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EVALUATION OF ANALGESIC AND SKELETAL MUSCLE RELAXANT ACTIVITY OF ETHANOLIC EXTRACT OF *NYCTANTHES ARBORTRISTIS* FLOWERS IN EXPERIMENTAL ANIMALS

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ABSTRACT

Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Inflammation is a response to noxious or injurious stimuli, characterized by warmth, redness of the skin, pain, swelling and loss of function. Skeletal muscle relaxants are drugs that are used to relax and reduce muscle tension. They act as both antispasmodic and anti-spasticity agents. *Nycthanthes arbortristis* flowers consist of essential oils, Nyctanthin, D-mannitol, tannins, flavonoids, glucose, Quercetin, Kaemferol, Apigenin, Anthocyanin, carotenoids, and glycosides and found to have analgesic and skeletal muscle relaxant properties. The main objective of this study is to evaluate the skeletal muscle relaxant activity and analgesic activity of ethanolic extract of the flowers of *Nyctanthes arbortristis* (*ENATF*) using Rota-Rod method and hot plate method. High doses of *ENATF* (500mg/kg) showed highly significant reduction in the time spent by the animals on the revolving rod when compared to the control ($P<0.0001$). *ENATF* at all the doses (250mg/kg and 500mg/kg) showed highly significantly ($P<0.0001$) increased pain latency thermally induced by hot plate method. Thus, the result suggested that the *ENATF* possess skeletal muscle Relaxant activity and analgesic activity may be due to presence of different chemical compounds present in the extract.

KEYWORDS

Analgesia, Skeletal muscles, Diazepam, Diclofenac sodium and Flavonoids.

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INTRODUCTON

Analgesics are drugs which reduce or relieve the sensation of pain without producing loss of consciousness or parallel depression of other senses. Pain is the most common symptomatic reason for seeking a medical consultation[1]. Everyone is affected by pain at some point in their lives, whether it is from headaches, cuts and bruises or more severe pain resulting from surgery. Pain can

be categorized according to its duration, acute or chronic, as well as based on other characteristics. NSAIDs are the most common medications taken worldwide for the treatment of pain, inflammation and fever. Although chemically disparate they produce therapeutic effects by the common ability to inhibit the activity of cyclooxygenase (COX) enzymes. The non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin and ibuprofen inhibit early steps in the biosynthesis pathway of prostaglandins by inhibition of COX enzymes and are the main drugs used to reduce the untoward consequences of inflammation and pain[2]. However, the side effects of the currently available anti-inflammatory drugs pose a major problem in their clinical use. NSAIDS induces ulcers are symptomatic only in 1% of patients after three to six months and in 2 to 4% of patients after one year. Stomach problems, including pain, constipation, diarrhoea, gas, nausea, and stomach ulcers, Kidney problems, Anaemia, Dizziness, Swelling in the legs, Abnormal liver tests (blood tests), Headaches, Easy bruising, Ringing in the ears, Rashes[3].

Skeletal muscle relaxants are drugs that reduce the muscle tone. They act peripherally at the neuromuscular junction (neuromuscular blockers)/muscle fiber itself or centrally in the cerebrospinal axis to reduce muscle tone or cause paralysis. The neuromuscular blocking agents are used for muscle relaxation for surgery, while centrally acting muscle relaxants are used for painful muscle spasms and spastic neurological conditions[4]. However, these drugs causes several adverse effects like Dry mouth, fatigue, light headedness, constipation or blurred vision. Some serious but unlikely side effects may be experienced, including mental or mood changes, possible confusion and hallucinations, and difficulty urinating. In a very few cases, very serious but rare side effects may be experienced: irregular heartbeat, yellowing of eyes or skin, fainting, abdominal pain including stomach ache, nausea or vomiting, lack of appetite, seizures, dark urine or loss of coordination[4]. Thus, there is a need for more effective, less toxic and cost-effective analgesic and skeletal muscle relaxant agents. In recent years, a widespread search has been launched to identify new analgesic and skeletal muscle relaxants from natural herbal sources. One such analgesic and skeletal muscle relaxant activity possessing natural source is *Nyctanthes arbortristis* as per traditional system of medicine.

Nyctanthes arbortristis, the night flowering jasmine or parijat, is a species of Nyctanthes native to south Asia and south East Asia belongs to family: Oleaceae. The whole plant and leaves also contains many important useful phytochemicals like beta cytosterol, nictanthic acid, olenoic acid, ascorbic acid, Saponins, flavonoids, and also many glycosides like D-mannitol, astragaline, flavono glycosides. The *Nyctanthes arbortristis,* flowers consist of essential oils, Nyctanthin, D-mannitol, tannins, glucose, carotenoids, glycosides including Beta-monogentiobioside ester of alpha-crocetin (crocin, beta-monogentiobioside-beta-D-monoglucoside ester of alpha-crocetin, and beta-digentiobioside ester of a-crocetin and flavonoids (apigenin)[5]. *Nyctanthes arbortristis* commonly used plant in medicinal field. Nyctanthes plant has various CNS (viz: hypnotic, local anesthetics, tranquillizing) and anti-inflammatory[6], Hepatoprotective property[7]. The present study was designed to evaluate the analgesic and skeletal muscle relaxant effect of ethanolic extract of *Nyctanthes arbortristis* flowering part in experimental animals.

MATERIAL AND METHODS

Drugs

Diclofenac sodium, diazepam

Plant Material

Flowers of *Nyctanthus arbortristis* are collected from the areas of "Bollaram, JNTU, Karimnagar, Mahaboob nagar districts of Telangana, and they are dried, powdered, extracted for the drug and used for the skeletal muscle relaxant and analgesic activity.

Animals

Healthy Wistar albino rats weighing in between (200-250gm) and mice (20-30gm) were used for the study. The animals were kept in polypropylene cages (6 in each cage) and animals were

acclimatized to our lab environment for about a 3-5days prior to the study, so that they could adapt to the new environment. Animal house were maintained under standard hygienic conditions, at 25 ± 2ºC, Humidity (60±10%) within 12 hrs day and night cycle, with food and water ad libitium.

Methods

Skeletal Muscle Activity

Rota-rod Apparatus

The Rota-rod apparatus consists of a metal rod (3 cm diameter), and 75 cm in length put in a rotation of 25 RPM. Rota-rod is divided into 6 sections by metallic discs allowing the simultaneous testing of 6 mice. The rod is at a height of about 50 cm above the table top in order to discourage the animals from jumping off the roller. Animals were remain on Rota-Rod (20 rpm) 5 min or more after low successive trials are selected in this study. The test and standard compound were administered 1hr before placing the mice on the Rota rod. The number of animals falling from the Rota rod during this period and fall off time, i.e., when the animal falls from the rotating rod, was recorded[8].

Methodology

Mice were divided into four groups consisting of six animals each. Group I (control) animals treated with saline solution, animals of group II received standard drug Diazepam at a dose of (10mg/kg, i.p.) while Group III and IV received the low (250mg/kg) and high doses (500mg/kg) of *Nyctanthes arbortristis* flowers extract. The animals were placed on the rotating rod after one hour administration test drug and fall off time i.e, when the animal falls from the rotating rod, was recorded, which was taken as grip strength.

Analgesic Activity

Eddy's Hot Plate Method

Swiss albino rats were divided into four groups consisting of six animals each. Group I animals treated with saline solution, animals of group II received standard drug Diclofenac sodium at a dose of (10mg/kg, i.p.) while Group III and IV received the low (250mg/kg) and high doses (500mg/kg) of *Nyctanthes arbortristis* flowers extract. The rats were placed on a Techno hot plate maintained at 55°C, and the time between placement of the rat on the platform and shaking of animal, paw licking, jumping response was recorded as the hot plate latency. Rats with baseline latencies higher than 10 s were eliminated from the study. The response time (the time at which animals reacted to the pain stimulus either by paw licking) was noted before and 60 minutes after the administration of extracts and Standard drug[9].

Statistical analysis

The results were expressed in multiple comparisons of Mean ± SEM and was carried out by one-way analysis of variance (ANOVA) followed by Dunnet Multiple Comparisons. The results obtained were compared with the vehicle control group. The $P<0.001$, $P<0.0001$ were considered to be statistically significant.

RESULTS AND DISCUSSION

Skeletal muscle relaxant activity

From Above table *ENAT* at all the doses (250mg/kg and 500mg/kg) showed highly significant reduction in the time spent by the animals on the revolving rod when compared to the control ($P<0.0001$). The standard drug (Diazepam) also showed a highly significant effect when compared to the control ($P<0.0001$). *ENATH* showed increase muscle relaxation than *ENATL*. *ENAT* showed dose-dependent increase in muscle relaxation. The result obtained from both standard and extract treated groups were compared with the control group. A highly significant****$P<0.0001$ reduction in the motor coordination was observed in the test drug at 60 min of duration.

ENAT at all the doses (250mg/kg and 500mg/kg) showed highly significantly ($P<0.0001$) increased pain latency thermally induced by hot plate method. The reaction time at the dose of 500mg/kg (28s) was found to be twice when compared with control group (14s). The standard drug (diclofenac sodium) also showed a highly significant effect when compared to the control ($P<0.0001$).

In recent years, the herbal medicines have been extensively used in various diseases due to their safety profile. The objective of the present study was to evaluate the effect of *ENAT* on muscle relaxant activity and analgesic activity in

experimental animals. Some of these abundant ingredients in herbs with analgesic properties are flavonoids. Flavonoids are present in flower part of *Nyctanthes arbortristis*[5]. Flavonoids prevent the production of prostaglandins through inhibiting cyclooxygenase in the inflamed tissue. Flavonoids such as apigenin, reduce the accumulation of flowing lipids necessary for signaling pain[10]. Therefore, flavonoids reduce inflammatory pain through inhibiting the receptors and the signaling cascade. Flavonoids are known to inhibit the enzyme prostaglandin synthetase, more specifically the endoperoxidase and reported to produce analgesic effect[11]. Since, prostaglandins are also involved in the pain perception; inhibition of their synthesis might be the possible reason for the analgesic activity of the ethanolic extract of *Nycthantes arbortristis.*

Preliminary phytochemical screening reveals the presence of anthraquinone, steroids, saponins, flavonoids sugars and tannins in the plant extract. Therefore, the observed skeletal muscle relaxant activity may be attributed to these compounds. Previous reported study possess CNS depressant activity[5] and anti-convulsant activity[5] means extract having sedative property that may decrease conduction of pain impulses from post synaptic neuron to muscle junction. Further studies are required to isolate the active constituents responsible for this activity. The major limitation of the study is that phytochemical analysis was not done to identify the exact constituents. Further, extensive phytochemical analysis and research are necessary to identify the exact constituents and elucidation of its possible mechanism of action underlying the muscle relaxant activity of *ENAT.*

Table No.1: Effect of ethanolic extract of *nyctanthes arbortristis* on muscle coordination using rota-rod method

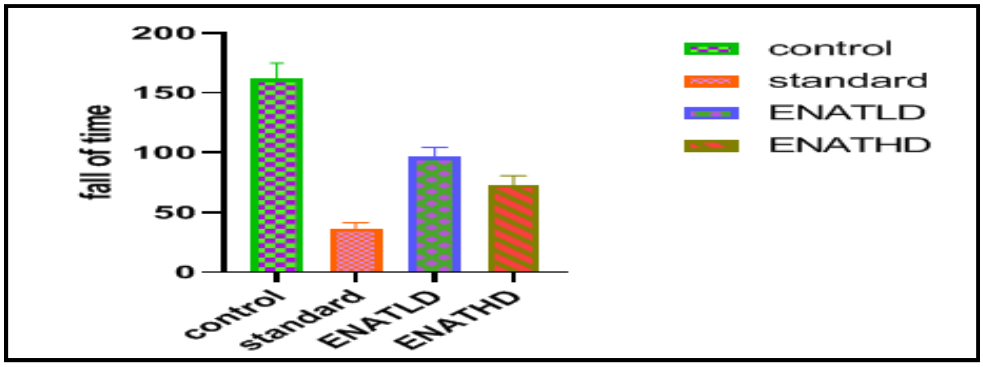
S.No	Groups treated	Dose	Fall of time (before)	After one hour
1	Control	Normal saline	161.5±19.5	161.83±13.13
2	Standard(diazepam)	10mg/kg	167±19.45	36.5±4.8***
3	*ENATL*	250mg/kg	163.3±19.95	96.66±7.95***
4	*ENATH*	500mg/kg	165±16.88	73±7.74***

One way ANOVA followed by Dunnet's test. Values are mean ± S.E.M; n = 6 in each group. ****P < 0.0001 when compared to control.

Table No.2: Analgesic effect of ethanolic extract of *Nyctanthes arbortristis* using Eddy's hot plate method

S.No	Groups treated	Dose	Basal reaction time
1	Control	Normal saline	14±1.09
2	Standard	Diclofenac sodium(10mg/kg)	37.5±1.37****
3	*ENALD*	(250mg/kg)	20.83±1.16****
4	*ENAHD*	(500mg/kg)	28.16±2.31****

One way ANOVA followed by Dunnet's test. Values are mean ± S.E.M; n = 6 in each group. ****P < 0.0001 when compared to control.



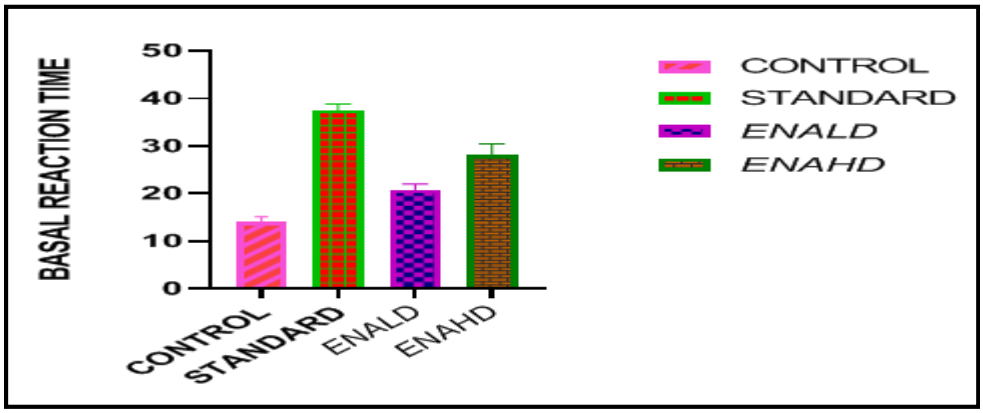


Figure No.1: Analgesic effect of ethanolic extract of *nyctanthes arbortristis* using Eddy's hot plate method

CONCLUSION

In conclusion, the ethanolic extract of *Nyctanthes arbortristis* at the doses of 250mg/kg and 500 mg/kg clearly demonstrated analgesic and skeletal muscle relaxant property in experimental model of animals Further, extensive phytochemical analysis and research are necessary to identify the exact constituents and elucidation of its possible mechanism of action underlying the muscle relaxant activity of *ENAT.*

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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