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Pharmacological Evaluation of Antidepressant-like Activity of Hydroalcoholic Extract of *Ixora coccinea* Flowers Using Standard Behavioural Despair Murine Models in Mice

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Abstract

The present study aimed to evaluate the antidepressant-like activity of the hydroalcoholic extract of Ixora coccinea flowers in mice using behavioral models such as the Forced Swim Test (FST) and Tail Suspension Test (TST). Adult mice were divided into different groups and treated with either standard antidepressant drugs (citalopram and desipramine) or graded doses (10, 20, and 40 mg/kg) of the plant extract. Immobility time was recorded to assess behavioral despair, a hallmark of depressive-like states in rodents. Citalopram and desipramine significantly reduced immobility time in both models, validating the sensitivity of the test paradigms. Ixora coccinea extract showed a dose-dependent reduction in immobility time, with the highest dose (40 mg/kg) producing a statistically significant effect comparable to standard drugs ($p < 0.05$). Lower doses did not produce meaningful behavioral changes. These results suggest that the extract exhibits promising antidepressant-like activity, likely due to the presence of phytoconstituents such as flavonoids and phenolic compounds. This study supports the traditional use of Ixora coccinea in mood disorders and highlights its potential as a natural therapeutic alternative. Further mechanistic and chronic studies are recommended to explore the underlying pathways and long-term efficacy.

Keywords: *Ixora coccinea, Antidepressant-like activity, Hydroalcoholic extract, Forced Swim Test (FST), Tail Suspension Test (TST), Behavioural despair models, Rodent model of depression, Natural antidepressants.*

INTRODUCTION

Depression is a major psychiatric disorder affecting millions of individuals worldwide, characterized by persistent feelings of sadness, hopelessness, and a general loss of interest in life. It is a multifactorial illness that impairs an individual's ability to function socially, occupationally, and emotionally. According to the World Health Organization (WHO), depression affects over 280 million people globally and is projected to become the leading cause of disease burden by 2030. Despite significant advances in neuroscience and psychopharmacology, the management of depression continues to pose a challenge due to the complexity of its pathophysiology and the limitations of current treatment strategies (Anderson et al., 2024; Beurel et al., 2020; Kendler, 2020; Shorey et al., 2022).

The most widely used classes of antidepressant drugs include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and

monoamine oxidase inhibitors (MAOIs). While these drugs have been clinically proven to be effective, they are often associated with a range of undesirable side effects such as weight gain, sexual dysfunction, insomnia, gastrointestinal disturbances, and, in some cases, increased risk of suicidal ideation, especially in adolescents. Additionally, a considerable proportion of patients do not respond adequately to available antidepressant medications or experience only partial relief. The delayed onset of therapeutic action, often requiring weeks to months, further complicates treatment outcomes. These limitations underscore the need for alternative therapeutic options, particularly those that are effective, safer, and affordable (Diener et al., 2021; Figee et al., 2022; Huang et al., 2024; Lu et al., 2024; McCarron et al., 2021; Monroe & Harkness, 2022).

In recent years, interest in natural products as sources of novel therapeutic agents has increased significantly. Medicinal plants, in particular, have received growing attention as potential alternatives to conventional antidepressants. Phytochemicals present in medicinal plants are believed to act through diverse mechanisms such as modulation of monoaminergic transmission, inhibition of monoamine oxidase, antioxidant activity, and neuroprotection. These multi-targeted actions make plant-based medicines particularly suitable for managing complex neuropsychiatric disorders like depression. Moreover, traditional systems of medicine such as Ayurveda and Siddha have long utilized herbal formulations to manage mood disorders, providing a historical and cultural basis for their therapeutic relevance (Chopra & Dhingra, 2021; Ekiert & Szopa, 2020; McNab et al., 2021; Scotti & Scotti, 2022; Xing et al., 2023). One such plant of interest is Ixora coccinea, commonly known as jungle geranium or flame of the woods. It belongs to the Rubiaceae family and is widely distributed in tropical and subtropical regions, including India, Sri Lanka, and Southeast Asia. Traditionally, different parts of the plant, including its roots, leaves, and flowers, have been used in indigenous medicine for the treatment of various ailments such as dysentery, skin diseases, fever, ulcers, and inflammation. The flowers, in particular, are known for their medicinal value and have been reported to exhibit anti-inflammatory, antioxidant, antimicrobial, and wound-healing activities (Kim et al., 2023; Krishnan et al., 2025; R et al., 2024; Unni et al., 2023).

Phytochemical analyses of *Ixora coccinea* have revealed the presence of bioactive constituents such as flavonoids, tannins, saponins, alkaloids, and phenolic compounds. These phytochemicals are of particular interest in neuropsychopharmacology due to their potential to interact with neurotransmitter systems, scavenge reactive oxygen species (ROS), and protect neuronal integrity. Flavonoids, for instance, have been shown to exert antidepressant effects by inhibiting monoamine oxidase enzymes and enhancing serotonergic, dopaminergic, and noradrenergic neurotransmission. Similarly, phenolic compounds are known to provide neuroprotection through their potent antioxidant properties, reducing oxidative stress which is increasingly recognized as a contributing factor in the pathophysiology of depression (Krishnan et al., 2025; Rajayan et al., 2024; Unni et al., 2023; Unni et al., 2022).

Despite the widespread traditional use of *Ixora coccinea* in various therapeutic contexts, limited scientific evidence is available to validate its potential use in mood disorders such as depression. Most studies conducted thus far have focused on the plant's anti-inflammatory, antimicrobial, and antioxidant properties, leaving a gap in knowledge regarding its possible antidepressant-like effects. Therefore, a systematic exploration of the plant's neurobehavioral effects using well-validated preclinical models of depression is warranted. Animal models play a crucial role in the screening and evaluation of novel antidepressant agents. Among them, the Forced Swim Test (FST) and Tail Suspension Test (TST) are two of the most widely used behavioral assays for assessing antidepressant-like activity in rodents. These tests are based on the principle that rodents, when placed in an inescapable situation, exhibit a state of behavioral despair characterized by immobility. Antidepressant agents typically reduce the duration of immobility, indicating a reversal of the depressive-like state. These models are considered sensitive, reproducible, and predictive of clinical efficacy, making them ideal for preliminary screening of plant extracts (Jiang et al., 2022; Tao et al., 2023; Zhu et al., 2024).

In this context, the present study was designed to investigate the antidepressant-like activity of the hydroalcoholic extract of *Ixora coccinea* flowers in mice using the Forced Swim Test and Tail Suspension Test as behavioral paradigms. The extract was prepared using a 70:30 ethanol-water mixture to ensure efficient extraction of both polar and non-polar phytoconstituents. The doses selected for evaluation were

based on preliminary toxicity assessments and existing literature on related plant extracts. In addition to assessing the extract's efficacy, comparisons were made with standard antidepressant drugs—citalopram (an SSRI) and desipramine (a TCA)—to validate the experimental models and contextualize the findings. The objectives of the study were threefold: first, to determine whether the hydroalcoholic extract of *Ixora coccinea* flowers exhibits significant antidepressant-like activity in acute behavioral models; second, to establish a dose-response relationship to identify the most effective dose; and third, to compare the efficacy of the plant extract with that of standard pharmacological agents. These objectives aim to provide a scientific foundation for the traditional use of *Ixora coccinea* in managing mood disorders and to explore its potential as a source for developing novel herbal antidepressant therapies (Jiang et al., 2022; Tao et al., 2023; Zhu et al., 2024). If the findings of this study confirm the antidepressant-like properties of *Ixora coccinea*, it would not only validate its traditional medicinal use but also pave the way for further research into its bioactive compounds and mechanisms of action. Given the global burden of depression and the limitations of existing therapies, the discovery of plant-based alternatives with fewer side effects could significantly impact public health, particularly in low-resource settings where access to conventional medications is limited. The growing interest in natural therapies and the need for safer, more effective antidepressant options highlight the importance of investigating medicinal plants such as *Ixora coccinea*. By systematically evaluating its antidepressant-like activity in validated animal models, the present study seeks to contribute meaningful insights into the potential role of this plant in the pharmacological management of depression.

MATERIALS AND METHODS

Animals

Two strains of healthy adult mice, each weighing between 22 and 30 grams, were selected for the study. The animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, and provided with free access to food and water. All experimental protocols involving the use of animals were reviewed and approved by the Institutional Animal Ethics Committee and conducted in accordance with CPCSEA guidelines.

Plant Material

Fresh flowers of *Ixora coccinea* were collected, cleaned, and shade-dried. The dried flowers were coarsely powdered and extracted using a hydroalcoholic solvent system (typically ethanol:water in a defined ratio such as 70:30). The extract was concentrated under reduced pressure using a rotary evaporator and stored at 4°C until further use.

Chemicals and Reagents

Dimethyl sulfoxide (DMSO) was procured from Fisher Chemicals, while sodium hydrogen phosphate was obtained from Merck, Germany. Standard reference drugs used in the study included the selective serotonin reuptake inhibitor (SSRI), citalopram, and the tricyclic antidepressant (TCA), desipramine, both obtained from Sigma-Aldrich. All chemicals and reagents used were of analytical grade.

Preparation of the Hydroalcoholic Extract of *Ixora coccinea*

Fresh flowers of *Ixora coccinea* were collected, thoroughly washed with distilled water to remove dirt and foreign matter, and shade-dried for 7–10 days. The dried flowers were then powdered using a mechanical grinder. About 200 grams of the powder were macerated in 70% ethanol (ethanol: water, 70:30 v/v) for 72 hours with occasional shaking. The mixture was then filtered using muslin cloth followed by Whatman No. 1 filter paper. The filtrate was concentrated using a rotary evaporator under reduced pressure at a temperature not exceeding 40°C to obtain a semi-solid crude hydroalcoholic extract. The extract was stored in airtight containers in a refrigerator at 4°C until further use.

Experimental Protocol for the Forced Swim Test (FST)

The Forced Swim Test (FST) was employed to assess the antidepressant-like activity of the extract. Mice were individually placed in a transparent cylindrical container (25 cm height × 10 cm diameter) filled with water at 25±1°C to a depth of 15 cm. Each mouse was observed for a total duration of 6 minutes. The initial 2 minutes allowed for acclimatization, while the duration of immobility was recorded during the last 4 minutes. Immobility was defined as the absence of active movements, except those required to keep the animal afloat. The animals were divided into several groups (n=6 per group): vehicle control, standard

drug groups (treated with citalopram or desipramine), and test groups receiving different doses of *Ixora coccinea* extract. A reduction in immobility time compared to control was considered indicative of antidepressant-like activity.

Experimental Protocol for the Tail Suspension Test (TST)

The Tail Suspension Test (TST) was also used to evaluate antidepressant-like behavior. Mice were suspended individually by the tail using adhesive tape affixed approximately 1 cm from the tip, at a height of 50 cm above the floor. The total test duration was 6 minutes, during which the immobility time was recorded in the last 4 minutes after an initial 2-minute habituation period. Mice were considered immobile when they ceased struggling and remained completely motionless. The animals were grouped similarly as in the FST: control (vehicle-treated), standard (citalopram or desipramine-treated), and test groups receiving graded doses of the flower extract. A significant decrease in immobility time compared to the control group indicated antidepressant-like activity.

Data Analysis

All experimental results were expressed as mean ± standard error of the mean (SEM) for each group, with six animals per group (n = 6). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by post hoc Tukey's multiple comparison test to determine the level of significance between treatment and control groups. A *p*-value of less than 0.05 was considered statistically significant. Graphical representations and statistical calculations were performed using GraphPad Prism software (version X.X).

RESULTS

Effect of Citalopram on Immobility Time in Forced Swim Test (FST)

The administration of citalopram produced a significant, dose-dependent antidepressant-like effect in mice, as observed in the Forced Swim Test (FST). Mice in the control group exhibited an average immobility time of 124 seconds, representing a normal behavioral despair response. When treated with 5 mg/kg of citalopram, the immobility time was reduced to 89 seconds, demonstrating a statistically significant reduction ($p < 0.05$). A further decrease to 74 seconds was observed at the 10 mg/kg dose, which was also statistically significant ($p < 0.05$). This progressive reduction in immobility time with increasing doses of citalopram confirmed its antidepressant efficacy and validated the sensitivity of the FST model in detecting pharmacological modulation of mood-related behaviors. These results served as a reliable benchmark for comparing the effects of the test extract.

Effect of Desipramine on Immobility Time in Forced Swim Test (FST)

Desipramine, a reference tricyclic antidepressant (TCA), was evaluated to further validate the test model. In the control group, the immobility time was recorded as 125 seconds. At a lower dose of 10 mg/kg, desipramine caused a mild reduction in immobility to 115 seconds, which was not statistically significant, indicating an insufficient dose to elicit a strong behavioral response. However, a marked reduction in immobility was observed at 20 mg/kg, where the average immobility dropped significantly to 85 seconds ($p < 0.05$). This result demonstrated that desipramine requires a relatively higher dose compared to SSRIs like citalopram to exert comparable antidepressant-like effects in the FST. These findings provided a useful comparative basis for evaluating the efficacy of the *Ixora coccinea* extract.

Table 1: Effect of Citalopram on Immobility Time in Mice

Citalopram Dose (mg/kg)	Immobility Time (sec)	Significance
0	124	–
5	89	*p < 0.05
10	74	*p < 0.05

Note: Values are expressed as mean ± SEM, and asterisk (*) denotes statistically significant difference compared to control (*p < 0.05).

Table 2: Effect of Desipramine on Immobility Time in Mice

Desipramine Dose (mg/kg)	Immobility Time (sec)	Significance
0	125	–
10	115	–
20	85	*p < 0.05

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Note: Values are expressed as mean ± SEM, and asterisk (*) denotes statistically significant difference compared to control (*$p < 0.05$).

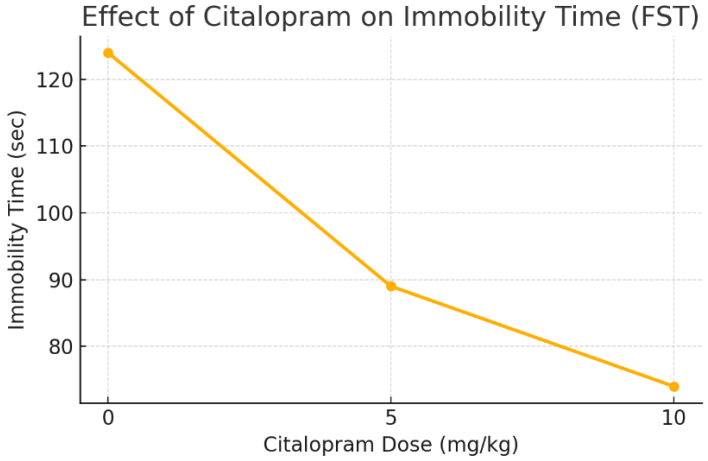

Figure 1. Effect of Citalopram on Immobility Time (FST)

Effect of *Ixora coccinea* Extract on Immobility Time in Forced Swim Test (FST)

The hydroalcoholic extract of *Ixora coccinea* was tested in graded doses (10, 20, and 40 mg/kg) to evaluate its antidepressant-like properties in the Forced Swim Test. Mice in the vehicle-treated control group showed an average immobility time of 126 seconds. Administration of the extract at 10 mg/kg resulted in a slight increase in immobility to 136 seconds, while the 20 mg/kg dose reduced immobility to 121 seconds. However, neither of these changes reached statistical significance, indicating minimal to no antidepressant-like effect at these lower doses. Interestingly, the 40 mg/kg dose produced a significant reduction in immobility time to 91 seconds ($p < 0.05$), suggesting a dose-dependent onset of action. The effect observed at this dose was comparable to that of standard drugs, indicating that higher concentrations of the extract may be required to achieve therapeutic effects. These findings highlight the potential of *Ixora coccinea* extract in modulating mood-related behaviors, likely through active phytoconstituents such as flavonoids and phenolics.

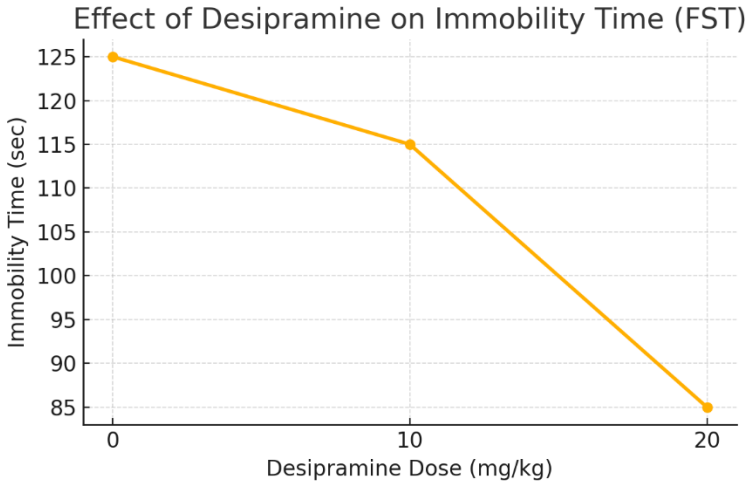

Figure 2. Effect of Desipramine on Immobility Time (FST)

Comparative Effect of Standard Antidepressants in Tail Suspension Test (TST)

To corroborate the results of the FST, the Tail Suspension Test (TST) was employed as a second behavioral model. This test is also widely used for assessing antidepressant activity in mice, and its results often parallel those of the FST. In the control group, the immobility time was recorded as 77 seconds. Mice treated with citalopram exhibited a significant reduction in immobility, recording an average of 44 seconds ($p < 0.05$). Similarly, desipramine-treated mice showed a further reduction to 41 seconds ($p < 0.05$). These results demonstrated the effectiveness of both standard drugs in decreasing behavioral despair in the TST model. The statistically significant reductions in immobility confirmed the validity of

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this test model and provided a reference to assess the potential effects of *Ixora coccinea* extract under similar conditions.

Effect of *Ixora coccinea* Extract on Immobility Time in Tail Suspension Test (TST)

The extract of *Ixora coccinea* was further evaluated in the TST to determine whether its antidepressant-like activity was consistent across behavioral paradigms. The control group showed a mean immobility time of 78 seconds. At the doses of 10 mg/kg and 20 mg/kg, immobility times were recorded as 77 and 67 seconds, respectively, with no statistically significant differences when compared to control values. However, a notable and statistically significant reduction in immobility time was observed at the 40 mg/kg dose, where the immobility duration dropped to 44 seconds ($p < 0.05$). This reduction mirrored the effect seen with standard antidepressants, suggesting that the extract, at higher doses, effectively reduced behavioral despair in mice. The consistency of results across both FST and TST models strengthened the reliability of the observed antidepressant-like effects and emphasized the potential therapeutic utility of *Ixora coccinea* in mood disorder management.

Table 3: Effect of *Ixora coccinea* on Immobility Time in Mice (FST)

***Ixora coccinea* Dose (mg/kg)**	**Immobility Time (sec)**	**Significance**
0	126	–
10	136	–
20	121	–
40	91	*p < 0.05

Note: Values are expressed as mean ± SEM, and asterisk (*) denotes statistically significant difference compared to control (*p < 0.05).

Table 4: Comparative Effect of Antidepressants on Immobility Time in Mice **(TST)**

Treatment	**Immobility Time (sec)**	**Significance**
Control (0 mg/kg)	77	–
Citalopram	44	*p < 0.05
Desipramine	41	*p < 0.05

Note: Values are expressed as mean ± SEM, and asterisk (*) denotes statistically significant difference compared to control (*p < 0.05).

Table 5: Effect of *Ixora coccinea* on Immobility Time in Mice (Short Scale)

***Ixora coccinea* Dose (mg/kg)**	**Immobility Time (sec)**	**Significance**
0	78	–
10	77	–
20	67	–
40	44	*p < 0.05

Note: Values are expressed as mean ± SEM, and asterisk (*) denotes statistically significant difference compared to control (*p < 0.05).

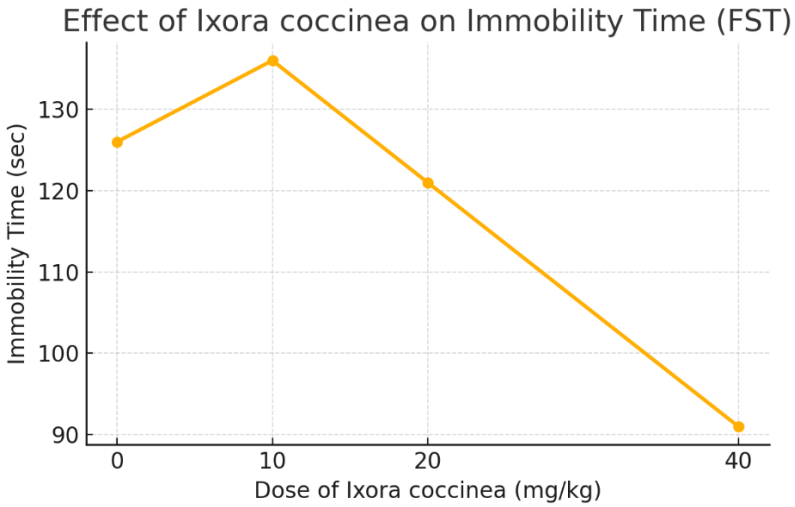

Figure 3. Effect of *Ixora Coccinea* on Immobility Time (FST)

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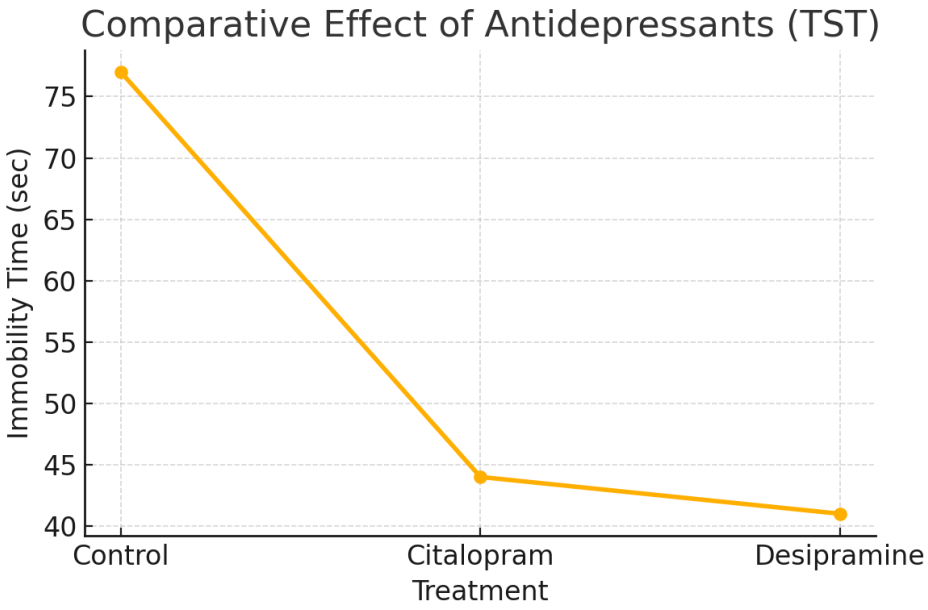

Figure 4. Comparative Effect of Antidepressants (TST)

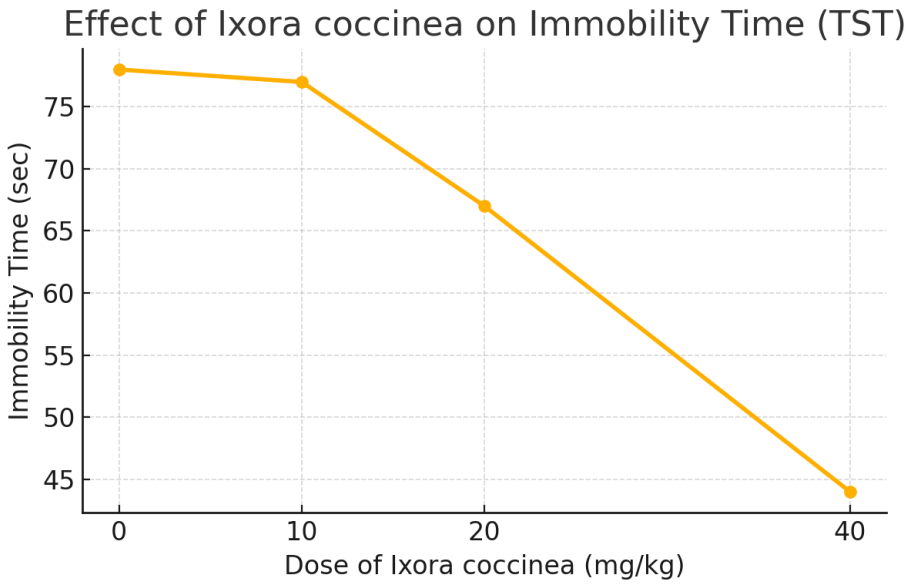

Figure 5. Effect of Ixora Coccinea on Immobility Time (TST)

DISCUSSION

The present investigation assessed the antidepressant-like effects of the hydroalcoholic extract of *Ixora coccinea* flowers using well-established behavioral paradigms—namely the Forced Swim Test (FST) and Tail Suspension Test (TST)—in adult mice. These models are widely employed to evaluate behavioral despair and the efficacy of antidepressant agents. Immobility in these tests is believed to reflect a state of behavioral despair analogous to depression in humans, and the reduction of immobility by pharmacological agents is interpreted as an antidepressant-like effect. In the current study, both standard drugs—citalopram, a selective serotonin reuptake inhibitor (SSRI), and desipramine, a tricyclic antidepressant (TCA)—produced significant reductions in immobility time, validating the reliability of the experimental models. Citalopram displayed a dose-dependent reduction in immobility in the FST, and desipramine showed a significant effect only at the higher dose of 20 mg/kg, which aligns with existing literature suggesting that TCAs often require higher dosages to exhibit measurable antidepressant activity in preclinical models. The hydroalcoholic extract of *Ixora coccinea* also showed a dose-dependent

reduction in immobility time, but only the 40 mg/kg dose demonstrated statistically significant effects in both FST and TST. This suggests that the extract may contain active phytoconstituents capable of modulating mood-regulating neurotransmitter systems, but higher concentrations are necessary to elicit therapeutic responses. These observations are consistent with previous reports of plant-based antidepressants that often require higher doses to demonstrate efficacy due to their polyherbal composition and synergistic interactions among constituents.

The potential mechanism of action for the observed activity may involve serotonergic or noradrenergic pathways, given that the extract's performance was comparable to that of SSRIs and TCAs. However, this study did not involve neurotransmitter estimation or receptor-binding studies, which limits the ability to conclude the precise mechanism. Nevertheless, the phytochemical profile of *Ixora coccinea* includes flavonoids, alkaloids, and phenolic compounds, all of which have been reported to exert central nervous system effects, including antidepressant, anxiolytic, and neuroprotective properties. Flavonoids in particular have been shown to inhibit monoamine oxidase (MAO) enzymes and increase brain levels of serotonin, norepinephrine, and dopamine, which are key neurotransmitters involved in mood regulation.

Another important aspect of this study was the absence of altered locomotor activity in the treated animals, which ruled out the possibility that the observed reductions in immobility were due to general stimulation or hyperactivity. This adds weight to the conclusion that the extract possesses specific antidepressant-like effects, rather than nonspecific behavioural changes. Although the results are promising, the study has limitations. The sample size was relatively small, and only acute behavioral effects were assessed. Chronic administration models and molecular analyses are required to determine whether the observed effects persist over time and to uncover the underlying mechanisms. Furthermore, isolation and characterization of the specific bioactive compounds within the extract would help in the development of more potent and standardized phytopharmaceuticals. In summary, this study provides preliminary evidence supporting the antidepressant-like potential of *Ixora coccinea* flower extract. Future investigations should focus on chronic models, mechanistic studies, and clinical validation to fully realize its therapeutic potential.

Summary

Collectively, the results of the current study demonstrated that the hydroalcoholic extract of *Ixora coccinea* flowers exhibits a dose-dependent antidepressant-like effect in murine models. While lower doses (10–20 mg/kg) were ineffective, the 40 mg/kg dose consistently produced significant reductions in immobility time in both the Forced Swim Test and Tail Suspension Test. These effects were comparable to those of established antidepressant drugs such as citalopram and desipramine. The results suggest that the extract may influence central neurotransmitter systems, possibly due to the presence of flavonoids and other active constituents known to have CNS activity. Further studies involving mechanistic evaluations and chronic treatment models are warranted to fully explore its therapeutic potential.

CONCLUSION

The findings from the present study clearly demonstrate that the hydroalcoholic extract of *Ixora coccinea* flowers possesses significant antidepressant-like activity in mice, particularly at a dose of 40 mg/kg. This effect was consistently observed in both the Forced Swim Test and Tail Suspension Test, two well-established behavioral models widely used to evaluate the efficacy of antidepressant agents. While lower doses of the extract (10 and 20 mg/kg) did not produce significant effects, the 40 mg/kg dose significantly reduced immobility time, indicating a robust antidepressant-like response. This dose-dependent trend suggests the presence of active phytoconstituents that may modulate central neurotransmitter systems involved in mood regulation. The extract's efficacy, especially at the highest tested dose, was comparable to that of standard antidepressants such as citalopram and desipramine, which are clinically effective drugs used to manage depression. This parallel efficacy strengthens the therapeutic relevance of *Ixora coccinea* and supports its ethnomedicinal application in traditional healing practices for mood-related disorders. The results also imply that the extract may exert its effects through pathways similar to those targeted by conventional antidepressants, potentially involving serotonergic or noradrenergic systems. The pharmacological potential of *Ixora coccinea* may be attributed to its rich content of flavonoids, polyphenols, and other secondary metabolites known for their central nervous system activities. These

compounds are often reported to exhibit antioxidant, anti-inflammatory, and neuroprotective properties—all of which are relevant to the pathophysiology of depression. Additionally, the absence of altered locomotor activity suggests that the reduction in immobility time was not due to general stimulation or sedation, thereby reinforcing the specificity of its antidepressant-like action. However, while the current findings are promising, they remain preliminary. Further studies are necessary to isolate the active constituents responsible for the observed activity and to evaluate their pharmacokinetics, safety, and mechanisms of action. Chronic models of depression and molecular assays could help elucidate the long-term effects and identify potential targets within the brain. Moreover, clinical studies would be essential to validate these findings in human populations. In conclusion, the hydroalcoholic extract of *Ixora coccinea* flowers shows significant potential as a natural antidepressant agent. It represents a promising alternative or adjunct to conventional therapy and warrants further investigation for its development into a safe and effective herbal treatment for depression.

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