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Phytochemical Screening, Analgesic And Anti-Inflammatory Activities Of Methanol Stem Bark Extract Of *Senna Siamea* Lam. (Kassod Tree)

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Abstract
The study aims at phytochemical screening, analgesic and anti-inflammatory activities of methanol stem bark extract of Senna siamea Lam. (kassod tree). Fresh stem bark of Senna siamea were air-dried, pulverized extracted using maceration method of extraction technique with methanol and yielded 12.60 %. w/w after being concentrated. The extract was screened for phytochemicals using standard methods. The phytochemical studies of the methanol extract of Senna siamea revealed the presence some chemical compounds such as alkaloid, flavonoids, cardiac glycosides, tannins, saponins, and terpenoids. The analgesic effect of the 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 stem bark extract was ≥5000 mg/kg. The methanol stem bark extract of Senna siamea caused an inhibition on the writhing response induced by acetic acid in a dose dependently. Similarly, the extract doses increased the time of tail flicking in a dose dependent manner. The stem bark extract also significantly ($P < 0.05$) inhibited inflammation induced by egg albumin in the rats paw. Thus, this study has scientifically justified that the plant possess some degree of action on peripheral and central nervous system thereby acting as an antidepressant in suppressing pain and inflammation. The proves the use of the plant locally for the management and treatment of pain related health problems.

Keywords: *Senna siamea, analgesic, bioactive, phytochemicals*

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I. Introduction

For centuries, natural products have provided medicine for human illness and most of these remedies were obtained from higher plants (Wink, 1999). Natural products have been an integral part of the ancient traditional medicine systems, for example Chinese, Ayurvedic and Egyptian (Sarker and Nahar, 2007). The use of medicinal plants in West Africa is probably as old as the duration of human settlement in the region (Abdulrahman *et al*., 2010; Sodipo *et al*., 2011). The reason for the use of herbs is because of their affordability, easy accessibility and effectiveness. In the last two centuries, there has being serious investigations into the chemical and biological activities of plants and these have yielded compounds for the development of synthetic organic chemistry and the emergence of medicinal chemistry as a route for the discovery of more effective therapeutic agents (Roja and Rao, 2000).

According to the World Health Organization (WHO), a medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes, or which are precursors for chemo-pharmaceutical semi synthesis. Such a plant will have its parts including leaves, roots, rhizomes, stems, barks, flowers, fruits, grains or seeds, employed in the control or treatment of a disease condition and therefore contains chemical components that are medically active (Liu, 2004). The availability, low cost and accessibility of these plants in Tropical and Sub-tropical Africa coupled with the global crisis of drug resistance incidences make it convenient for in-depth survey of medicinal plants from this part of the world (Usman *et al*., 2009).

Senna (from Arabic *sanā*), the *sennas*, is a large genus of flowering plants in the legume family Fabaceae, and the subfamily Caesalpinioideae. This diverse genus is native throughout the tropics, with a small number of species in temperate regions. The number of species is estimated to be from about 260 *(*Marazzi *et al*., 2006) to 350 (Randell and Barlow, 1998).

The leaves, stems, roots, flowers and seeds of *S. siamea* regardless of the subspecies have been used for the treatment of several illnesses including mostly malaria (Koudouvo *et al*., 2011). According to the ethnic differences of populations from localities, the plant is used alone or in combination with other plants or with natural substances for preparation, especially in decoction (Maurya and Dongarwar, 2012).

In Burkina Faso, Ghana and Nigeria, the decoction of the whole stem or stem bark is taken or used for body bath against malaria and liver disorders (Adebayo and Krettli, 2011). These same uses were reported in Malaysia (Al-Adhroey *et al*., 2010). The dried stems of *C siamea* mixed with the fruit of *Xylopia aethiopica* are pulverized and administered as a laxative (Kiepe, 1995). The decoction of the stem bark is used to treat diabetes. It is also used as a mild, pleasant, safe and purgative in Japan. Dalziel (1963); Odason and Kolawole, (2007) also indicated that this decoction is also used for scabies, urogenital diseases, herpes and rhinitis in Cambodia. Inspite of the global advancement in discovery of drugs, conventional drugs still remain a major concern due to negative scientific reports regarding their adverse effects. More so, 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. This has necessitated the search for a safer, affordable, available and assessable means of treatments within the plant kingdom. 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.

II. Materials And Methods

Plant Extraction

One (1) kilogramme of the pulverized stem bark 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, labeled and subjected to further analysis.

Preliminary Phytochemical Screening

The extract fraction of the stem bark was screened qualitatively for phytochemical constituents using standard procedures (Brain and Turner, 1975; Vishnoi, 1979; Markham, 1987; Silver *et al*., 1998; Sofowora, 2008; Evans, 2009).

Pharmacological Investigations of the Methanol Stem Bark Extract 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).

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 and allowed water *ad libitum.*

Acute Toxicity Evaluation (LD_{50})

The acute toxicity (LD_{50}) of the crude stem bark extract of methanol were determined using standard conventional procedure as described by Lorke (1983). 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 using the formula:

$LD_{50} = \sqrt{a \times b}$
Where a = least dose that killed a rat
b = highest dose that did not kill a rat

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); Correa *et al.* (1996); Nwafor (1998); Santos *et al*. (1994). 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 the extract (*ip*). 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:

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

Tail Immersion

Method described by Owoleye *et al*. (2004) 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:

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

Anti-inflammatory Studies
Albumin-Induced Rat Paw Oedema Model

The anti-inflammatory study was carried out using the method described by Winter *et al* (1963). 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.

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

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 InStat, 2000). Values of $P<0.05$ were considered significant at 95 % confidence level.

III. Results And Discussion

Plant Extraction

The extraction of the stem of *Senna siamea* using methanol produced extract with greenish brown colours which was powdery. The methanol extract had a yield of 12.39% . The result of the extraction profile is shown on Table 1:

Phytochemical Screening of the Stem Bark Extract

The preliminary phytochemical screening of the stem bark using methanol as solvents revealed the presence of some phytochemicals such as flavonoids, terpenoids, cardiac glycosides, saponins, tannins and flavonoids. The result of the phytochemical screening of the gradient extraction is shown in Table 2:

Table 1: The extraction profile of air dried powdered stem bark of *Senna siamea*

Extract	Mass (g)	% Recovery ($^{w}/_{w}$)	Colour	Texture
Ethanol stem bark extract	61.93	12.39	greenish brown	powdery

Table 2: Results of Phytochemical Screening of Stem Bark Extract of *Senna siamea*

S/N	PHYTOCHEMICAL TEST	SSMSE
1	**Test Tor Carbohydrates**	
i	General test-Molish	+
ii	Test for reducing sugar-fehling test	+
iii	Test for combined reducing sugar	+
iv	Test for ketoses	+
v	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	+
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**	+

SSESE- *Senna siamea* methanol stem bark extract;

Acute Toxicity (LD_{50})

Tables 3 present the result of acute toxicity of the methanol stem bark extract of *Senna siamea* on rats. No death was recorded on administration of up to 5000 mg/kg dose of the methanol extract via both the oral and intraperitoneal routes. Thus LD_{50} of the crude methanol extract of *Senna siamea* on rats administered via both oral and intraperitoneal routes was ≥ 5000 mg/kg bd. wt.

Analgesic Effect of Methanol stem bark Extract of *Senna siamea*

Acetic Acid-Induced Writhing

The methanol stem bark extract of *Senna siamea* also exerted an inhibition on the writhing response induced by acetic acid in a dose dependent manner at ($P< 0.05$) [Table 4]. 32.80±0.37, 27.80±0.37 and 22.00±2.17mean number of writhing for doses of 100, 200 and 300 mg/Kg bd. wt.(*i.p*) was observed as compared to the reference drug(positive control) (18.60±0.51) as shown in table (4). The effect was more pronounced at a high dose of 300mg/kg bd. wt. which gave a high percentage of inhibition (64%) of the abdominal constriction induced by acetic acid. This was found to be significantly lower than the effect of the synthetic drug (pentazocine, 20 mg/kg bd. wt) and significantly higher than animals treated with distilled water with mean number of writhes at 21.40±1.28 and 62.00±0.70 in the extent to which the writhing or stretching induced by acetic acid was reduced.

Thermally-Induced Nociception (Tail Immersion Test)

Figure 4 represent the mean time of tail flick at increasing doses of methanol stem bark 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 bd. wt. 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 (6.20±0.20, 6.20±0.207.00±0.54 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

The methanol stem bark 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 decrease in diameter of4.92±0.25, 4.32±0.11 and 3.80±0.17 respectively. The percentage inhibition of the inflammation caused by the extract was comparable to that obtained with Pentazocine (20 mg/kg) which was used as standard (Figure 1). The effect of the stem bark extract was also dose-dependent.

Table 3: Acute toxicity effect of methanol stem bark 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	0/1

$LD_{50} \geq 5000$ mg/kg

Table 4: Effect of methanol stem bark extract of *Senna siamea* on acetic acid induced writhes in mice

Group	Treatment (mg/kg)	No. of Writhes mean±S.E.M	% Protection
A	H_2O (-ve control)	62.00±0.70	0
B	100	32.80±0.37	47
C	200	27.80±0.37	55
D	300	22.00±2.17	64
E	10 pentazocine (+ve control)	21.40±1.28	65

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

Table 5: Analgesic effect of *Senna siamea* stem bark extract on rats (Tail Immersion Method)

Group	Treatment (mg/kg)	Mean±S.E.M tail flick (min)			
		30	60	90	120
A	H_2O (-ve control)	4.80±0.20	4.80±0.20^{b}	4.60±0.24^{a}	4.20±0.20^{a}
B	200	6.20±0.20^{b}	6.20±0.20^{ab}	5.20±0.20^{a}	4.80±0.20^{a}
C	400	6.40±0.24^{ab}	6.20±0.37^{ab}	5.20±0.37^{a}	4.80±0.37^{a}
D	600	7.40±0.40^{a}	7.00±0.54^{a}	7.20±0.37	5.20±0.37
E	10 pentazocine (+ve control)	9.60±0.24	9.60±0.50	8.60±0.24	6.80±0.37

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

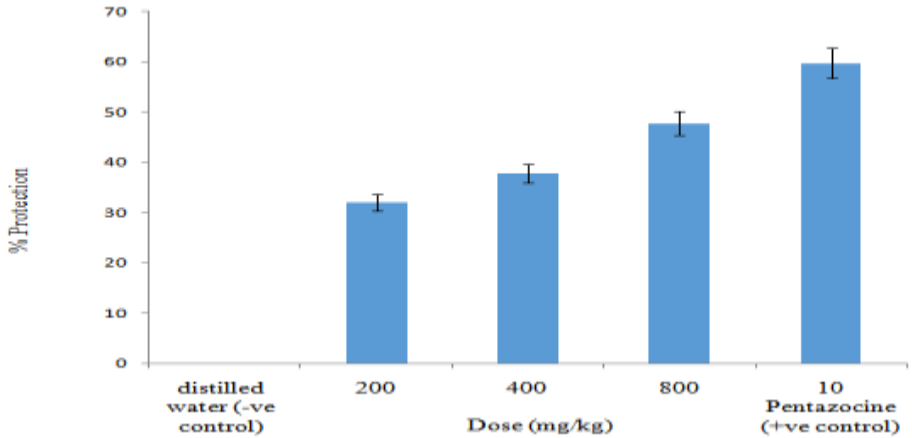

Figure 2: Anti-inflammatory Effect of Methanol Stem Bark Extract of *Senna siamea*

IV. Discussion

The phytochemical studies of the methanol stem bark extract of *Senna siamea* revealed some useful chemical compounds such as flavonoids, cardiac glycosides, tannins, saponins, terpenoids and alkaloids. These compounds have been known to exert pharmacological and antagonistic effects and still some are capable of protecting the active ingredient in herbs from decomposing either chemically or physiologically

Many researchers have given various reasons for anti-inflammatory activity. It was observed that the flavonoids detected in both extracts are known to be good anti-inflammatory agents. Studies of Raju *et al*. (2005) on anti-inflammatory potential of *Cassia fistula* revealed the responsibility of flavonoids and alkaloids in anti-inflammatory reactions. Similarly, flavonoid with antiinflammatory potential are reported from *Morinda tinctoriaroxb*, and *Vernonia amygdalina* (Sivaraman and Muralidharan, 2010; Udeme *et al*., 2009). Inspite of flavonoids, steroids were noticed in both the extracts (ethyl acetate and methanol) and studies of Neto *et al.* (2005) reported the presence of steroids with anti-inflammatory potential in *Pafaffia glomerata*. Terpenes have been reported to posses important biological activities, such as analgesic (Guimaraes *et al*., 2013; Quintans *et al*., 2013), anticonvulsant (De Sousa *et al*., 2007), cardiovascular (Silva-Filho *et al*., 2012) antimalarial and antibacterial (Evans, 2009). Alkaloids have pharmacological applications as anesthetics and CNS stimulants (Madziga *et al.*, 2010). More than 12,000 alkaloids are known to exist in about 20 % of plant species and only few have been exploited for medicinal purposes.

Denaturation of proteins is a well-documented cause of inflammation. Irritant-induced inflammation occurs in two qualitatively distinguishable phases (Asif, 2011). The early phase begins within minutes of phlogistic challenge due to the release of biogenic amines such as histamine, while the latter phase involves the synthesis of prostaglandins. Drugs with known cyclooxygenase inhibitory activity such as Non-Steroidal Anti-inflammatory Drugs (NSAID) suppress this later phase of oedema formation (Asif, 2011). Egg white is an alternative phlogistic agent that triggers the release of inflammatory process via release of mediators (Vogel, 2008). Edema represents the early phase of inflammation and a number of mediators have been identified to be released in a sequential manner. There is an initial release of histamine and 5-hydroxytryptamne producing an increased vascular permeability followed by release of kinins further contributing to the increased vascular permeability and finally, the prostaglandins and slow reacting substance are released to maintain the increased vascular permeability by histamine, 5-hydroxytryptamine and kinins (Crunkhorn and Meacock, 1971). The tail immersion has been used to study centrally acting analgesics (Woolfe and MacDonald, 1994; Bachlav *et al*., 2009). In these tests, the nociceptors are sensitise by sensory nerves and the involvement of endogenous substances such as prostaglandins are minimized. Thus from the results, we can conclude that the analgesic activity of *Senna siamea* may be fully mediated through central mechanism.

Inhibition of acetic acid-induced writhing in mice by extract (200 and 400 mg/kg) suggested that the analgesic affect of the extract may be peripherally mediated via the inhibition of the synthesis and release of prostaglandins (Koster *et al*., 1959). The acetic acid induced mouse writhing test has been used extensively to qualify analgesic agents that have peripheral analgesic activity (Neves *et al*., 2007). Writhing induced by chemical substances injected intraperitoneally, are due to sensitization of nociceptors by prostaglandins.

Alkaloids, flavonoids and saponins are known to possess analgesic activity (Evans, 2009).The activity of the extracts was found to be dose dependent and significant at $P<0.05$.

V. Conclusion

The phytochemical study revealed the presence of saponins, cardiac glycosides, tannins, flavonoids, terpenoids, alkaloids and carbohydrates in the stem bark extract of the plant. The stem bark extract had an LD_{50} $\geq$5000 mg/Kg. The stem bark extract induced some degree of effects on the peripheral and central nervous system as it exert anti-inflammatory and induced analgesia. However, Purification, isolation and characterization using physical technique such as HNMR, ^{13}CNMR and IR-Spectroscopy should be carried out in order to confirm the chemical structures of the bioactive constituents responsible for the plant's pharmacologic actions.

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