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ASSESSMENT OF PAIN-RELIEVING POTENTIAL AND NEUROPHARMACOLOGICAL ACTIVITIES OF NYCTANTHES ARBOR-TRISTIS AND CLITORIA TERNATEA IN SWISS ALBINO MICE

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ABSTRACT

Background: *Nyctanthes arbor-tristis* and *Clitoria ternatea* are two examples of traditional herbs that have recently come to attention due to the growing need for better, safer options in the treatment of neurological disorders and pain. The synergistic effects of these two substances have been understudied despite their well-documented neuroactive and analgesic potential. **Methods:** Mice were used for acute toxicity testing and phytochemical screening of a combination of *N. arbor-tristis* and *C. ternatea* extracts. Hot plate and tail flick tests were used to assess the extract's analgesic effects, while forced swim, tail suspension, light-dark box, and open field tests were used to assess its neuropharmacological effects. The results were compared to those of conventional medications. **Results:** The extract showed analgesic effectiveness in hot plate and tail flick experiments, where the latency increased in a dose-dependent manner. There was a significant decrease in both immobility time and locomotor activity in the neuropharmacological tests, which might indicate antidepressant and anxiolytic effects. The exact action mechanism, however, is yet unknown. **Conclusion:** At 100 mg/kg, the combined extract shows significant analgesic, depressive, and anxiolytic effects in rats, which calls for more research into how it could be used therapeutically.

KEYWORDS: *Nyctanthes arbor-tristis*, *Clitoria ternatea*, analgesia, neuropharmacology, herbal combination, mice model.

INTRODUCTION

Anxiety, depression, and pain often coexist because they share neurochemical mediators and neurobiological pathways. There is a strong correlation between mood disorders and chronic pain since it affects not only the sensory but also the emotional and cognitive systems.[1–4] While pharmacological therapies like antidepressants, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs) work at various points along this route, they are often constrained by side effects and the possibility of dependence.[5–7]

Mild depression, lack of interest in pleasurable activities, and impaired mental function characterize major depressive disorder (MDD), which is one of the most common disorders worldwide.[8] Its pathogenesis includes neuroinflammation, dysregulation of monoamines (serotonin, norepinephrine, and dopamine), the HPA axis, and decreased neurotrophic support (e.g., BDNF).[9–12] Although SSRIs and SNRIs remain first-line therapy, they often demonstrate delayed onset and side effects.[13] Anxiety and depression often coexist because they share pathophysiological traits including disruption of the HPA axis and monoamine deficiencies. A lack of regulation of the GABA, serotonin, or norepinephrine systems is a hallmark of anxiety disorders.[14,15] Although SSRIs and benzodiazepines are effective conventional therapies for managing anxiety,

they pose the risk of dependence and other negative side effects.[16]

With the present pharmaceutical treatments having their limits and these disorders causing a considerable burden, there is a rising interest in plant-based alternatives. These alternatives might provide mechanisms that target many targets while also improving safety profiles. Therefore, the current investigation aims at evaluating analgesic, antidepressant, and anxiolytic effects of a combination of *Clitoria ternatea* and *Nyctanthes arbor-tristis*.

MATERIALS AND METHODS

Drugs and Chemicals: The analytical grade methanol, fluoxetine, diazepam, and ketoprofen were purchased from SD Fine Chemicals. All of the other chemicals used were of analytically-grade.

Collection and Authentication of Plant Material: The local market was scoured for *Nyctanthes arbor-tristis* and *Clitoria ternatea* flowers and leaves, which was then verified by a botanist.

Extraction Procedure: After the plants were cleaned, they were left to dry in the shade for seven days at room temperature. After that, they were oven-dried for twelve hours at 40°C. The dried flowers (100 g) and leaves (75 g) were ground into powders and then soaked in 300 mL of methanol at 50°C for 48 hours in a Soxhlet extraction. Following filtering and concentration in a rotary evaporator, 15.95 g of leaf extract (equivalent to 21.27% of the total) and 5.70 g of floral extract (equivalent to 5.7% of the total) were obtained.[17]

Preliminary Phytochemical Screening: In order to identify potential phytoconstituents, the methanolic extracts underwent a series of qualitative screenings tests.

Acute Toxicity Study: According to OECD guideline 423, acute toxicity was evaluated. Over the course of 14 days, mice were observed for symptoms of toxicity, behavioral alterations, and mortality after a single oral dosage of 2000 mg/kg.[18]

Experimental Animals: Both male and female healthy Swiss albino mice weighing 25-30 g and 6-8 weeks old were procured from Vab BioScience. They were housed at the Animal House, TKR College of Pharmacy, under regulated conditions (27 ± 2°C, 55-65% humidity, natural light/dark cycle). For the week leading up to the trials, the animals were allowed to acclimate and given unrestricted access to normal water and standard feed.

Ethical Approval: In accordance with the regulations set out by the Swiss Academy of Sciences and the Swiss Academy of Medical Sciences (1995), the Institutional Animal Ethics Committee (IAEC No. 2008/Po/Re/S/18 CPCSEA) gave its approval to all of the study protocols.

Grouping and Dosing: Six groups of mice were randomly assigned to each of the six groups. Specifically, three standard groups were prepared for the purpose of comparative evaluation: one for analgesic activity with ketoprofen (10 mg/kg, i.p.), one for anxiolytic assessment with diazepam (2 mg/kg, p.o.), and one for antidepressant evaluation with fluoxetine (10 mg/kg, p.o.).

Table 1: Animal grouping.

Group	Treatment	Dose
I	Control	Normal saline (1 mL/100 g, p.o.)
II	Ketoprofen (standard)	10 mg/kg, i.p.
III	Diazepam (standard)	2 mg/kg, p.o.
IV	Fluoxetine (standard)	10 mg/kg, p.o.
V	Combination Extract I (CE 50)	50 mg/kg, p.o.
VI	Combination Extract II (CE 100)	100 mg/kg, p.o.

Analgesic Activity Evaluation

Hot Plate Test: Performed with the use of Eddy's hot plate that was kept at a temperature of 55 ± 1°C. The timing of the pain response, which was measured by paw licking or leaping, was recorded at 0, 30, 60, 90, and 120 minutes after treatment. To ensure safety, a 20-second cutoff was set.[19]

Tail Flick Test: Analgesiometer measurements were taken before and at different intervals (0-360 min) after treatment to determine the tail flick delay to heat stimulation.[20]

Neuropharmacological Activity Evaluation

Forced Swim Test (FST): On Day 0, the mice were trained to swim for 15 minutes in a Plexiglas tank with water at a temperature of 25°C. On the second day after treatment, we timed how long animals remained immobile during the last four minutes of a six-minute session.[21]

Tail Suspension Test (TST): After 6 minutes of suspension by the tail, the total immobility period of the mice was recorded. The medicine that was used as a reference was fluoxetine (10 mg/kg).[22]

Anxiolytic Activity Evaluation

Light-dark box Test: A 44 × 8.5 × 25 cm rectangular box was utilized, with light and dark sections that were equally separated and linked by a 17 cm-high aperture. After putting each animal on its dark side, with its back to the door, then monitored them for ten minutes.

Symptoms of anxiety were measured by keeping track of how much time participants spent in each section. In the time between each test, 70% ethanol was used to clean the box.[23]

Open Field Test (OFT): Throughout a 60×60 cm arena, the number of squares crossed was precisely tracked at 2-minute intervals after treatment. The total number of crossings and activity in the middle zone was recorded.[24]

Statistical Analysis

The mean ± SEM was used to represent the data. This study was conducted using GraphPad Prism v5.04, specifically a one-way ANOVA followed by Tukey's post hoc test. Statistical significance was determined by a p-value less than 0.05.

RESULTS

Preliminary Phytochemical Screening

The combined extract's (CE) phytochemical screening yielded qualitative findings, which are shown in Table 3.1. Color changes and responses were used to establish the presence of different secondary metabolites.

Table 2: Phytochemical Screening Results.

S. No.	Test Name & Method	Observation	Result
1	Fats (Sudan Red Test) – Sample + Sudan Red reagent	Red color	Positive
2	Tannins (Ferric Chloride Test) – Sample + Ferric Chloride solution	Green color	Positive
3	Alkaloids (Wagner's Test) – Sample + Wagner reagent	Reddish-brown color	Positive
4	Sugars (Benedict's Test) – Sample + Benedict reagent	Green color	Positive
5	Amino Acids (Millon's Test) – Sample + Millon's reagent	Brick red color	Positive
6	Proteins (Biuret Test) – Sample + Biuret reagent	Violet color	Positive
7	Flavonoids (Sodium Hydroxide Test) – Sample + 10% NaOH	Orange color	Positive
8	Saponins (Foam Test) – Sample + Water	Persistent foam formation	Positive
9	Glycosides (Fehling's Test) – Sample + Fehling's reagent	Brick-red color	Positive
10	Starch (Iodine Test) – Sample + Iodine solution	Blue-black color	Negative

Acute Toxicity Study

Mice were observed for 72 hours after being orally administered dosages of the combination extract (CE) ranging from 500 to 2000 mg/kg. No mortality or noticeable behavioral abnormalities were noted. The calculated LD_{50} exceeds 2000 mg/kg, suggesting that the extract has a low toxicity profile, according to these data.

Two dosage levels were chosen according to these results

- CE 50 (50 mg/kg): 1/10th of the lowest tested toxic dose.
- CE 100 (100 mg/kg): Double the lower experimental dose.

Evaluation of Analgesic Activity

Hot Plate Test: By observing how long it takes for an animal to respond to a heat stimulation (in seconds), this test may determine its pain threshold. Compared to the control group, the delay time increased significantly (and dose-dependently) after oral administration of CE 50 and CE 100. At the 60-and 90-minute marks, the effect was its strongest.

Table 3: Analgesic Activity via Hot Plate Test.

Group	0 min	15 min	30 min	60 min	90 min
Control	4.00±0.37	4.00±0.26	3.70±0.33	3.50±0.22	3.70±0.21
CE 50	4.20±0.31	5.20±0.48	5.30±0.67	6.30±0.56^{c}	6.00±0.63
CE 100	4.20±0.40	5.80±0.65	6.20±0.60^{c}	8.00±0.73^{a}	7.80±1.00^{b}
Standard (Ketoprofen 10 mg/kg)	4.00±0.37	5.80±0.60	6.70±0.56^{b}	8.20±0.87^{a}	8.00±0.73^{b}

Values represent mean ± SEM. $^{a}p < 0.001$, $^{b}p < 0.01$, $^{c}p < 0.05$ vs. control. Statistical analysis was done by using Tukey's post hoc test after one-way ANOVA.

Tail Flick Test: Thermal nociception was assessed by measuring the tail flick latency. There was a dose-dependent increase in delay with both CE dosages. The peak activity of CE 100 was seen at 60 minutes (8.2 seconds).

Table 4: Analgesic Activity via Tail Flick Test. Values represent mean ± SEM. [a]p < 0.001, [b]p < 0.01, [c]p < 0.05 vs. control. Statistical analysis: One-way ANOVA followed by Tukey's post hoc test.

Group	0 min	15 min	30 min	60 min	90 min
Control	2.70±0.33	2.70±0.33	2.70±0.33	2.50±0.22	2.30±0.21
CE 50	2.50±0.22	2.50±0.34	4.80±0.40[c]	5.00±0.37[c]	4.80±0.40[b]
CE 100	2.80±0.31	4.50±0.43[c]	5.70±0.49[a]	8.20±0.75[a]	7.50±0.56[a]
Standard (Ketoprofen 10 mg/kg)	2.70±0.33	4.50±0.43[c]	6.30±0.49[a]	9.00±0.73[a]	8.20±0.54[a]

Evaluation of Neuropharmacological Activity

Antidepressant Activity

A) Forced Swim Test (FST)

With antidepressant-like effects, CE 50 and CE 100 considerably decreased immobility time ($p < 0.001$) as compared to the control. CE 100 showed results similar to the standard drug, fluoxetine.

Table 5: Antidepressant Activity via FST. Values represent mean ± SEM. [a]p < 0.001 vs. control. Statistical analysis: One-way ANOVA followed by Tukey's post hoc test.

Group	Immobility Time (sec)
Control	241±6.3
CE 50	177±3.1[a]
CE 100	143±6.6[a]
Fluoxetine (standard)	146±5.9[a]

B) Tail Suspension Test (TST)

The immobility duration in TST was significantly reduced by both dosages of CE, with CE 100 demonstrating the most potent effects, similar to the standard drug fluoxetine ($p < 0.001$).

Table 6: Antidepressant Activity via TST. Values represent mean ± SEM. [a]p < 0.001, [b]p < 0.01 vs. control. Statistical analysis: One-way ANOVA followed by Tukey's post hoc test.

Group	Immobility Time (sec)
Control	230±6.4
CE 50	196±5.5[b]
CE 100	149±5.5[a]
Fluoxetine (standard)	156±5.4[a]

ANXIOLYTIC ACTIVITY

A) Light-dark box test

There was a dose-dependent reduction in dark zone time after CE injection, which is consistent with the hypothesis of gradual anxiolytic effects. A more noticeable response ($p < 0.001$) was evoked by the larger dosage, in contrast to the modest activity induced by the lower dose. Consistent with its established anxiolytic effectiveness, the standard medication group had the most significant decrease in dark box time ($p < 0.001$).

Table 7: Anxiolytic Activity via Light-dark box Test. Values represent mean ± SEM.

Groups	Time spent in dark box (Sec)
Control	**241±4.7**
CE 50	**171±7.9[a]**
CE 100	**131±3.4[a]**
Diazepam	**124±3.9[a]**

[a]p < 0.001 vs. control. Statistical analysis: One-way ANOVA followed by Tukey's post hoc test.

B) Open Field Test (OFT)

The number of square crossings were decreased by both CE 50 and CE 100 as compared to the control group. This suggests that the extract has dose-dependent anxiolytic characteristics.

Table 8: Anxiolytic Activity via OFT. Values represent mean ± SEM. [a]p < 0.001, [b]p < 0.01, [c]p < 0.05 vs. control. Statistical analysis: One-way ANOVA followed by Tukey's post hoc test.

Group	Squares Passed
Control	40±2.9
CE 50	30±2.6[c]
CE 100	27±2.3[b]
Diazepam (standard)	23±2.1[a]

DISCUSSION

A preliminary phytochemical screening of the combination extract (CE) found lipids, tannins, alkaloids, sugars, flavonoids, proteins, amino acids, saponins, and glycosides. Known for their various pharmacological activities, these secondary metabolites may synergistically cause analgesic, antidepressant, and anxiolytic effects. Alkaloids and flavonoids modulate neurotransmitter systems, which may explain CE's depressive and anxiolytic effects.[25–27] Tannins and saponins may explain the extract's analgesic properties by reducing inflammation and stabilizing membranes.[28,29] Through complimentary processes, glycosides and amino acids may enhance central nervous system function.[30] These phytochemicals may affect several neurological and inflammatory pathways, supporting CE's multi-target therapeutic potential.

To measure the analgesic effect, we used two well-established models to distinguish between the processing of pain at the spinal level and that at the supraspinal level: the hot plate test and the tail flick test.[31] An increase in latency suggests greater central analgesia in the hot plate test, which examines complicated, centrally mediated pain responses. With a reaction time of 90 minutes longer after CE administration, it was clear that the drug had a strong analgesic effect on the central nervous system. On the other hand, the primary goal of the tail flick test is to gauge the spinal reflex reactions to heat stimuli. CE, particularly at 100 mg/kg, increased tail flick latency similar to ketoprofen. This provides further evidence that CE's analgesic effects are due to its involvement in both cerebral and peripheral pathways.

Consistent with earlier results showing that larger dosages produced peak effects, the extract's powerful analgesic efficacy is supported by the dose-dependent increase in latency.[32]

The monoaminergic theory is still central to neuropsychiatric understanding of depression, although it fails to explain treatment-resistant cases.[33] Results from the forced swim test (FST) and the tail suspension test (TST) show that CE administration significantly reduces immobility time, suggesting that it has antidepressant-like effects. The effectiveness of CE in these behavioral models of behavioral despair and acute stress demonstrates its promise as a treatment for depression.[34–36]

The co-occurrence of anxiety and depression often complicates therapeutic therapy and prognosis.[37,38] One prevalent comorbidity is social anxiety, which has been associated with both the development and worsening of mood disorders.[39,40] Confirmation of CE's anxiolytic potential was provided by the light-dark box and open field tests. These measures assess risk-avoidance behavior that is seen in anxiety, and locomotor activity, which is normally lower in anxious circumstances. CE had dose-dependent effects on locomotion that were similar to diazepam, indicating that it may have central nervous system depressive and anxiolytic effects.

Given CE's similar performance to standard medicines in the analgesic, antidepressant, and anxiolytic domains, it has potential as a supplementary treatment. This has the ability to lower the dosage of traditional pharmaceuticals, which might reduce the side effects of high-dose pharmacotherapy. However, in order to determine CE's clinical relevance, more research into its safety profile, pharmacokinetics, and long-term effectiveness is necessary. This investigation will provide the groundwork for the incorporation of the *Nyctanthes arbor-tristis* and *Clitoria ternatea* combination into evidence-based pain, depression, and anxiety treatment techniques.

CONCLUSION

The analgesic, depressive, and anxiolytic effects were most likely caused by a mix of central and peripheral processes, as the extracts of *Nyctanthes arbor-tristis* and *Clitoria ternatea* showed. These results provide credence to its long-standing usage in pain management and the treatment of mental health issues. Additional research on the extract's safety, effectiveness, and interactions with neurotransmitter systems might lead to its use as a complementary or replacement for current treatments.

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