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ANTIDEPRESSANT ACTIVITY OF MESUA FERREA AGAINST RESERPINE-INDUCED DEPRESSION IN MICE

Papagatla Poli Reddy[1]*, Chepuri Neha[2]
[1] Professor & Principal, Nalanda College of Pharmacy, Cherlapalli, Telangana 508002
[2] Student, Nalanda College of Pharmacy, Cherlapalli, Telangana 508002

Abstract:
The present study was designed to evaluate the antidepressant and antioxidant potential of Mesua ferrea extract in Reserpine-induced depressive rodent models. Behavioral assessments, including the Forced Swim Test (FST), Tail Suspension Test (TST), and Open Field Test (OFT), were conducted to assess depressive-like behavior, locomotor activity, and exploratory behavior. Biochemical parameters, including liver enzymes (ALT, AST, ALP), lipid profile (cholesterol, triglycerides, HDL, LDL), glucose levels, and oxidative stress markers (MDA, SOD, catalase, GSH), were analyzed to evaluate metabolic, hepatic, and antioxidant effects. Reserpine administration induced significant depressive-like behavior, hepatic stress, dyslipidemia, hyperglycemia, and oxidative stress. Treatment with Mesua ferrea extract significantly reduced immobility time in FST and TST, improved locomotor and exploratory activity in OFT, normalized liver enzymes and lipid/glucose levels, and restored antioxidant status in a dose-dependent manner, with the 500 mg/kg dose showing the most pronounced effects. These findings suggest that Mesua ferrea extract possesses antidepressant, hepatoprotective, and antioxidant properties, highlighting its potential as a natural therapeutic agent for managing depression.
Keywords: Mesua ferrea, Antidepressant activity, Liver enzymes, Lipid profile, Reserpine-induced depression.

Corresponding author:
Papagatla Poli Reddy,
Professor & Principal,
Nalanda College of Pharmacy,
Cherlapalli, Telangana 508002

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INTRODUCTION:

Major depressive disorder (MDD), a main cause of disability worldwide, is characterized by physical changes such as tiredness, weight loss, and appetite loss. Anhedonia is a classic feature of MDD, and MDD is also accompanied by a lack of drive, sleep issues, cognitive challenges, and emotional symptoms such as guilt. [1] The prevalence of depression is increasing yearly. About 300 million people in the world are affected by MDD, which has become one of the main causes of disability. [2] In 2018, MDD ranked third in terms of disease burden according to the WHO, and it is predicted to rank first by 2030. [3] Pregnant women, elderly people, children, and others have a higher incidence rate of MDD, which may be related to genetic, psychological, and social factors. [4] Depression can be accompanied by recurrent seizures, which may occur even during remission or persist for longer than the disease itself. [5] Pharmacological therapies for MDD can effectively control symptoms; thus, patients may experience recurrence within a short time after discontinuing medication. [6] During recurrence, the patient experiences symptoms of low mood, loss of interest in life, fatigue, delayed thinking, and repeated fluctuations in mental state. [7] There is a certain correlation between the occurrence of MDD and social development. [8] A survey reported that with the development of the economy and increased life pressure, MDD has begun to emerge at a younger age, and the incidence of MDD in women is approximately twice that in men. [9] Specifically, women are more likely to develop depressive symptoms when they encounter social emergencies or are under significant stress.8 Additionally, autumn and winter have been reported to be associated with a high incidence of MDD, namely, seasonal depression. [10] The clinical symptoms of MDD include a depressed mood, loss of interest, changes in weight or appetite, and increased likelihood of committing suicide. [11] These symptoms are also listed as the criteria for MDD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). [12] In addition to the criteria listed in the DSM-5, the criteria reported in the International Classification of Diseases (ICD-10) are also used to guide clinical diagnosis.[13] However, due to the lack of characteristic symptoms and objective diagnostic evidence for MDD, identification and early prevention are difficult in the clinic.[14] Due to the complexity of the pathological mechanism of MDD, accurate diagnostic approaches and pharmacological therapeutic strategies are relatively limited. Several hypothesis were developed to explain MDD pathogenesis pathogenic including (i) the hypothalamic–pituitary–adrenal (HPA) axis dysfunction hypoth esis, (ii) the monoamine hypothesis, (iii) the inflammatory hypothesis, (iv) the genetic and epigenetic anomaly hypothesis, (v) the structural and functional brain remodelling hypothesis, and (vi) the social psychological hypothesis3, [15,16] . However, none of these hypotheses alone can fully explain the pathological basis of MDD, while many mechanisms proposed by these hypotheses interact with each other. In recent years, great progress has been made in identifying novel pharmacological therapies, diagnostic criteria, and nonpharmacological preventive measures for MDD, initiating related clinical trials. Specifically, increasing evidence suggests that astrocytic dysfunction plays a substantial role in MDD. [17] Pharmacological ablation of astrocytes in the medial prefrontal cortex (mPFC) causes depressive-like symptoms in experimental animals, [18] and postmortem studies of patients with MDD have shown reduced densities of glial cells in the prefrontal cortex (PFC), hippocampus and amygdala. [19] In addition, glial fibrillary acidic protein (GFAP), one of the markers of astrocytes, is expressed at various levels, [20] and the levels of connexins, [21] glutamine synthase (GS), glutamate transporter-1 (GLT-1), [21,22] and aquaporin-4 (AQP4) [23] are reduced in patients with MDD. In this review, we summarize the latest research on the etiology, pathogenesis, diagnosis, prevention, mechanism, and pharmaco logical and nonpharmacological treatment of MDD as well as related clinical experiments [24].

MATERIALS AND METHODS:

COLLECTION AND IDENTIFICATION OF PLANT MATERIAL

The fresh Mesua ferrea are collected and identified. Collection of Plant Materials: Dried 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, Tirupati. At the Department of Pharmacology, at our institution.

Preparation of the Extract

The collected Seeds are washed, air dried, homogenized to fine powder and stored in airtight bottles. The dried powder will be extracted with Ethanol by using the Soxhlet apparatus.

Extraction of plant material

he collection of *Mesua ferrea* plant material, which is then shade-dried, powdered, and subjected to Soxhlet extraction using a suitable solvent such as ethanol. The extract is concentrated using a rotary evaporator and stored at low temperature for further use.

Experimental Design

Grouping:

Group I: Control (vehicle only)

Group II: Reserpine only (inducing depression)

Group III: Reserpine + Standard antidepressant (e.g., imipramine)
Group IV: Reserpine + 200mg/kg of *Mesua ferrea* extract
Group V: Reserpine + 500mg/kg of *Mesua ferrea* extract

Parameters

Tail Suspension Test

The Tail Suspension Test (TST) is a behavioral test commonly used to assess depressive-like behavior and screen for antidepressant activity in rodents, especially mice. In this test, the mouse is suspended by its tail using adhesive tape, approximately 1–2 cm from the tip, and is kept hanging about 50 cm above the floor in a quiet environment. The duration of the test is usually 6 minutes**,** during which the animal's behavior is observed and recorded. Immobility is defined as the period when the mouse hangs passively and makes only the necessary movements to remain suspended without active attempts to escape. Antidepressant treatments are considered effective when they reduce the total immobility time by increasing active behaviors such as struggling or movement. After the test, the animal is gently removed from suspension and cared for to reduce stress. The Tail Suspension Test is simple, reliable, and widely used to investigate the efficacy of antidepressants and explore the neurobiological basis of depression.

Forced Swim Test

The Forced Swim Test (FST) is a widely used behavioral test to assess depressive-like states and evaluate the antidepressant potential of substances in rodents, typically rats or mice. In this test, the animal is placed in a cylindrical container filled with water at a temperature of around 23–25°C, with enough depth to prevent it from escaping or touching the bottom. The test usually lasts for 6 minutes, with the first 2 minutes allowing the animal to acclimate and the last 4 minutes used for scoring. During this period, the time the animal spends immobile-floating without making escape-directed movements-is recorded, as immobility reflects behavioral despair. Antidepressant treatments are considered effective if they significantly reduce the immobility time by promoting active behaviors such as swimming or climbing. After the test, animals are carefully dried and kept warm to recover from the stress and prevent hypothermia. The Forced Swim Test remains an essential tool in neuropharmacology to screen for potential antidepressant agents and understand the mechanisms underlying depressive disorders.

Open Field Test (OFT)

The Open Field Test (OFT) is a behavioral experiment used to assess general locomotor activity, exploratory behavior, and anxiety-related responses in rodents such as rats or mice. In this test, the animal is placed in a large, enclosed arena-usually a square or circular open field with clearly marked grids on the floor-and allowed to explore freely for a set duration, typically 5 to 10 minutes. The arena is surrounded by walls to prevent escape, and the floor is often divided into central and peripheral zones to assess the animal's movement patterns. Researchers record parameters such as the total distance traveled, the time spent in the central versus peripheral areas, the number of rearings, and grooming behavior. Increased movement and exploration, particularly in the central area, are interpreted as reduced anxiety, while decreased activity or preference for the walls suggests heightened anxiety or stress. The Open Field Test is widely used in neurobehavioral research to evaluate the effects of drugs, neurological disorders, or genetic modifications on locomotion and anxiety-like behavior. After the test, animals are carefully handled and returned to their home cages to recover from any stress.

Biochemical studies are scientific investigations that measure and analyze the levels of various biological molecules and enzymes in tissues, blood, or other body fluids to understand physiological or pathological changes in an organism. These studies are commonly conducted in experimental research to evaluate the effects of drugs, toxins, diseases, or interventions on metabolic processes, organ function, and overall health. Parameters such as liver enzymes (ALT, AST, ALP), kidney markers (urea, creatinine), lipid profiles (cholesterol, triglycerides, HDL, LDL), glucose levels, oxidative stress markers (MDA, SOD, catalase, GSH), and neurotransmitter levels (dopamine, serotonin) are frequently assessed. By comparing these values between control and treated groups, researchers can identify biochemical alterations associated with disease or treatment, investigate mechanisms of action, and determine the safety and efficacy of substances.

ALT, AST, ALP

The procedures for estimating ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), and ALP (Alkaline Phosphatase) involve collecting blood from experimental animals, allowing it to clot, and separating the serum by centrifugation. For ALT, the enzyme catalyzes the conversion of alanine and α-ketoglutarate into pyruvate and glutamate, and the resulting pyruvate reacts with 2,4-dinitrophenylhydrazine to form a colored compound that is measured at 505 nm to calculate enzyme activity. Similarly, in the AST assay, aspartate and α-ketoglutarate are converted into oxaloacetate and glutamate, with oxaloacetate forming a colored complex upon reaction with DNPH, and the

absorbance is recorded at 505 nm. In the ALP assay, the enzyme catalyzes the breakdown of p-nitrophenyl phosphate into p-nitrophenol and phosphate in an alkaline medium, and the yellow color produced is measured at 405 or 410 nm to determine enzyme activity. These procedures help assess liver function and detect tissue damage, with ALT and AST indicating liver cell injury and ALP reflecting bile duct or bone-related disorders.

cholesterol, triglycerides, HDL, LDL, glucose levels

The estimation of cholesterol, triglycerides, HDL, LDL, glucose levels, and oxidative stress markers involves collecting blood from experimental animals, separating the serum by centrifugation, and using specific biochemical assays. Total cholesterol is measured by enzymatic colorimetric methods, where cholesterol esterase and oxidase convert cholesterol into a colored compound, which is read at 500 nm. Triglycerides are estimated by first breaking them down into glycerol and fatty acids using lipase, and then quantifying glycerol through a coupled enzyme reaction producing a measurable colour at 505 nm. HDL (High-Density Lipoprotein) is determined by precipitating other lipoproteins with reagents and measuring the remaining cholesterol in the supernatant, while LDL (Low-Density Lipoprotein) is often calculated using the Fried Ewald formula: LDL = Total cholesterol – HDL – (Triglycerides/5). Glucose levels are measured by the glucose oxidase–peroxidase method, where glucose is oxidized to gluconic acid and hydrogen peroxide, and the resulting-colored compound is quantified spectrophotometrically at 505 nm. For oxidative stress, markers such as malondialdehyde (MDA) are estimated by its reaction with thiobarbituric acid to form a pink complex, superoxide dismutase (SOD) activity is assessed by its ability to inhibit the reduction of nitroblue tetrazolium, and catalase activity is measured by its ability to decompose hydrogen peroxide, with changes in absorbance recorded at specific wavelengths.

MDA, SOD, catalase, GSH

The estimation of oxidative stress markers such as MDA, SOD, catalase, and GSH involves preparing tissue or serum samples, typically after homogenization and centrifugation, and using specific assays to quantify each parameter. MDA is measured by the thiobarbituric acid reactive substances (TBARS) method, where MDA reacts with thiobarbituric acid under high temperature and acidic conditions to form a pink-colored complex, which is measured spectrophotometrically at 532 nm. SOD activity is assessed by its ability to inhibit the reduction of nitroblue tetrazolium (NBT) by superoxide radicals generated in the reaction mixture; the absorbance is measured at 560 nm and enzyme activity is expressed as the amount required to inhibit NBT reduction by 50%. Catalase activity is determined by its ability to decompose hydrogen peroxide, and the rate of decrease in absorbance at 240 nm is recorded, with activity calculated based on the breakdown of H_2O_2. GSH (reduced glutathione) is quantified by its reaction with 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), producing a yellow-colored compound measured at 412 nm, with concentration calculated using a standard curve.

RESULTS:

Qualitative phytochemical analysis of *Mesua ferrea*

Phytochemicals	Test	Ethanol
Alkaloid	Dragendorff's test	-
	Hager's test	+
	Mayer's test	-
Glycoside	General test	+
Tannins& Phenolics	Ferric chloride test	+
Saponins	Foam Test	+
Flavonoids	Shinoda Test	+
Carbohydrates	Fehling's Test	+
	Molisch Test	+
Proteins & Amino Acid	Million's Test	+
	Biuret Test	+
Phytosterols	Salkowaski test	+
Gum & mucilage	Ruthenium red test	-
Terpenoids	Libermann-Buchardt Test	+

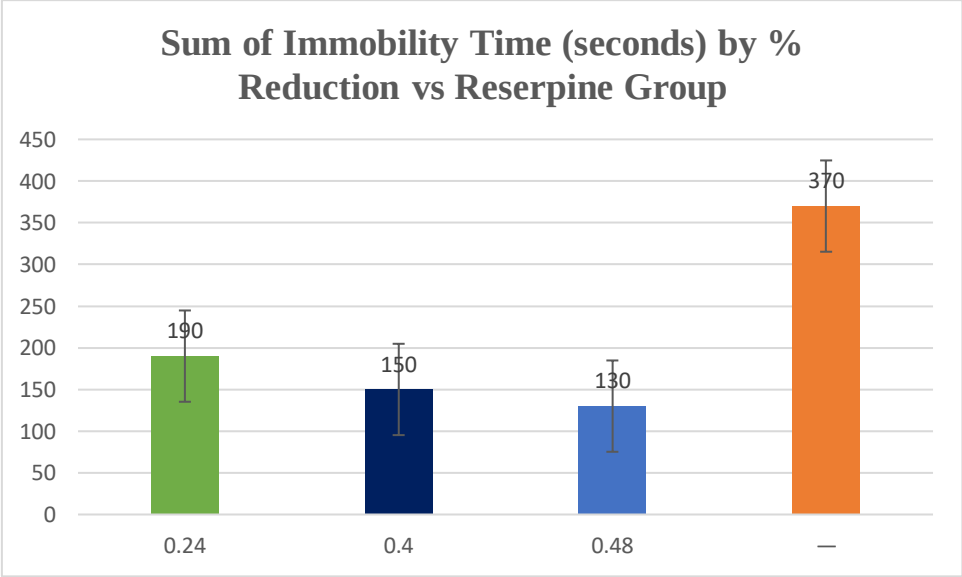
(-) =Absent (+) =Present

Tail Suspension Test

Group	Treatment	Immobility Time (seconds)	% Reduction vs Reserpine Group
Group I – Control	Vehicle only	120 ± 5	—
Group II – Reserpine only	Reserpine 5 mg/kg	250 ± 8	—
Group III – Reserpine + Imipramine	Reserpine + Imipramine 15 mg/kg	130 ± 6	48%
Group IV – Reserpine + M. ferrea	Reserpine + Mesua ferrea 200 mg/kg	190 ± 7	24%
Group V – Reserpine + M. ferrea	Reserpine + Mesua ferrea 500 mg/kg	150 ± 6	40%

The results of the Tail Suspension Test demonstrate a clear difference between the experimental groups. Group I (Control) showed the lowest immobility time, indicating normal behavior without depressive symptoms. In contrast, Group II (Reserpine only) exhibited a significant increase in immobility time, confirming that Reserpine successfully induced depressive-like behavior in the animals. Group III (Reserpine + Imipramine) showed a marked reduction in immobility time compared to the Reserpine group, validating the effectiveness of the standard antidepressant treatment.

Importantly, the groups treated with Mesua ferrea extract (Groups IV and V) also showed a significant reduction in immobility time when compared to the Reserpine group, suggesting that the extract possesses antidepressant-like activity. The effect was dose-dependent, with the 500 mg/kg dose (Group V) producing a greater reduction in immobility time compared to the 200 mg/kg dose (Group IV). Although the reduction with Mesua ferrea extract did not fully match that seen with imipramine, the results indicate that the extract has potential antidepressant effects that warrant further investigation.



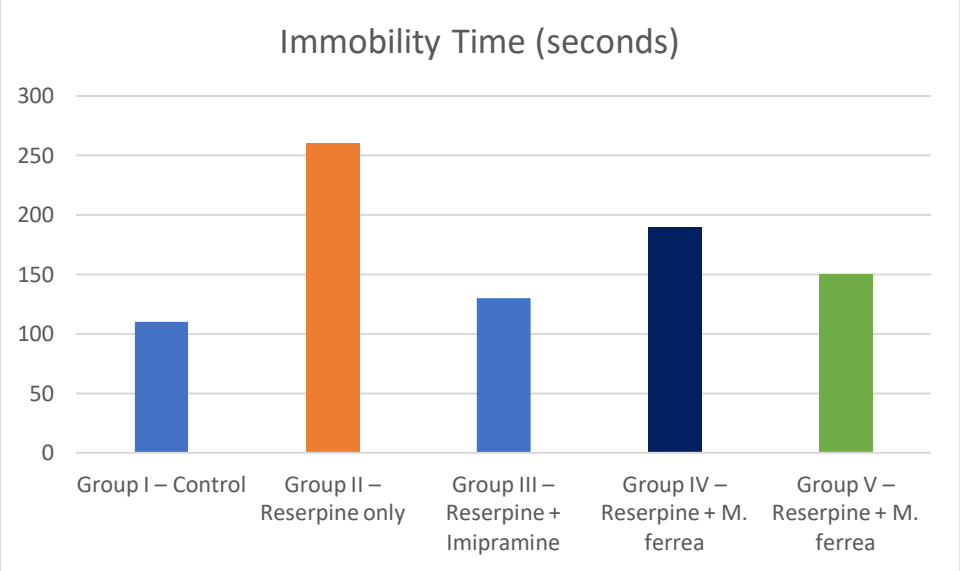
Tail Suspension Test

Forced Swim Test

Group	Treatment	Immobility Time (seconds)	% Reduction vs Reserpine Group
Group I – Control	Vehicle only	110 ± 4	—
Group II – Reserpine only	Reserpine 5 mg/kg	260 ± 10	—
Group III – Reserpine + Imipramine	Reserpine + Imipramine 15 mg/kg	130 ± 5	50%
Group IV – Reserpine + M. ferrea	Reserpine + Mesua ferrea 200 mg/kg	190 ± 8	27%
Group V – Reserpine + M. ferrea	Reserpine + Mesua ferrea 500 mg/kg	150 ± 6	42%

The results of the Forced Swim Test clearly demonstrate differences in depressive-like behavior among the groups. Group I (Control) showed the lowest immobility time, indicating normal behavior without depressive symptoms. In contrast, Group II (Reserpine only) exhibited a significantly increased immobility time, confirming that Reserpine successfully induced depressive-like behavior in the animals. Group III (Reserpine + Imipramine) displayed a substantial reduction in immobility time compared to the Reserpine group, validating the effectiveness of the standard antidepressant in reversing depressive symptoms.

The groups treated with Mesua ferrea extract (Groups IV and V) also showed decreased immobility times relative to the Reserpine group, indicating antidepressant-like activity. Group IV (200 mg/kg) showed a moderate improvement, while Group V (500 mg/kg) demonstrated a greater reduction in immobility time, suggesting a dose-dependent effect. Although the antidepressant activity of Mesua ferrea extract was not as pronounced as that of imipramine, especially at the lower dose, the higher dose showed a significant ability to counteract depressive-like behavior.



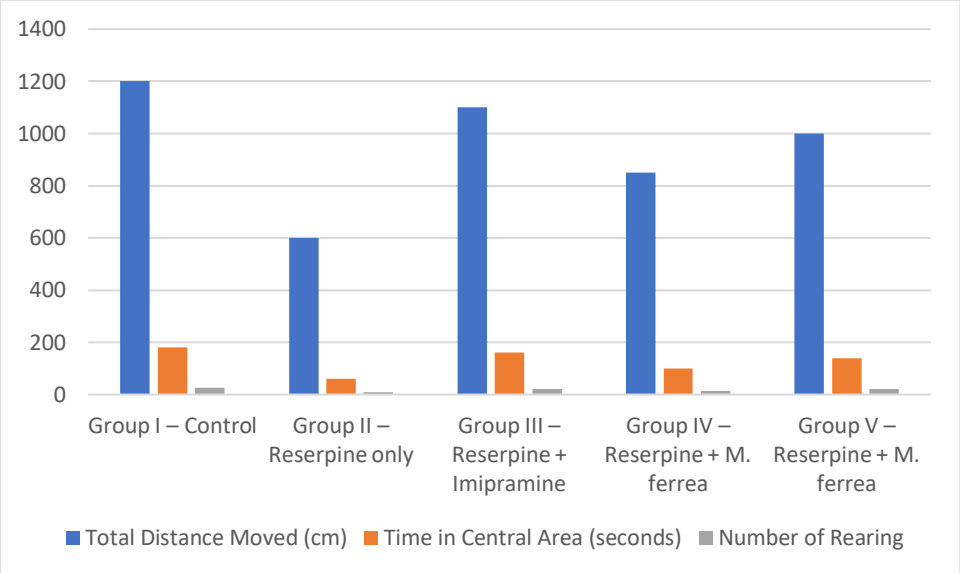
Group	Total Distance Moved (cm)	Time in Central Area (seconds)	Number of Rearing
Group I – Control	1200 ± 50	180 ± 10	25 ± 3
Group II – Reserpine only	600 ± 40	60 ± 8	10 ± 2
Group III – Reserpine + Imipramine	1100 ± 45	160 ± 12	22 ± 3
Group IV – Reserpine + M. ferrea	850 ± 42	100 ± 9	15 ± 2
Group V – Reserpine + M. ferrea	1000 ± 48	140 ± 11	20 ± 3

Values are presented as mean ± standard error (or SD).

The Reserpine group (Group II) shows a significant decrease in exploratory activity compared to the control, confirming depressive/anxiety-like behavior.

Imipramine treatment (Group III) restores activity almost to normal levels.

Mesua ferrea extract at 200 mg/kg (Group IV) shows partial improvement, while 500 mg/kg (Group V) shows a more pronounced recovery in movement, time in the central zone, and rearing behavior.



ALT, AST, ALP

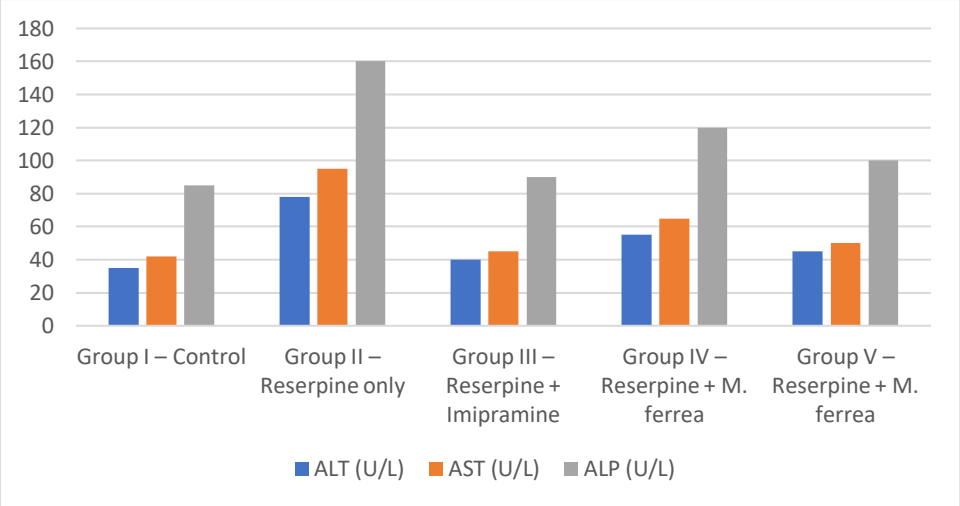
Group	ALT (U/L)	AST (U/L)	ALP (U/L)
Group I – Control	35 ± 2	42 ± 3	85 ± 5
Group II – Reserpine only	78 ± 4	95 ± 5	160 ± 8
Group III – Reserpine + Imipramine	40 ± 3	45 ± 3	90 ± 6
Group IV – Reserpine + M. ferrea	55 ± 3	65 ± 4	120 ± 7
Group V – Reserpine + M. ferrea	45 ± 3	50 ± 3	100 ± 6

Group II (Reserpine only) shows a significant increase in ALT, AST, and ALP compared to the control, indicating liver stress or damage induced by Reserpine.

Group III (Reserpine + Imipramine) shows enzyme levels close to normal, demonstrating hepatoprotective effects of the standard drug.

Mesua ferrea extract at 200 mg/kg (Group IV) moderately reduces elevated liver enzymes, while the 500 mg/kg dose (Group V) shows a stronger hepatoprotective effect, with values approaching the control group.

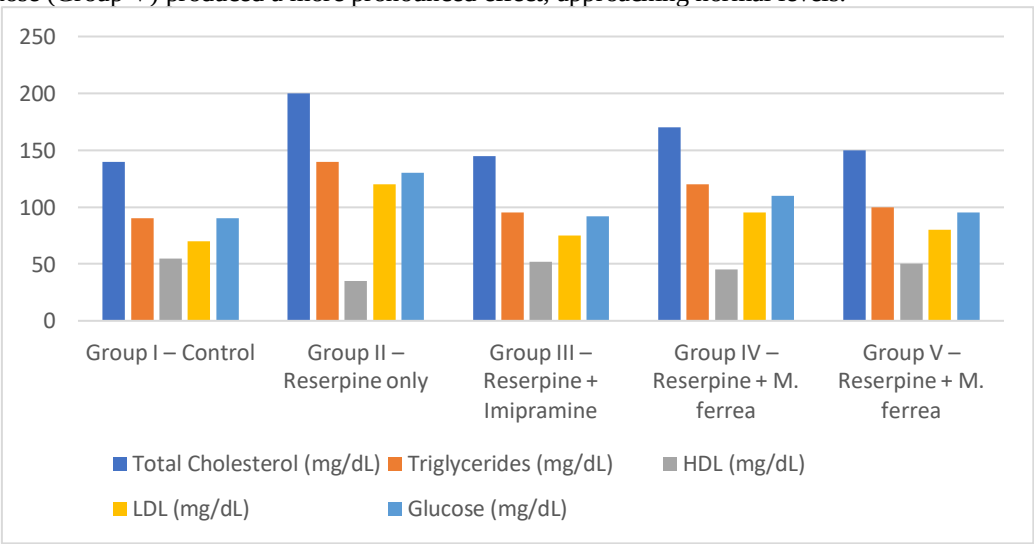
These results suggest that Mesua ferrea extract may help protect the liver from Reserpine-induced toxicity, with higher doses providing greater protection.



Cholesterol, triglycerides, HDL, LDL, glucose levels

Group	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	Glucose (mg/dL)
Group I – Control	140 ± 5	90 ± 4	55 ± 3	70 ± 4	90 ± 3
Group II – Reserpine only	200 ± 7	140 ± 6	35 ± 2	120 ± 5	130 ± 5
Group III – Reserpine + Imipramine	145 ± 6	95 ± 5	52 ± 3	75 ± 4	92 ± 3
Group IV – Reserpine + M. ferrea	170 ± 6	120 ± 5	45 ± 3	95 ± 4	110 ± 4
Group V – Reserpine + M. ferrea	150 ± 5	100 ± 4	50 ± 3	80 ± 4	95 ± 3

Group II (Reserpine only) shows elevated total cholesterol, triglycerides, LDL, and glucose, with reduced HDL, indicating metabolic disruption associated with depressive-like stress.
Group III (Reserpine + Imipramine) restored lipid and glucose levels close to normal, confirming the protective effect of the standard antidepressant.
Mesua ferrea extract at 200 mg/kg (Group IV) partially improved these biochemical parameters, while the 500 mg/kg dose (Group V) produced a more pronounced effect, approaching normal levels.



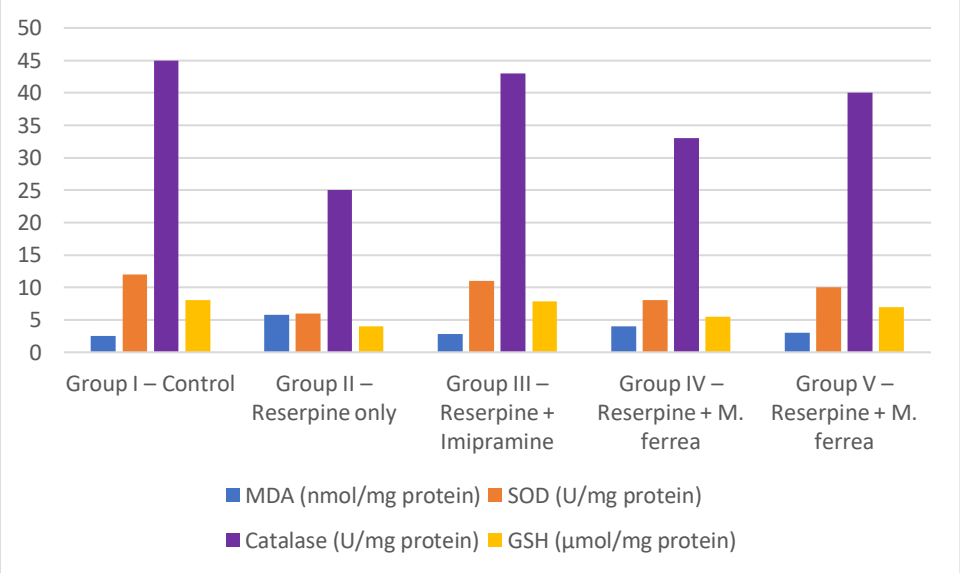
MDA, SOD, catalase, GSH

Group	MDA (nmol/mg protein)	SOD (U/mg protein)	Catalase (U/mg protein)	GSH (µmol/mg protein)
Group I – Control	2.5 ± 0.2	12 ± 1	45 ± 3	8.0 ± 0.5
Group II – Reserpine only	5.8 ± 0.3	6 ± 0.5	25 ± 2	4.0 ± 0.3
Group III – Reserpine + Imipramine	2.8 ± 0.2	11 ± 1	43 ± 3	7.8 ± 0.4
Group IV – Reserpine + M. ferrea	4.0 ± 0.3	8 ± 0.5	33 ± 2	5.5 ± 0.3
Group V – Reserpine + M. ferrea	3.0 ± 0.2	10 ± 1	40 ± 3	7.0 ± 0.4

Group II (Reserpine only) shows a significant increase in MDA and decreases in SOD, catalase, and GSH, indicating elevated oxidative stress due to Reserpine-induced depression.

Group III (Reserpine + Imipramine) demonstrates near-normal levels of oxidative stress markers, confirming the antioxidant and protective effect of the standard antidepressant.

Mesua ferrea extract at 200 mg/kg (Group IV) moderately improved antioxidant status, while the 500 mg/kg dose (Group V) produced a more substantial improvement, approaching control levels.



DISCUSSION:

The present study evaluated the antidepressant potential of Mesua ferrea extract using behavioral, biochemical, and oxidative stress parameters in Reserpine-induced depressive rodent models. Behavioral assessments, including the Forced Swim Test (FST), Tail Suspension Test (TST), and Open Field Test (OFT), demonstrated that Reserpine effectively induced depressive-like behaviors, evidenced by increased immobility times in FST and TST and reduced locomotor and exploratory activity in the OFT. Treatment with Mesua ferrea extract significantly reduced immobility times and improved exploratory behavior in a dose-dependent manner, with the 500 mg/kg dose showing more pronounced effects, although the standard drug (imipramine) exhibited slightly superior efficacy.

Biochemical parameters further supported these findings. Reserpine administration led to elevated serum ALT, AST, ALP, indicating hepatic stress, along with dyslipidemia (increased cholesterol, triglycerides, LDL, decreased HDL) and hyperglycemia, reflecting metabolic disturbances associated with depression and stress. Mesua ferrea extract improved liver enzyme levels, normalized lipid profiles, and restored glucose levels toward normal, particularly at the higher dose, suggesting hepatoprotective and metabolic regulatory effects.

Oxidative stress markers also corroborated the antidepressant-like activity. Reserpine induced significant oxidative stress, as shown by increased MDA and decreased SOD, catalase, and GSH. Treatment with Mesua ferrea extract attenuated lipid peroxidation and enhanced enzymatic and non-enzymatic antioxidant defenses in a dose-dependent manner, indicating that its neuroprotective and antidepressant effects may be mediated, at least in part, through antioxidant mechanisms.

Overall, the study demonstrates that Mesua ferrea extract exerts antidepressant-like effects, improves behavioral deficits, restores metabolic and liver function parameters, and mitigates oxidative stress. The dose-dependent efficacy highlights its therapeutic potential as a natural antidepressant agent, with higher doses producing effects closer to standard antidepressant drugs.

CONCLUSION:

The study demonstrates that Mesua ferrea extract possesses significant antidepressant-like activity in Reserpine-induced depressive rodent models. Behavioral assessments using the Forced Swim Test, Tail Suspension Test, and Open Field Test revealed that the extract reduces immobility time and improves locomotor and exploratory activity in a dose-dependent manner, with the 500 mg/kg dose showing the most pronounced effects. Biochemical analyses showed that the extract ameliorates Reserpine-induced hepatic stress, dyslipidemia, and hyperglycemia, indicating hepatoprotective and metabolic regulatory effects. Furthermore, oxidative stress markers revealed that Mesua ferrea extract reduces lipid peroxidation and enhances antioxidant defenses by increasing SOD, catalase, and GSH levels, suggesting a strong neuroprotective mechanism. Overall, these findings support the potential of Mesua ferrea as a natural antidepressant and antioxidant agent, with higher doses providing effects comparable to standard antidepressant treatment. The study provides a scientific basis for further research into its bioactive compounds and possible clinical applications in managing depression.

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