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Central and Peripheral Analgesic Activities of Aqueous Extract of Centella Asiatica (AECA) Leaves in Rats and Mice

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Keywords: Central analgesic, Peripheral analgesic, Centella asiatica, Aqueous extract, Tail-flick, Writhing, Glacial acetic acid.

Abstract: The demand of herbal based medicines are increasing all over the world and the focus on plant research has increased. Centella asiatica (CA) is a medicinal herb used in traditional medicine as remedy for a variety of diseases. It is widely used in Ayurvedic medicines. The present study evaluated the Analgesic Activity of Aqueous Extract of the leaves of Centella asiatica (AECA). Acute oral toxicity test was performed according to Organization for Economic Cooperation and Development, 2008 (OECD) guidelines. The tail flick method and glacial acetic acid-induced writhing tests were used to study the central and peripheral analgesic activities of AECA, respectively. AECA (200mg/kg) produced significant analgesia in both central and peripheral mechanisms compared to the control. The maximal analgesic effect was observed after 90 minutes of drug administration in the tail-flick method. In the glacial acetic acid-induced writhing test, AECA (200 mg/kg, p.o) produced a significant decrease (71.07%) in the number of writhes ($p<0.01$) when compared to the control. Therefore, CA can be a very promising herbal-based medicine for treatment of various painful conditions. Further investigations are needed to determine the precise mechanism and site of action of AECA.

Introduction

Pain represents the most commonly reported health problem in the clinical setting and the general population (1). The non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medication for pain and inflammation (2). The use of NSAIDs for a wide range of rheumatic conditions and other musculoskeletal disorders is increasing (3). However, NSAIDs are among the most common causes of adverse drug reactions (2). Due to the extensive use of analgesic and anti-inflammatory agents, toxicity and untoward effects often occur, especially when the therapy of pain and inflammation involves using higher doses for extended periods (4). It has been observed that, despite recent developments in pain therapies, the medical community still needs safe, effective, and potent analgesic drugs for the treatment of different painful conditions (5). As the available drugs have many side effects, it necessitates a quest for new drugs from several sources, of which medicinal plants are the major ones (4). Plants have been used as treatments for thousands of years, based on experience and folk remedies, and continue to draw wide attention for their role in treating mild and chronic diseases (6). The underdeveloped world does not have access to this modern medicine of synthetic origin. Therefore, large areas of the world continue to use traditional medicine based on the direct use of medicinal plants due to their low cost (7).

Medicinal plants are globally valuable sources of new drugs (8). Medicinal plant utilization significantly increases worldwide due to its mild features and low side effects (9). The demand for herbal-based medicine, health products, pharmaceuticals, food supplements, nutraceuticals, and cosmetics is increasing worldwide (10). India has been known to be a rich repository of medicinal plants. The forest in India is the principal repository of medicinal and aromatic plants, collected mainly as raw materials for manufacturing drugs and perfumery products (11).

Centella asiatica (CA) is a vital medicinal herb (see Figure 1) used in the orient, which is also becoming popular in the West (12). Centella asiatica is a common edible plant used in traditional medicine in Asia for thousands of years. Centella asiatica belongs to the family Umbelliferae, which can grow up to 30 cm in height with one fan-shaped leaf. All parts of Centella asiatica can be used for medicinal purposes (13). Centella asiatica (Gotu kola) is widely used in Ayurvedic medicine as a remedy for various diseases (14). In traditional Asian medicine, Centella asiatica has been used for hundreds of years to get better from burns, small wounds, hypertrophic wounds, and scratches in dermatological conditions. It is also suggested as an anti-inflammatory agent, primarily in eczema, treating vein insufficiency, antipyretic, anti-cancer agent, diuretic agent, antibacterial, and antiviral drug for improving cognition and helpful in relieving anxiety (15). Centella asiatica has been used to treat syphilis, hepatitis, stomach ulcers, mental fatigue, epilepsy, diarrhea, fever, and asthma. Today herbalists use Centella asiatica for disorders that cause connective tissue swelling, such as scleroderma, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis (16).

Figure 1. A photograph of *Centella asiatica*.

The primary active constituents of Centella asiatica are triterpene saponins, mainly asiaticoside, asiatic acid (ASA), madecassoside, and madecassic acid (13). Madecassoside is a pentacyclic triterpene saponin from Centella asiatica with multiple pharmaceutical activities. Animal experiments have confirmed that oral madecassoside (30mg/kg) can significantly reduce the symptoms of arthritis and can inhibit the secretion of inflammatory cytokines (17). A study by Inamdar et al. (1996) reported bioactive terpene acids such as asiatic acid and madecassic acid from the water-methanol extraction of Centella asiatica. These phytocompounds in the crude extract of Centella asiatica may account for the antinociceptive and anti-inflammatory activities (18, 19). The results of a study by Somchit MN et al. (2004) strongly indicated that the water extract of Centella asiatica possesses antinociceptive activities in mice. The potency of antinociception was less than morphine and aspirin at similar doses (19). A recent study by Xiao Y et al. (2023) also demonstrated the analgesic activities of Centella asiatica in cats undergoing ovariohysterectomy (13).

A detailed investigation and documentation of plants used in local health traditions and pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable plant drugs for many diseases. The purpose and renewal of research on *Centella asiatica* are to strengthen the scientific data on this plant. Therefore, the present study has been undertaken to evaluate both central and peripheral analgesic activities of aqueous extract of leaves of *Centella asiatica* in experimental animal models. For selecting the doses of AECA, an acute toxicity test was performed.

Materials and Methods

Experimental Animals

Prior approval from the Institutional Animal Ethics Committee (IAEC), Assam Medical College, Dibrugarh, Assam was taken to undertake the study with approval number IAEC/AMC/16 dated 21/11/16, and the study was conducted following the CPCSEA (Committee for the Purpose of Control and Supervision on Experiments on Animals) guidelines. For our experiment, healthy adult albino rats (Wister strain, age between 6 to 8 months) of either sex (male and female) weighing between 150-200 gm and healthy adult albino mice of either sex (male and female) weighing 20–30 gms were selected. The animals were taken from the Central Animal House, Assam Medical College & Hospital, Dibrugarh, Assam (CPCSEA registration number: 634/GO/Re/S/02/CPCSEA). All the animals were housed in standard conditions with natural light and dark cycles and adequate ventilation. Standard animal diet was maintained with Bengal gram, wheat, maize, and carrot in sufficient quantity daily. Water was given ad libitum. Our study used male and female rats and mice, as it did not affect the study outcome. Various other studies on *Centella asiatica* used animals of either sex (20, 21).

Plant Material

Centella asiatica (CA) fresh mature leaves were collected from Assam Medical College & Hospital, Dibrugarh, Assam, from April to May 2017. The plant was authenticated by the department of Life Sciences, Dibrugarh University.

Extract Preparation

Three Kilograms (Kg) of fresh leaves of *Centella asiatica* were air-dried at room temperature and powdered (See **Figure 2**). We collected aqueous CA

extract through the Soxhlet apparatus by hot continuous extraction method. Soxhlet apparatus is an automatic, continuous method that does not require further manipulation. As the solvent vapor traveled up a distillation arm into a condenser, the condensed vapors dripped back into the chamber housing the solid material. The chamber containing the solid material slowly filled up with warm solvent. When the Soxhlet chamber was almost full, the chamber was automatically emptied by a siphon side arm, with the solvent running back down to the distillation flask. The cycle continues, and the process runs for 16 hours. After extraction, the solvent was removed using a rotary evaporator. The yield of the aqueous extract was 8.9%. The extract was stored in a refrigerator until further studies (22, 23).

Figure 2. Powdered dried leaves of Centella asiatica.

Acute Toxicity Tests

For selecting a safe dose, acute toxicity of aqueous extracts of leaves of *Centella asiatica* (AECA) was studied by the OECD (Organization for Economic Cooperation and Development) guidelines (adopted 2008), Test No. 425. AECA was dissolved in water and administered orally to overnight fasted animals. The animals were observed at regular intervals for 48 hours, and no mortality was recorded up to the dose of 2000 mg/kg. Hence 1/10th of the maximum dose tested (1/10th of 2000 mg/kg, i.e., 200 mg/kg) was selected as the test dose for the present study.

Experimental Design

For evaluation of the central analgesic activity of AECA, 30 numbers of healthy albino rats of either sex weighing 100-200 gm were used, and for peripheral analgesic activity, 18 numbers of healthy adult albino mice (24) of either sex (male and female) weighing 20–30 gm were selected.

Central Analgesic Activity

The central analgesic activity was tested by the tail-flick method in albino rats. They were divided into 5 groups, with six rats in each group. Each group is treated as follows:

1. Group A (Control): Normal saline (NS) at the dose of 10 ml/kg, orally;
2. Group B: Naloxone 1 mg/kg subcutaneously;
3. Group C: AECA 200 mg/kg, orally;
4. Group D: AECA 200 mg/kg, orally + Naloxone 1 mg/kg subcutaneous injection;
5. Group E (standard): Pethidine 5mg/kg subcutaneously.

A tail-flick analgesiometer assessed the animals' tail-flick latencies (reaction time). Basal reaction time to radiant heat was taken by placing the tip (last 2 cm) of the tail on the radiant heat source. Tail withdrawal from the heat (flicking response) was the endpoint. A cut period of 10 seconds was observed to prevent damage to the tail. The mean reaction time was recorded at pre-drug 0, 15, 30, 60, 90, 120, 150, and 180 min after administration of the vehicle or drugs. Pethidine was taken as the standard drug (25). To assess the involvement of the opioid receptor in the analgesic effect of AECA, naloxone was injected for 15 min before administering the test sample in Group D (5).

Peripheral Analgesic Activity

The glacial acetic Acid Induced Writhing Test tested the peripheral analgesic activity in albino mice. The animals were divided into three groups, with six in each group.

1. Group A (Control): normal saline 10 ml/kg orally;
2. Group B: AECA 200 mg/kg orally;
3. Group C: Aspirin 100 mg/kg orally

One hour after administration of the drugs, induction of writhing was done in mice by giving an intraperitoneal injection of glacial acetic acid (1%) at a dose of 10 ml /kg body weight. The number of writhing responses was counted and recorded for 20 minutes. Aspirin was taken as the standard drug (26). The percentage protection against thermal pain stimulus was calculated using the following formula (5).

$$Percentage\ protection\ (\%) = \frac{Mean_{test} - Mean_{control}}{Mean_{control}} x100$$ **Equation 1**

Statistical Analysis

Statistical Analysis was done using the software Graph pad Prism version 5. All the values were expressed as mean ± SEM. The results were analyzed for statistical significance using one-way ANOVA and Dunnett's test. A p-value that was below 0.01 were considered significant.

Results

The results of the analgesic activity of the aqueous extract of leaves of *Centella asiatica* are shown in **Table 1**. The control group (injected by vehicle) did not show any significant difference in the reaction time on tail flick throughout the observation time. AECA (200 mg/kg) revealed a significant increase ($p<0.01$) in the response time when compared to the control group, with maximum activity appearing after 90 minutes. At 90 min percentage protection shown by AECA (200 mg/kg) against thermal protection was 36.74%. **Table 1** shows that the AECA (200 mg/kg) induced analgesic effect was inhibited in animals treated with naloxone (Group D) in the tail-flick method. In this group (Group D), the maximum protection at 90 min was 24.31%. Pethidine administration significantly ($p<0.01$) increased the response time of the animals, with maximal percentage inhibition (91.99%) at 90 minutes of drug administration. The group that received naloxone alone showed no increase in latency time.

Table 1. Analgesic activity of aqueous extract of Centella asiatica (AECA) in the tail-flick method.

Group	Reaction Time (Mean ± SEM) (Sec) with Percentage Inhibition (%)							
	0 min	**15 min**	**30 min**	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**
A (Control)	3.57 ± 0.04	3.55 ± 0.01	3.60 ± 0.02	3.64 ± 0.02	3.62 ± 0.01	3.56 ± 0.02	3.53 ± 0.03	3.64 ± 0.02
B (Naloxone)	3.53 ± 0.03	3.43 ± 0.02	3.47± 0.02	3.47 ± 0.02	3.50 ± 0.01	3.46 ± 0.01	3.44 ± 0.01	3.44 ± 0.02
C (AECA)	3.45 ± 0.03	4.00 ± 0.03a (12.68%)	4.30 ± 0.02a (19.44%)	4.70 ± 0.02a (29.12%)	4.95 ± 0.02a (36.74%)	4.72 ± 0.03a (32.58%)	4.33 ± 0.03a (22.67%)	3.98 ± 0.03a (9.34%)
D (AECA+ Naloxone)	3.50 ± 0.05	3.70 ± 0.02a (4.22%)	3.91 ± 0.02a (8.61)	4.22 ± 0.02a (15.93%)	4.50 ± 0.03a (24.31%)	4.25 ± 0.02a (19.38%)	4.08 ± 0.03a (15.58%)	3.78 ± 0.02 (3.84%)
E (Pethidine)	3.68 ± 0.01	4.77 ± 0.03a (34.37%)	5.32 ± 0.03a (47.78%)	6.44 ± 0.03a (76.92%)	6.95± 0.05a (91.99%)	6.12 ± 0.04a (71.91%)	5.26 ± 0.08a (49.01%)	4.67 ± 0.05a (28.30%)

Note: One Way ANOVA followed by Dunnett's multiple comparison tests was done. ([a], $p<0.01$) shows a significant difference compared to the normal control group.

Table 2. Peripheral analgesic activity of aqueous extract of Centella asiatica (AECA) on glacial acetic acid-induced writhing response in albino mice.

Group	Drug Dose	No of writhes (mean ± SEM)	Reduction in writhes count (%)
Group A	Normal saline 5 ml/kg orally	60.5±1.20	
Group B	AECA 200mg/kg, orally	17.5±0.62[a]	71.07
Group C	Aspirin 100 mg/kg orally	7.17±0.40[a]	88.12

Note: ([a], $p<0.01$) shows a significant difference compared to the normal control group.

In the glacial acetic acid-induced writhing test, AECA (200 mg/kg, p.o) and aspirin produced a significant decrease ($p<0.01$) in the number of writhes as compared to the control group. The number of writhes by aspirin decreased more than AECA (Table 2).

Discussion

The present study was undertaken to evaluate the Analgesic Activity of Aqueous Extract of the leaves of *Centella asiatica* (AECA) on experimental Animals. Analgesics (non-steroidal anti-inflammatory drugs) act primarily on peripheral pain mechanisms but may also act on the central nervous system (27). Centrally-acting analgesics increase the threshold for pain and alter the physiological response to pain. However, peripherally acting drugs inhibit the generation of pain impulses at the chemoreceptor level. The tail flick studied the analgesic activity of AECA and glacial acetic acid-induced writhing tests, standard pharmacological models for assessing analgesia by natural products (5).

In our present study, AECA produced more central and peripheral analgesia than the control. In the tail flick method, AECA (200 mg/kg, p.o) and pethidine

(5mg/kg s.c.) produced a significant ($p<0.01$) increase in the reaction time as compared to the control. The increase in reaction time in the pethidine-treated group (Gr E) was more than test group (Gr C). Peak analgesic effects of both the test group, the standard group, and the pethidine-treated group were observed after 90 min of administration. It is observed that the analgesic effect induced by AECA (200 mg/kg) was not completely inhibited by naloxone (Group D) in the tail-flick method, indicating that the analgesic effect was not fully mediated through central mechanisms.

The glacial acetic acid-induced abdominal contraction (writhing test) is frequently used for peripherally acting drugs. Pain induction occurs by liberating endogenous substances and other pain mediators, such as arachidonic acid metabolites, via cyclooxygenases, such as prostaglandins (28). When compared to the control group, both AECA (200 mg/kg, p.o) and aspirin produced a significant decrease ($p<0.01$) in the number of writhes. After 20 minutes of observation, the percentage reductions in writhes count were 71.07% and 88.12% in the test and the standard groups, respectively.

Our study's results are consistent with the results of Somchit MN et al. (2004), which supported the analgesic effect of the aqueous extract of Centella asiatica. The results of their study indicated that Centella asiatica possessed centrally and peripherally mediated antinociceptive properties (19). In a recent study, Xiao Yi et al. (2023) strongly demonstrated the analgesic effects of Centella asiatica (200 mg/kg, orally) in cats that underwent ovariohysterectomy, where the extract was given at 12 h before surgery and at 4, 24, 48, and 72 h after surgery (13).

Our study demonstrated the analgesic activity of the aqueous extract of the leaves of Centella asiatica. It could be suggested that AECA might contain pharmacologically active constituents (other than those involved in the central analgesia) that can block the release or the effect of endogenous substances responsible for the excitation of nerve endings (a peripheral mechanism).

Conclusion

Our study aimed to demonstrate the analgesic effect of the aqueous extract of the leaves of *Centella asiatica* (AECA). The present study strongly demonstrates that AECA acts as an excellent analgesic agent, and it may be helpful in different painful conditions. The analgesic effect of AECA may be due to its ability to act either by central or peripheral mechanisms. Further pharmacological and biochemical investigations are needed to determine the precise mechanism and site of action of AECA and the active constituents involved.

Declarations

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Conflict of Interest

The authors declare no conflicting interest.

Data Availability

The unpublished data is available upon request to the corresponding author.

Ethics Statement

Funding Information

Not applicable.

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