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BIOACTIVE COMPOUNDS, ANALGESIC AND ANTI-INFLAMMATORY EFFICACIES OF METHANOLIC LEAF EXTRACT OF *SENNA SIAMEA* LAM. (KASSOD TREE)

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ABSTRACT

This study was aimed at evaluation of the effect of ethanol leaf extract of *Senna siamea* on the central and peripheral nervous systems through analgesic and anti-inflammatory studies using laboratory animals. Fresh leaves of *Senna siamea* were collected, air-dried, pulverized and extracted using maceration with 95 % methanol and yielded 12.60 %. $^{w}/_{w}$ after being concentrated. The extract was screened for phytochemical constituents using standard methods. The phytochemical studies of the methanol leaf extract of *Senna siamea* showed the presence some secondary metabolites such as alkaloids, flavonoids, cardiac glycosides, tannins, saponins, and terpenoids. The analgesic effect of the methanol leaf extract was evaluated with acetic acid induced writhing and thermally induced nociception for pain while the anti-inflammatory effect was evaluated using albumin-induced rat paw oedema model. The LD_{50} of the leaf extract was 3807 mg/kg. The methanol leaf extract of *Senna siamea* produced an inhibition on the writhing response induced by acetic acid as well as increased the time of tail flicking in a dose dependent manner. The leaf extract also significantly ($P < 0.05$) inhibited the inflammation induced by egg albumin in the rats paw. This study revealed that the methanol leaf extract of *Senna siamea* had effect on the central nervous systems through analgesic and anti-inflammatory analysis. Thus, it has scientifically justified the local use of the plant for the management and treatment of pain and inflammation.

KEYWORDS

Senna siamea, Analgesic, Anti-inflammation and Phytochemicals.

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INTRODUCTION

Medicinal plants have been identified and used throughout human history. Plants make many chemical compounds for biological function including defence against insects, fungi and herbivorous mammals. At least 12,000 such compounds have been isolated; this is estimated to be less than 10% of the total (Tapsell *et al.*, 2006[1], Lai and Roy, 2004)[2]. Approximately 70,000 plant

species have been used for medicinal purposes (Neelesh *et al*., 2014)[3]. These plants are cheaper and more accessible to most of the population in the world whose medicinal value lies in some chemical substances that produce a definite physiological action on the human body (Edeoga *et al*., 2005)[4]. Over the years, they have assumed a very central stage in modern civilization as natural sources of chemotherapy as well as amongst scientists in search for alternative sources of drugs. The global demand for herbal medicinal products has increased significantly in recent years. It is estimated that the world's population will be more than 7.5 billion in the next 10 to 15 years.

To date, herbs have remained useful not only as remedy for different diseases that affect humans and animals, but also as good starting points for the discovery of bioactive molecules for drug development. The scientific exploitation of herbs used in ethno medicine for pain relief, wound healing and abolishing fevers has resulted in the identification of a wide range of compounds that have been developed as new therapies for cancer, hypertension, diabetes and as anti-infectives (Harvey 2008)[5]. *Senna* (from Arabic *sanā*), the sennas, is a large genus of flowering plants in the legume family Fabaceae, and the subfamily Caesalpinioideae. *S. siamea*, also still commonly referred to by its old name, *Cassia siamea*, is a popular forestry and ornamental tree, native to South-East Asia and probably adjacent countries. It has been widely introduced to other humid tropical climates around the world, and has more recently been noted as naturalised and invasive in Australia (especially the Cape York Peninsula, Queensland), Mexico, the Caribbean (Dominican Republic and Puerto Rico), the Pacific (Fiji and French Polynesia) and Ghana.

The leaves, stems, roots, flowers and seeds of *C. siamea* regardless the subspecies have been used for the treatment of several illnesses including mostly malaria, a tropical endemic disease with high morbimortality (Koudouvo *et al*., 2011)[6]. In Nigeria, the dried leaves are mixed with lemon's leaves (*Cymbopogoncitratus*), pawpaw's leaves (*Carica papaya*), and the lime's leaves (*Citrus lemonum*) and are boiled within an hour. In spite of the use of *Senna siemea* in traditional medicine by the local people in the northeast of Nigeria, only a few studies have been done to evaluate the pharmacological activities most especially analgesic and anti-inflammatory effect. Despite the popularity of this therapy among the healthcare workers and the general public, it is still not known whether the benefits of analgesic and anti-inflammatory therapy outweigh its risks. It is therefore necessary to examine the phytochemicals responsible for its medicinal uses. Thus, this study aims at screening for phytoconstituents responsible for the folkloric use of *Senna siamea* for the treatment and management of pain and inflammation.

MATERIAL AND METHODS

Plant Extraction

One (1) kilogramme of the powdered leaves of *Senna siamea* was extracted exhaustively by maceration method of extraction using methanol. The crude extract was concentrated to dryness at reduced pressure in a vacuum using a rotary evaporator at 40^{o} C. The extract was weighed, labelled and subjected to further analysis.

Preliminary Phytochemical Screening

The extract fraction of the leaf was screened qualitatively for phytochemical constituents using standard procedures (Brain and Turner 1975[7], Vishnoi 1979[8], Markham 1987[9], Silver *et al*., 1998[10], Sofowora 2008[11], Evans 2009)[12].

Pharmacological Investigations of the Methanol Leaf and Stem Bark Extracts of *Senna siamea*

All the experiments performed on laboratory animals in this study followed the standard procedure for the treatment of animals. The animals were handled according to the International Guiding Principle for Biomedical Research involving animals, (CIOMS and ICLAS, 2012)[13].

A total of one hundred and forty eight (74) albino rats (100-180 g) and fifty (25) mice (20-28 g) of both sexes were purchased from the Animal House of the Faculty of Pharmacy, University of Maiduguri, Borno State. They were housed in clean plastic, well-ventilated cages with saw dust as beddings under 12 hours light/12 hours dark cycle

conditions of normal room temperature and humidity in the Pharmacology, Physiology and Biochemistry Laboratory, Faculty of Veterinary Medicine, University of Maiduguri for the analysis. They were fed with standard feed (ECWA, Jos) and allowed water *ad libitum.*

Acute Toxicity Evaluation (LD_{50})

The acute toxicity (LD_{50}) of the crude leaf extract of methanol were determined using standard conventional procedure as described by Lorke (1983)[14]. In this study, two different routes of administration were considered; the oral and intraperitoneal. In phase I, rats were divided into 3 groups of three rats each for each route (a total of nine rats) and then treated with the crude methanol extract at doses of 10, 100 and 1000 mg/kg bd. wt. intraperitoneally and orally and observed for 24 hours for mortality. In the phase II, the animals of each group (for each route) were divided into three groups of one animal each and the methanol extract was administered at doses that were determined after the phase I. The rats were observed for signs of toxicity and mortality for the first critical four hours and thereafter daily for 7 days. The LD_{50} was then calculated.

ANALGESIC EVALUATION

Effect of Extract on Acetic Acid -Induced Writhing on Mice

The abdominal constriction resulting from intraperitoneal injection of acetic acid (0.6% v/v) consisting of a contraction of abdominal muscle, together with a stretching of hind limbs, was carried out according to the procedure described by Abdulrahman (2004)[15], Correa *et al.* (1996)[16], Nwafor (1998)[17], Santos *et al.* (1994)[18]. Twenty (25) mice were divided into 5 groups of 5 mice each. Groups 1 and 5 served as the negative and positive controls respectively, while groups 2, 3 and 4 were pretreated (*i.p*) with doses of 100, 200 and 300 mg/kg. b. wt. of extract (i.p). 30 minutes later, acetic acid (0.6% v/v) was administered. The number of writhing movements was counted for 30 minutes. Antinociception was expressed as the reduction of the number of abdominal constriction between negative control mice (distilled water treated mice), mice pretreated with the extract and the positive control (10 mg/kg pentazocine treated mice) and was calculated using the formula:

$$\% \text{ Protection} = \frac{(\text{Mean no. of writhes in Control group} - \text{Mean no. of writhes in Test group}) \times 100}{\text{Mean no. of writhes in Control group}}$$

Tail Immersion

Method described by Owoleye *et al.* (2004)[19] was adopted. Rats were treated intraperitoneally with 200, 400 and 600 mg/kg of the extracts, distilled water and 10mg/kg, pentazocine (10 mg/kg) served as the negative control and positive control respectively. Measurements of extract effect were carried out within time intervals of 30, 60, 90 and 120 min after administration of the extracts. Water was heated to 50.0 ±1.0 ^{o}C in a water bath. The time taken for the animal to remove it tails out of the water was recorded**.**

The increase in pain threshold was calculated using the formula:

$$\% \text{ Increase in pain threshold} = \frac{(\text{Mean reaction time in test group} - \text{Mean reaction time in control group}) \times 100}{\text{Mean reaction time in test group}}$$

Anti-inflammatory Studies

Albumin-Induced Rat Paw Oedema Model

The anti-inflammatory study was carried out using the method described by Winter *et al* (1962)[20]. 25 rats were divided into five groups, 1 and 2 serving as negative control (distilled water 10 ml/kg) and positive control (Pentazocine, 10 mg/kg), while groups 3, 4 and 5 received 200 mg/kg, 400 mg/kg, and 800 mg/kg of the extract respectively. Treatments were administered 1hour before albumin injection. Albumin was separated from the yolk and was injected underneath the planter region of the paws of the rats. The paw size was measured with a digital vernier calliper at 0, 1, 2, 3, 4, 5 and 6 hours after albumin injection.

$$\% \text{ Increase in pain threshold} = \frac{(\text{Mean reaction time in test group} - \text{Mean reaction time in control group}) \times 100}{\text{Mean reaction time in test group}}$$

Statistical Analysis

Data generated during the study were expressed in mean ± standard Error of mean (SEM) and analysed by one way analysis of variance (ANOVA) Using Instat Graphpad version 3.10 (Graphpad In Stat, 2000)[21]. Values of $P<0.05$ were considered significant at 95 % confidence level.

RESULTS AND DISCUSSION

PHASE 1: CHEMICAL ANALYSIS

Extraction

The extraction of the leaf of *Senna siamea* using methanol produced extract with greenish brown colours which was gummy mass. The methanol leaf extract had yield of 12.60 %. The result of the extraction profile is shown in Table No.1.

Phytochemical Screening of the Methanol Leaf Extract

The preliminary phytochemical screening of the leaf using methanol as solvent revealed the presence of some phytochemicals such as flavonoids, terpenoids, cardiac glycosides, saponins, tannins and flavonoids. The result of the phytochemical screening of the extract is shown in Table No.2.

PHASE II: PHARMACOLOGICAL STUDY

Acute Toxicity (LD_{50})

Tables No.3 present the result of acute toxicity of the methanol leaf extract of *Senna siamea* on rats. Death was recorded on administration of 5000 mg/kg of the methanol leaf extract and the i.p. LD_{50} was calculated to be 3807 mg/kg. Though behavioural signs of toxicity were observed in rat when 5000 mg/kg of the extract was administered via i.p. route (which included paw licking, stretching and reduced activity) but it revived 5 hrs after the exhibition of these clinical signs.

Analgesic Effect of Methanol Leaf Extract of *Senna siamea*

Acetic Acid-Induced Writhing

The methanol leaf extract of *Senna siamea* caused an inhibition on the writhing response induced by acetic acid in a dose dependent manner at ($P< 0.05$) [Figure No.1]. 45.30 %, 51.50 % and 67.10 % inhibition for doses of 100, 200 and 300 mg/Kg bd. wt.(*i.p*) was observed as compared to the reference drug (positive control) (71.80 %) as shown in Figure No.1. The effect was more pronounced at a high dose of 300 mg/kg bd. wt. which gave a high percentage inhibition (67.10 %) of the abdominal constriction induced by acetic acid. This was found to be significantly lower than the effect of the synthetic drug (pentazocine, 10 mg/kg bd. wt) and significantly higher than animals treated with distilled water with % inhibition of 71.80 % and 0 % respectively.

Thermally-Induced Nociception (Tail Immersion Test)

Table No.4 represents the mean time of tail flick at increasing doses of methanol leaf extract of *Senna siamea* in the evaluation of thermally induced nociception of ethanol extract on rats. The extract doses of 200, 400 and 600 mg/kg body weight significantly ($p<0.05$) increased the time of tail flicking. The extract is observed to be more effective at 60 minutes after administration in a dose dependent manner (5.80±0.20, 6.20±0.20 and 6.80±0.20 at doses of 200, 400 and 600 mg/kg respectively). However pentazocine significantly increased the time of tail flick with a superior effect when compared to the extract.

Anti-inflammatory Effect

Figures No.2 presents the anti-inflammatory activity test. The methanol leaf extract of *Senna siamea* (200, 400 and 800 mg/kg) caused statistically significant ($P < 0.05$) inhibition of inflammation induced by egg albumin in the rats paw with % protection of 33.80 %, 35.20% and 46.00 % respectively. The anti-inflammatory effect of the extract was observed to be high at the third hour which was used to calculate the percentage protection. The percentage protection of the inflammation caused by the extract was comparable to that obtained with Pentazocine (10 mg/kg), 61.00 % which was used as standard. The effect of the leaf extract was also dose-dependent.

DISCUSSION

The phytochemical studies of the methanol leaf and stem bark extracts of *Senna siamea* revealed some useful chemical compounds such as flavonoids, cardiac glycosides, tannins, saponins, terpenoids and alkaloids. Flavonoids exhibit several biological effects such as antihepatotoxic, anti-inflammatory and antiulcer activity (Bors *et al*., 1990[22], Colerige *et al*., 1980)[23]. Saponins have been reported to posses insecticidal activity (Geyter *et al*., 2007)[24], antitumorigenic effect (Man *et al*., 2010)[25], molluscicidal effect (Huang *et al*., 2010)[26], spermicidal (Garg *et al*., 1993)[27], anxiolytic

(Chakraborty *et al*., 2010)[28] and anti-bacterial activities (Ibrahim *et al*., 2006)[29]. Terpenes have been reported to possess important biological activities, such as analgesic (Guimaraes *et al*., 2013[30], Quintans *et al*., 2013)[31], anticonvulsant (De Sousa *et al*., 2007)[32], cardiovascular (Silva-Filho *et al*., 2012)[33] antimalarial and antibacterial effects (Evans, 2009)[12]. The saponins also exhibits antimicrobial (Mandal *et al*., 2005)[34], antioxidant (Gulcin *et al*., 2004)[35] and anti-inflammatory activities (Gepdireman *et al*., 2005)[36]. The presence of saponins, steroids and triterpenoids in the plant extracts of *Senna siamea* supports the claim that these compounds have anti-inflammatory properties since saponins, steroids and triterpenoids have been found in other natural products with anti-inflammatory properties (Yeonju *et al*, 2012)[37]. Alkaloids have pharmacological applications as anesthetics and CNS stimulants (Madziga *et al.,* 2010)[38]. Other important alkaloids of plant origin include the addictive stimulants, caffeine, nicotine (III), bufotenin (IV), codeine, atropine, morphine, ergotamine, cocaine, nicotine and ephedrine (Madziga *et al.,* 2010)[38]. The extract potently and significantly prolonged reaction time in mice subjected to thermal stimuli, indicative of an analgesic effect, comparable with the opioid agonist pentazocine. The tail immersion test of nociception screens for substances with central nervous system activity (Sulaiman *et al*., 2010)[39]. The hot plate test however, does not discriminate between central analgesics and muscle relaxants/sedatives, which also prolong reaction time in the hot plate test (Vogel, 2008)[40]. Anti-nociceptive model; tail immersion test was used to evaluate the analgesic activity, since tests of analgesic drugs commonly measure nociception and involve the reaction of animals to painful stimuli (Rang *et al*., 2003)[41]. The stimulus may be thermal (tail immersion or hot plate tests), chemical (acetic acid-induced writhing or formalin tests) or mechanical (tail or paw pressure tests) (George *et al*., 2009)[42]. The methanol leaf extract showed a dose-dependent and significant ($P < 0.001$) increase in the pain threshold post-treatment with dose of extracts in the tail immersion test. The effects of the extracts were significantly ($P < 0.001$) lower than those produced by pentazocine in the same tests. The tail immersion has been used to study centrally acting analgesics (Woolfe and Mac Donald, 1994[43], Bachlav *et al*., 2009)[44]. In these tests, the nociceptors are sensitised by sensory nerves and the involvement of endogenous substances such as prostaglandins are minimized. Thus from the results, it may be concluded that the analgesic activity of *Senna siamea* may be fully mediated through central mechanism. The abdominal constriction method used in evaluation of the effect of the plant extract is a very sensitive one and can detect antinociceptive effect of a substance at a dose that cannot be detected by other methods such as tail-flick test (Koster *et al*., 1959[45], Collier *et al*., 1968)[46]. Inhibition of acetic acid-induced writhing in mice by extract (200 and 400 mg/kg) suggested that the analgesic effect of the extract may be peripherally mediated via the inhibition of the synthesis and release of prostaglandins (Koster *et al*., 1959)[45]. The acetic acid induced mice writhing test has been used extensively to qualify analgesic agents that have peripheral analgesic activity (Neves *et al*., 2007)[47]. Writhing induced by chemical substances injected intraperitoneally, is due to sensitization of nociceptors by prostaglandins.

Table No.1: The Extraction Profile of Air-Dried Powdered Leaf of *Senna siamea*

S.No	Extract	Mass (g) %	Yield ($^{w}/_{w}$)	Colour	Texture
1	Methanol leaf	63.00	12.60	greenish brown	gummy mass

Table No.2: Phytochemical Screening of Leaf Extract of *Senna siamea*

S.No	PHYTOCHEMICAL TEST	SSMLE
1	**Test Tor Carbohydrates**	
I	General test-Molish	+
Ii	Test for monosaccharides-Barfoed	-
Iii	Test for reducing sugar-fehling test	-
Iv	Test for combined reducing sugar	-
V	Test for ketoses	+
Vi	Test for pentoses	_
2	**Test for Tannins**	
I	Ferric chloride test	+
Ii	Lead acetate	_
3	**Test for Phlobatannins**	_
4	**Test for Steroids/Triterpenes**	
I	Salkwoski test	+
Ii	Liebermann-burcharde test	+
5	**Test for Flavonoids**	
I	Shinoda's test	_
Ii	Ferric chloride test	+
Iii	Lead acetate test	_
Iv	Sodium hydroxide	_
6	**Test for Saponnins**	
I	Frothing test	+
7	**Test for Soluble Starch**	_
8	**Test for Alkaloids**	
I	Dragendroff's reagent	+
Ii	Meyer's reagent	+
9	**Test for Steroidal Nucleus**	
I	Keller- killiani's test	+
10	**Test for Terpenoids**	+

SSLE- *Senna siamea* leaf extract

Keys: + = positive - = negative

Table No.3: Acute Toxicity Effect of Methanol Leaf Extract of *Senna siamea* on Rats

Phase	Dose (mg/kg)	No. of rat	Mortality rate	
			Oral route	IP route
I	10	3	0/3	0/3
	100	3	0/3	0/3
	1000	3	0/3	0/3
II	1600	1	0/1	0/1
	2900	1	0/1	0/1
	5000	1	0/1	1/1

I.p. LD_{50}= $\sqrt{ab}$ (Lorke's method)

Where a = Where a = least dose that killed a rat

b = highest dose that did not kill a rat

= $\sqrt{5000 \times 2900}$ = 3807 mg/kg

Table No.4: Analgesic Effect of *Senna siamea* leaf Extract on Rats (Tail Immersion Method)

Group	Treatment (mg/kg) Mean±S.E.M tail flick (min)				
		30	**60**	**90**	**120**
A	Distilled H_2O (-ve control)	4.00±0.00[a]	3.40±0.24	3.80±0.20	3.80±0.20[a]
B	200	5.40±0.24[a]	5.80±0.20[a]	5.20±0.20[b]	4.40±0.24[ab]
C	400	5.40±0.24[a]	6.20±0.20[a]	5.60±0.24[ab]	4.40±0.24[b]
D	600	6.00±0.45[a]	6.80±0.20[a]	6.60±0.24[a]	5.00±0.00[b]
E	10 pentazocine (+ve control)	8.40±0.51	9.00±0.32	8.00±0.45	6.20±0.37

Values across column with same superscript are not statistically ($p>0.05$) significant
Values across column with no or/different superscript are statistically ($p<0.05$) significant

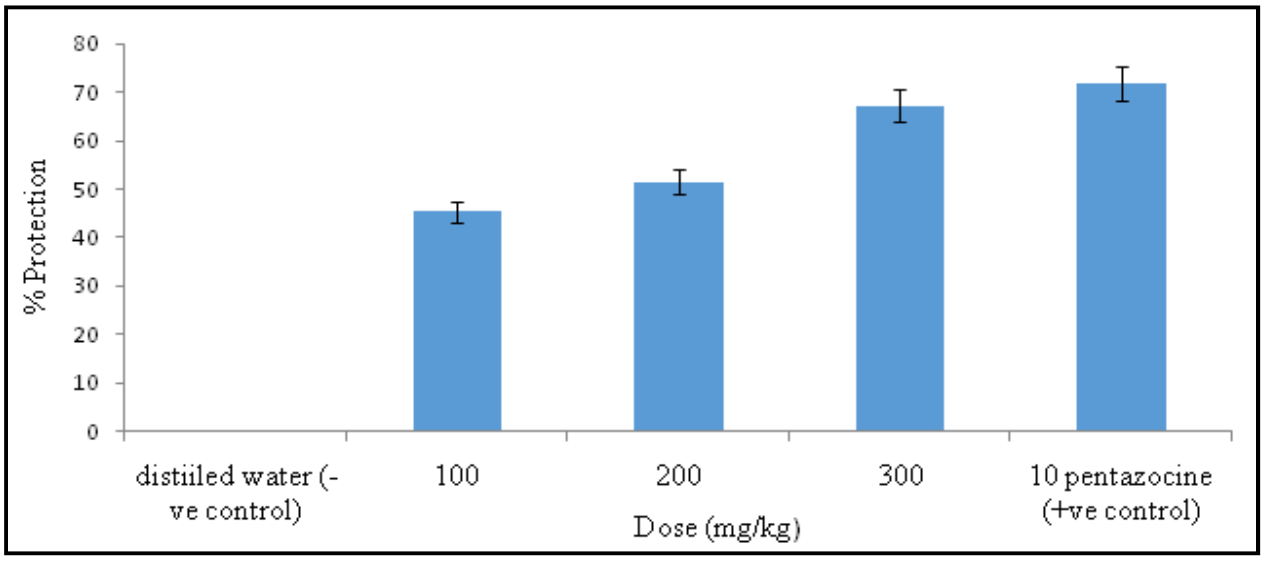

Figure No.1: Effect of Methanol Leaf Extract of *Senna siamea* on Acetic acid induced writhes in mice

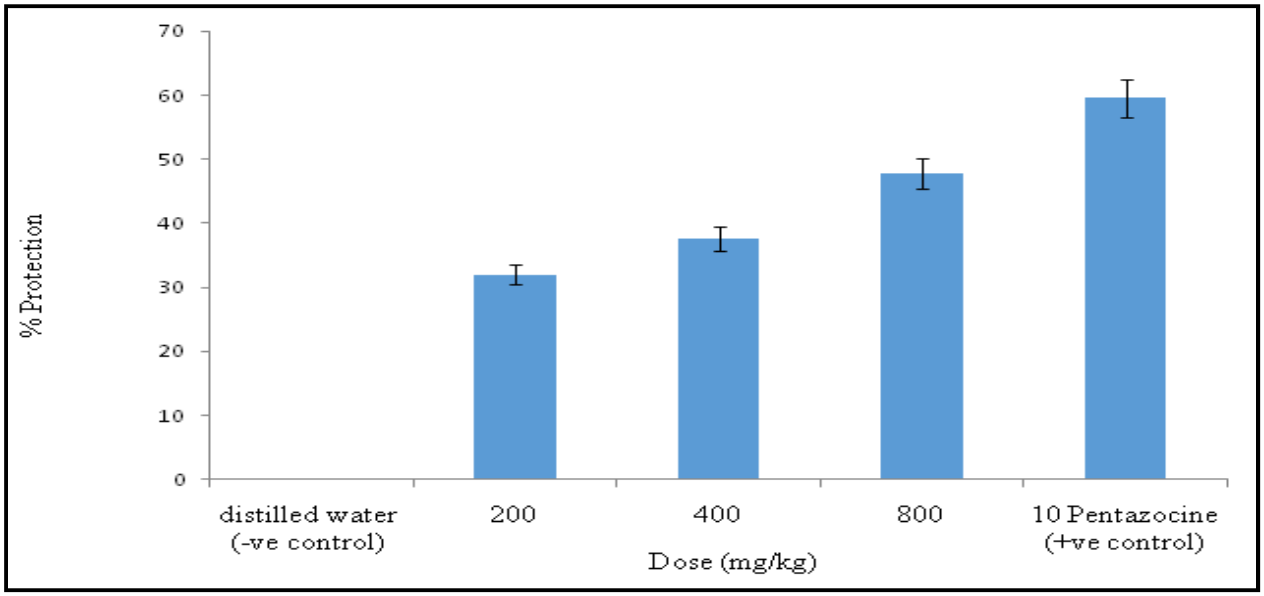

Figure No.2: Anti-inflammatory Effect of Methanol Leaf Extract of *Senna siamea*

CONCLUSION

The phytochemical study revealed the presence of saponins, cardiac glycosides, tannins, flavonoids, terpenoids, alkaloids and carbohydrates in the leaf extract of the plant. The LD_{50} of the leaf extract was 3807 mg/Kg. The leaf extract induced some degree of effects on the peripheral and central nervous systems as they exerted anti-inflammatory effect and induced analgesia. However, bio-guided assay isolation of bioactive compound(s) responsible for the analgesic and anti-inflammatory efficacies should be further studied.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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