidase and enhance central monoamine levels, which could counteract the depletion caused by reserpine. behavioral findings across all three models consistently demonstrate that Mesua ferrea extract reverses reserpine-induced depressive-like symptoms in rats. The convergence of results from despair-based tests and locomotor assessment strengthens the evidence for its antidepressant potential. Further studies involving neurotransmitter estimation and receptor binding assays would help elucidate the precise mechanism underlying this activity.

Conclusion

The present study demonstrates that reserpine successfully induced depressive-like behavior in rats, evidenced by increased immobility in the Forced Swim Test and Tail Suspension Test, along with reduced locomotor and exploratory activity in the Open Field Test. Treatment with the standard antidepressant Fluoxetine significantly reversed these behavioral alterations, validating the experimental model. The ethanolic extract of Mesua ferrea produced a clear dose-dependent antidepressant effect, with the highest dose (200 mg/kg) showing results comparable to the standard drug. The improvement observed across multiple behavioral paradigms indicates genuine antidepressant-like activity rather than nonspecific stimulation of locomotion. Mesua ferrea possesses antidepressant potential, possibly due to its bioactive phytoconstituents acting through modulation of monoaminergic pathways. Further biochemical and mechanistic studies are warranted to substantiate and characterize its therapeutic potential.

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