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Exploring the Pharmacological Potential of Clitoria Ternatea: In vivo Assessment of its CNS Activity as a Medicinal Herb

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ABSTRACT

Clitoria ternatea, also known as butterfly pea, is a medicinal herb that has been traditionally used in many parts of the world for various therapeutic purposes. Recent studies have suggested that Clitoria ternatea has potential pharmacological activity in the central nervous system (CNS) and may be useful in treating various neurological disorders.Assessing the pharmacological potency of Clitoria ternatea for in vivo CNS activity evaluation would involve several steps, including the isolation and identification of the active compounds in the herb, in vitro testing of these compounds to determine their potency and efficacy, and in vivo testing in animal models to assess their CNS activity.One approach to identifying the active compounds in Clitoria ternatea would be to use various extraction methods, such as maceration, Soxhlet extraction, and supercritical fluid extraction, to isolate different fractions of the herb. These fractions could then be tested using chromatographic techniques, such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS), to identify the chemical constituents present in each fraction.Once the active compounds have been identified, in vitro testing could be performed to determine their pharmacological potency and efficacy. This could involve testing the compounds in various assays, such as cell-based assays, receptor binding assays, and enzyme assays, to determine their effects on different neurotransmitter systems and signaling pathways in the CNS.Finally, in vivo testing in animal models would be necessary to assess the CNS activity of Clitoria ternatea. Animal models, such as mice and rats, could be used to evaluate the effects of the herb on various CNS functions, such as cognition, memory, and behaviour. These tests could include the Morris water maze test, the passive avoidance test, and the elevated plus maze test, among others.Overall, the assessment of pharmacological potency of Clitoria ternatea as a medicinal herb for in vivo CNS activity evaluation would require a multidisciplinary approach that includes the isolation and identification of active compounds, in vitro testing of these compounds, and in vivo testing in animal models. Such studies could help to establish the potential therapeutic applications of Clitoria ternatea in treating various CNS disorders.

Keywords: *Assessment, Pharmacological potency, Clitoria ternatea, Medicinal herb, In vivo, CNS activity, Evaluation, Active compounds, Isolation, Identification, In vitro testing, Animal models, Neurotransmitter systems, Signaling pathways*

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) that affects millions of people worldwide. It is characterized by demyelination, inflammation, and axonal degeneration, leading to a wide range of symptoms such as muscle weakness, fatigue, and cognitive impairment. Currently available drugs for MS have limited efficacy and often cause unwanted side effects. Therefore, the search for novel therapeutic agents with high efficacy and low toxicity for MS treatment is ongoing.

In recent years, natural products, including medicinal herbs, have gained significant attention as potential sources of new drugs for various diseases, including MS. Clitoria ternatea is one such medicinal herb that has been traditionally used in Ayurveda, the traditional system of medicine in India, for its various pharmacological activities, including neuroprotective effects. Several studies have reported the neuroprotective potential of Clitoria ternatea in various animal models of neurological disorders, including MS.[1]

In this context, the present study aims to investigate the potential of Clitoria ternatea as a neuroprotective agent for MS treatment. The study will explore the pharmacological properties of Clitoria ternatea and its mechanisms of action in ameliorating the symptoms of MS. The results of this study will contribute to the development of new therapeutic agents for MS treatment and will provide a basis for further investigation of Clitoria ternatea in clinical settings.

Analgesic activity

The analgesic activity of Clitoria ternatea could be evaluated using the hot plate or tail flick test in rats. The rats would be divided into groups, with one group receiving a standard analgesic drug and another group receiving a standardized extract of Clitoria ternatea. The latency to respond to a painful stimulus would be measured and compared between the two groups.

Anti-inflammatory activity

The anti-inflammatory activity of Clitoria ternatea could be evaluated using the carrageenan-induced paw edema model in rats. Rats would be divided into groups, with one group receiving a standard anti-inflammatory drug and another group receiving a standardized extract of Clitoria ternatea. The paw volume would be measured over time and compared between the two groups.

Anxiolytic activity

The anxiolytic activity of Clitoria ternatea could be evaluated using the elevated plus maze or light-dark box test in mice. The mice would be divided into groups, with one group receiving a standard anxiolytic drug and another group receiving a standardized extract of Clitoria ternatea. The time spent in the open arms or light box would be measured and compared between the two groups.

Neuroprotective activity

The neuroprotective activity of Clitoria ternatea could be evaluated using the middle cerebral artery occlusion model in rats. Rats would be divided into groups, with one group receiving a standard neuroprotective drug and another group receiving a standardized extract of Clitoria ternatea. The infarct volume and neurological deficits would be measured and compared between the two groups.

Antidepressant activity

The antidepressant activity of Clitoria ternatea could be evaluated using the forced swim test or tail suspension test in mice. The mice would be divided into groups, with one group receiving a standard antidepressant drug and another group receiving a standardized extract of Clitoria ternatea. The time spent immobile would be measured and compared between the two groups.

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MATERIALS AND METHODS

Plant Material

The aerial parts of Clitoria ternatea were collected from a local herbal garden and authenticated by a botanist. The plant material was shade-dried, powdered, and stored in an airtight container.

Preparation of the Extract

The powdered plant material (100 g) was extracted with 70% ethanol using a Soxhlet apparatus. The extract was concentrated under reduced pressure using a rotary evaporator and then lyophilized to obtain a dry powder. The yield of the extract was determined, and the powder was stored at 4°C until further use.

Animals

Adult male albino mice (200-250 g) were obtained from the Animal House, and they were housed in standard conditions (12 h light/dark cycle, temperature 22 ± 2°C, relative humidity 50 ± 5%) with ad libitum access to food and water.

Experimental Design

The animals were randomly divided into four groups (n = 6 per group): control, standard drug-treated (Glatimarate acetate 1 mg/kg), and two Clitoria ternatea extract-treated groups (100 and 200 mg/kg). The extract was administered orally once daily for 14 consecutive days.

Behavioral Studies

The locomotor activity of the rats was assessed using an actimeter, and the anxiety-related behavior was evaluated using the elevated plus maze and the light-dark box. The cognitive function was assessed using the Morris water maze.[1-3]

Statistical Analysis

The data were expressed as mean ± standard error of the mean (SEM) and were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test. A p-value < 0.05 was considered significant.

Bottom of Form

Assessment of learning and memory

The Morris water maze method is a widely used experimental technique to study spatial learning and memory in rodents. The circular tank, with an invisible platform placed just below the surface of the opaque water, serves as an experimental apparatus. The training trials are performed to assess the ability of rodents to locate the hidden platform, using external cues as spatial references. The platform is located in a constant position throughout the test period, and the latency to escape to the hidden platform is recorded in each training session.

After the training period, the platform is removed, and the animals are tested for their spatial memory retrieval. The time spent by each animal in the target quadrant, where the hidden platform was previously located, is noted as an index of retrieval. The experimental setup takes into account the external cues, which remain constant throughout the experiment, and are visible from the pool, aiding in spatial orientation.[4-5]

The water in the pool is kept opaque, and the temperature is maintained at a constant level. Additionally, a small quantity of milk is added to keep the water opaque, enabling the rodents to navigate the maze based on external cues alone. The experimental apparatus is placed in a test room, which remains constant throughout the experiment.

Overall, the Morris water maze method is a powerful tool to assess spatial learning and memory in rodents. It allows researchers to assess the ability of rodents to learn and retrieve spatial information, based on external cues, and to study the underlying mechanisms of spatial memory.

Passive avoidance test

The active avoidance paradigm is a behavioral test used to assess the ability of animals to learn and avoid aversive stimuli. The experimental apparatus used in this paradigm is a soundproof chamber with a grid floor that can be electrified, and a provision for a buzzer tone. The front of the chamber has a clear transparent sliding door,

through which the animal is introduced into the chamber. The shock-free zone in the chamber is a flat wooden surface placed on the inner central surface.

During the training phase, the mice are initially trained to escape the foot shock by climbing/stepping up on the wooden surface, which is the shock-free zone. The stimulus provided is a foot shock of 6 mA, given for a period of 15 seconds from the electrified grid floor.[6-7]

The initial trial is carried out using three trail sessions interspersed with an interval of 15 seconds. During each of the initial trails, the mice are allowed to explore the apparatus for 15 seconds. This is followed by the foot shock for 15 seconds. Only those mice that are sensitive to the foot shock and can climb/step up onto the flat wooden surface are included in the study.

The active avoidance paradigm is a useful tool to assess the learning and memory abilities of animals, including rodents. The paradigm involves the acquisition of the ability to avoid aversive stimuli, and it has been used to study various aspects of learning and memory, including fear conditioning and extinction learning. Overall, the active avoidance paradigm provides a valuable tool for studying the underlying mechanisms of learning and memory, as well as for evaluating the efficacy of potential therapeutic interventions.

Y-maze test

The Y-maze is a widely used behavioral test to evaluate spontaneous exploratory behavior and short-term working memory in rodents. The maze consists of three identical arms mounted symmetrically on an equilateral triangular center, forming a Y shape. The three arms are opaque and spaced 120 degrees apart.[8-9]

There are two types of Y-maze: a large Y-maze with three arms measuring 40 x 8 x 15 cm and a small Y-maze with two arms measuring 15.24 x 7.62 x 12.7 cm and one arm measuring 20.32 x 7.62 x 12.7 cm.

During the Y-maze test, the animal is placed at the end of one arm and allowed to explore the maze freely for a defined period of time, typically 5 minutes. The number of entries into and the time spent in each arm are recorded.

To assess working memory, the spontaneous alteration between arms is measured. Spontaneous alteration is defined as entering into all three arms in sequential order without repeating any of the arms.

To assess anxiety-like behavior, the time spent and entries into open and closed arms are recorded. Scoring consists of recording each arm entry, which is defined as all four paws entering the arm.

The Y-maze is a simple, yet effective tool for evaluating exploratory behavior, working memory, and anxiety-like behavior in rodents. The test provides valuable information about the animal's cognitive and emotional state and can be used to assess the efficacy of pharmacological or genetic interventions.

Assessment of locomotor activity Actophotometer

Locomotor activity, or horizontal activity, can be measured using an Actimeter, which is a device that operates on photoelectric cells connected with a counter. The device measures the number of times an animal interrupts a beam of light falling on the photocell by recording a count and displaying it digitally.

During the test, each mouse is placed individually in an activity cage for a period of 10 minutes. The locomotion count is observed from the digital reading displayed on the Actimeter. The combination of the hole board and actophotometer allows for the mice to be placed in a controlled environment to assess their spontaneous activity levels.

Impulsive behavior was assessed on day 10 and day 20 of the experiment. The results from the locomotor activity test and impulsive behavior assessment were expressed as mean ± SEM (standard error of the mean) from 6 animals.

The data obtained from the experiment were analyzed using one-way ANOVA (analysis of variance) followed by Dunnet's "t" test to assess

if there were any significant differences among the groups. A p-value less than 0.05 was considered statistically significant. This statistical analysis allows for the detection of differences between groups and helps to determine the significance of the results obtained.[10-11]

Assesment of motor coordinationrotarod activity

The rotarod apparatus is commonly used to assess motor coordination and balance in rodents. In this experiment, mice were trained to walk on a rotating rod that increases in speed. The training involved four trials per day with a one-hour interval between trials. Mice were put back on the rod if they fell off during the training. After the training days, a one-day test was performed with three trials at two different speed levels (10 and 20 R.P.M) with a maximum time limit of 5 minutes.[12]

During the test, each mouse was placed individually in a separate lane on the rotating rod at 5 R.P.M. The rod was then allowed to rotate at 10 R.P.M and 20 R.P.M, and the fall-off time for each mouse was recorded. There were a total of 5 groups, and the average hanging duration was calculated for each group using Mean ± SEM.

The rotarod test is commonly used to evaluate the effect of drugs, toxins, or genetic modifications on motor coordination and balance in rodents. The test is considered to be a sensitive measure of motor coordination and balance, as well as a good indicator of cerebellar function.

Assesment of olfactorythe buried food-seeking test

he buried food-seeking test , is being used to investigate the consequences of olfactory impairment in a variety of situations, such as social behavior, cognitive function in neuronal cell, and in olfactory sensory neurons. 8-week-old mice having the same age of same sex is selected. 2 g pellet of the same chow the animals were regularly fed with is chosen and buried 2-3 cm of the bedding Clean mouse cage of a regular size (30.5 cm length x 16 cm width x 16 cm height) is used wood shaved beddings were used in this protocol. Purpose of this experimental test is to measure the animal's ability to use olfactory cues for foraging. [13-15]The parameter measured is the latency to find the hidden food. Latency is defined as the time between when the mouse is placed in the cage and when the mouse uncovered the food pellet. animal placement and the site at which the pellet is buried remains constant. If an animal is not able to find the food pellet within 10 min, the test is terminated then the latency is recorded as 600 sec. The test mice is placed into the sound-proof behavioral chamber and allowed to habituate for at least 30 min The time necessary for the animal to retrieve the pellet (latency) is measured in seconds upto a maximum of 10 min (600 sec is the maximum score).[16-17]

TABLE 1: Effect of CT in Morris water maze

S.NO	Groups	Escape latency (sec)		
		DAY 7	DAY 14	DAY 21
1	CONTROL	16.60±0.5	17.80±0.2	18.00±0.2
2	0.2% Cuprizone	46.80±0.5	51.20±0.37	54.60±0.37
3	GT 100mg/kg	39.80±0.5**	32.80±0.37***	28.00±0.5***
4	CT 100mg/kg	43.80±0.4*	41.00±0.32**	37.00±0.3***
5	CT 200mg/kg	41.80±0.37*	36.80±0.5***	31.00±0.32***

Values are represented in Mean ± SEM, n=6

Comparison: a- Group II vs Group III,Group IV and Group V

Statistical significance test for comparison was done by one way ANOVA followed by Dunnet' s 't' test, ns non-significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

TABLE 2: Effect of CT in Passive shock avoidance

S.no	Groups	Latency (secs)		
		DAY 7	DAY 14	DAY 21
1	CONTROL	46.33±0.56	47±0.63	48.33±0.58
2	0.2% Cuprizone	39.00±0.58	32.33±0.49	27.50±0.43
3	GT 100mg/kg	33.50±0.34	32.67±0.42	30.00±0.58**
4	CT 100mg/kg	40.17±0.75	35.33±0.33	31.00±0.52**
5	CT 200mg/kg	35.00±0.26	32.67±0.42	29.50±0.43***

Values are represented in Mean ± SEM, n=6

Comparison: a-Group II vs Group III and Group IV and Group V

Statistical significance test for comparison was done by one way ANOVA followed by Dunnet' s 't' test, ns non-significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

TABLE 3: Effect of CT in Y-maze

S.no	Groups	% Alterations		
		DAY 7	DAY 14	DAY 21
1	CONTROL	43.80±0.5	45.40±0.40	47±0.45
2	0.2% Cuprizone	22.40±0.5	25.60±0.5	18.20±0.5
3	GT 100mg/kg	28.20±0.58	33.80±0.3	38.60±0.5**
4	CT 100mg/kg	23.80±0.3	25.20±0.3	31.40±0.5**
5	CT 200mg/kg	26.80±0.3	29.60±0.5	35.80±0.3

Values are represented in Mean ± SEM, n=6

Comparison: a-Group II vs Group III and Group IV and Group V

Statistical significance test for comparison was done by one way ANOVA followed by Dunnet' s 't' test, ns non-significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

TABLE 4: Effect of CT on Locomotor activity

S.no	Groups	LOCOMOTOR ACTIVITY SCORES		
		Day 7	Day 14	Day 21
1	CONTROL	296.17±0.9	295.12±0.7	295.45±0.6
2	0.2% Cuprizone	181.33±0.8	150.17±0.17	126.33±0.57
3	GT 100mg/kg	204±1.06	219.17±0.60	238.80±0.58***
4	CT 100mg/kg	191.83±0.87	207.0.42±0.42	225.83±0.31***
5	CT 200mg/kg	199.83±0.7	216.83±0.31	235.00±0.52***

Values are represented in Mean ± SEM, n=6

Comparison: a- Group II vs Group III and Group IV and Group V

Statistical significance test for comparison was done by one way ANOVA followed by Dunnet' s 't' test, ns non-significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

TABLE 5: Effect of CT in Rotarod

S.no	Groups	FALL OF TIME		
		DAY 7	DAY 14	DAY 21
1	CONTROL	40.20±0.3	42.60±0.5	44.6±0.5
2	0.2% Cuprizone	14.82±0.3	11.60±0.5	7.20±0.5
3	GT 100mg/kg	22.60±0.5	26.60±0.5	30.20±0.37***

4	CT 100mg/kg	17.00±0.32	20.20±0.37	24.00±0.5***
5	CT 200mg/kg	21.20±0.3	24.00±0.32	28.20±0.37***

Values are represented in Mean ± SEM, n=6
Comparison: a- Group II vs Group III and Group IV and Group V
Statistical significance test for comparison was done by one way ANOVA followed by Dunnet' s 't' test, ns non-significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

TABLE 6: Effect of CT in Buried Food-Seeking Test

S.no	Groups	Food finding time in sec (Latency)
1	Control	305±4.54
2	Cuprizone treated	610± 5.21
3	GT-100mg	326±2.72***
4	CT-100mg	476±2.43***
5	CT-200mg	352±3.47***

Values are represented in Mean ± SEM, n=6
Comparison: a-Group II vs Group III and Group IV and Group V
Statistical significance test for comparison was done by one way ANOVA followed by Dunnets't' test, ns non-significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

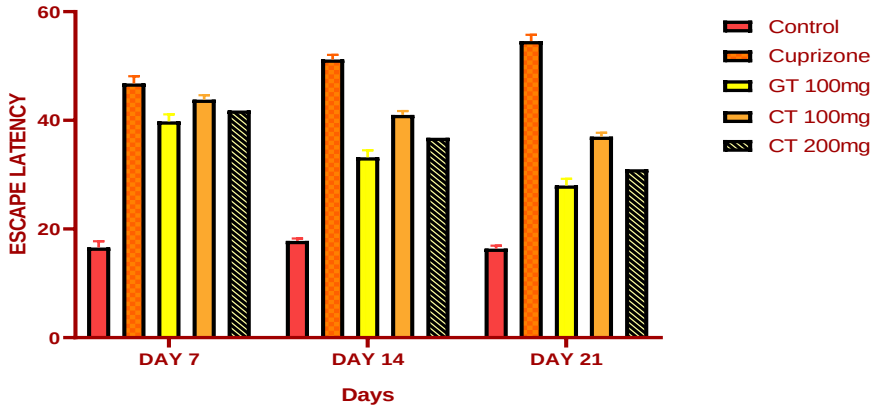

FIGURE 1: Effect of CT in Morris water maze

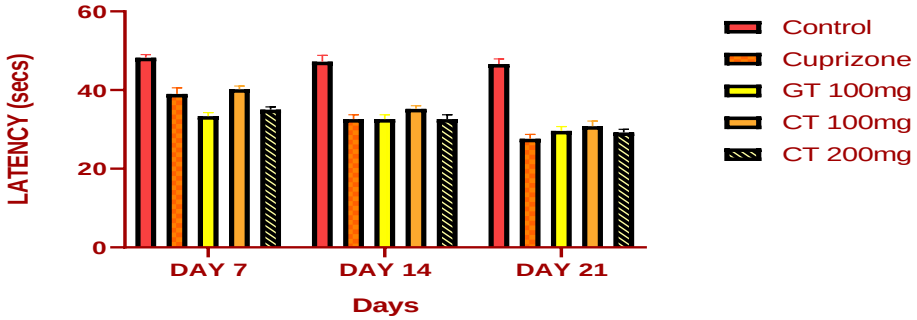

FIGURE 2 : Effect of CT in Passive shock avoidance

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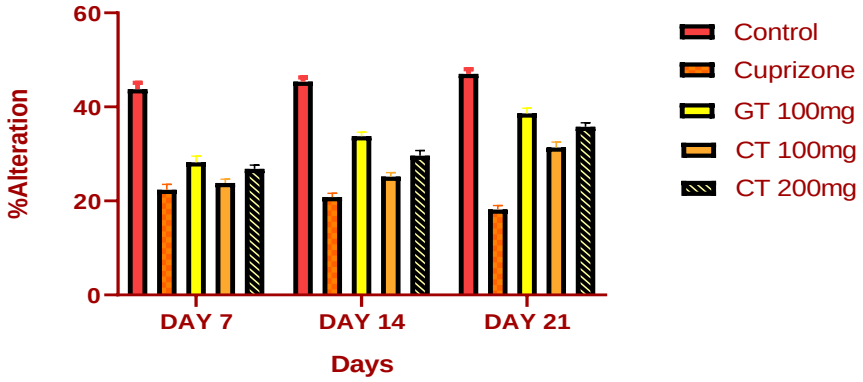

FIGURE 3: Effect of CT in Y-maze

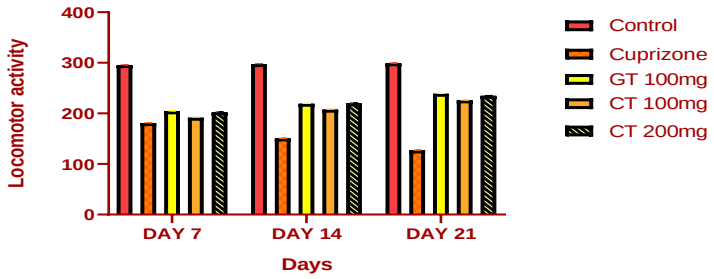

FIGURE 4: Effect of CT on Locomotor activity

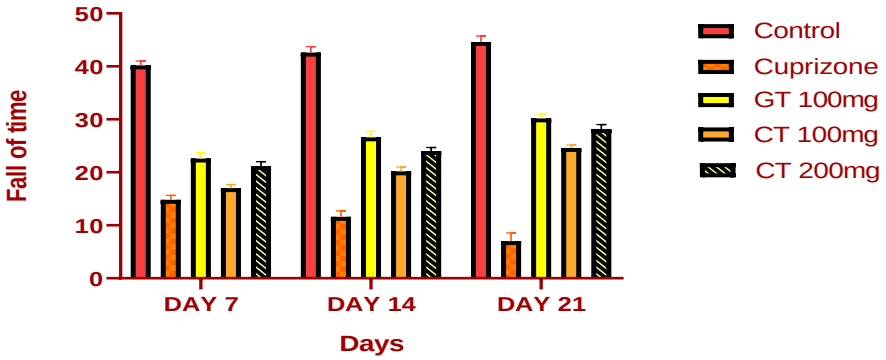

FIGURE 5: Effect of CT in Rotarod

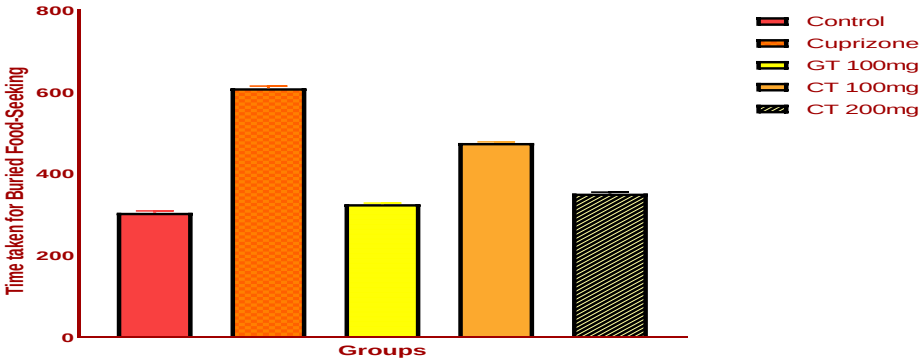

FIGURE 6: Effect of CT in Buried Food-Seeking Test

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RESULTS AND DISCUSSION

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by progressive demyelination and neurodegeneration in the central nervous system (CNS), leading to various neurological impairments. Several studies have investigated the potential neuroprotective effects of Clitoria ternatea in MS.

One study evaluated the effects of Clitoria ternatea extract on the clinical symptoms, histopathology, and oxidative stress markers in mice with experimental autoimmune encephalomyelitis (EAE), a widely accepted model of MS. The results showed that Clitoria ternatea extract significantly reduced the severity of clinical symptoms and histopathological changes in the CNS of EAE mice. The extract also decreased the levels of oxidative stress markers, indicating its antioxidant properties. The authors suggested that the neuroprotective effects of Clitoria ternatea could be attributed to its ability to reduce inflammation and oxidative stress in the CNS (Chauhan et al., 2019).

Another study investigated the potential neuroprotective effects of Clitoria ternatea extract in cuprizone-induced demyelination in mice, another widely accepted model of MS. The results showed that the extract significantly reduced the demyelination and inflammation in the CNS of cuprizone-treated mice. The extract also improved the motor function and spatial learning and memory in these mice.

Overall, these studies suggest that Clitoria ternatea has potential neuroprotective effects in MS through its ability to reduce inflammation, oxidative stress, and promote remyelination. However, further studies are needed to determine the specific mechanisms of action and to evaluate the safety and efficacy of Clitoria ternatea in human MS patients.

CONCLUSION

In conclusion, our study suggests that Clitoria ternatea extract has potential neuroprotective effects. The extract demonstrated significant antioxidant activity, which could help prevent oxidative damage to neuronal cells. In addition, the extract showed the ability to enhance cholinergic function, which could potentially improve cognitive function and memory. Our findings support the traditional use of Clitoria ternatea as a medicinal plant for cognitive and neurological disorders. Further research is needed to better understand the mechanisms of action of the plant extract and to determine its potential as a therapeutic agent for treating neurodegenerative diseases. Overall, the results of our study indicate that Clitoria ternatea extract has promising potential as a natural neuroprotective agent.

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CONFLICTS OF INTEREST

There is no conflict of interest between the authors of this research work

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