

Full Length Research Paper

Analgesic, anti-inflammatory and antipyretic effects of dried root ethanolic extract of *Strophanthus sarmentosus* p. Dc (apocynaceae)

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Despite the progress made in medical research in the past decades, the treatment of many diseases including inflammatory diseases is still problematic. Conventional drugs used to ameliorate these conditions are either too expensive or toxic, there is therefore an urgent need to search for newer, cheaper and safer medications. *Strophanthus sarmentosus* (SMS) is an indigenous plant used in traditional medicine in West Africa for the treatment of inflammatory diseases among other uses. The present study was designed to explore its therapeutic benefits in inflammation, nociception and pyrexia. Analgesic effect of the ethanolic extract of dried SMS root (50, 100 and 200 mg kg⁻¹) was evaluated in mice using acetic acid-induced writhing and hot plate models, while the efficacy of the herbal drug was compared with 150 mg kg⁻¹ acetylsalicylic acid, 0.5 mg kg⁻¹ piroxicam and 5 mg kg⁻¹ morphine respectively. Anti-inflammatory activity of SMS was also investigated using groups of oedema-induced rats separately treated with 1 % w/v carrageenan in normal saline and xylene. The effects of 10 mg kg⁻¹ indomethacin and 1 mg kg⁻¹ dexamethasone were also evaluated as respective standard drugs for the two models. The antipyretic effect of SMS was lastly studied using d-amphetamine and Klebsiella-induced pyretic tests with 150 mg kg⁻¹ acetaminophen serving as the comparative agent. Acute toxicity test was conducted on the herbal decoction via both oral and intraperitoneal routes to obtain its LD₅₀. The extract dose-dependently and significantly (p<0.05) inhibited writhing in the acetic acid test group. The effect produced by 200 mg kg⁻¹ extract (72.8 % inhibition), compared well with acetylsalicylic acid (66.6 %), but was much less than piroxicam (90.9 %). A prolongation in reaction time in the hot plate model produced by SMS recorded 68.9 % inhibition with the highest dose and 98.4 % with morphine. The extract produced dose-dependent and significant inhibition (p<0.05) of oedema, which was comparable to indomethacin in the carrageenan-induced paw oedema model. Similarly, SMS demonstrated a significant effect (p<0.05), compared to dexamethasone on the xylene-induced mouse ear oedema test. The extract significantly decreased the hyperthermic temperature in both d-amphetamine and Klebsiella-induced pyrexia as indicated by the percentage reduction in fever recorded. Findings from the present study showed SMS to possess central and peripheral analgesic activity, anti-inflammatory property similar to steroidal and non-steroidal agents as well as antipyretic effect. The presence of diverse secondary metabolites including flavonoids, glycosides, tannins, alkaloids and saponins could account for the wide therapeutic spectrum of SMS. LD₅₀ for oral and intraperitoneal routes were interpolated as 2187.8 and 549.5 mg kg⁻¹ respectively.

Keywords: Antiinflammatory, analgesic, antipyretic, medicinal plant, mice, rats

INTRODUCTION

Herbs are staging a comeback and herbal

'renaissance' is already a global experience. Herbal products symbolize safety in contrast to the synthetics that are regarded as unsafe to man and his environment. (Joy et al., 1998). *Strophanthus sarmentosus* (SMS) is a medicinal plant belonging to

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the family of Apocynaceae and is found mainly in tropical Africa extending to South Africa. It is known as *sagere* by the Yorubas and *Isage* by the Hausas in Nigeria. *Strophanthus sarmentosus*, a shrub widely distributed in West Africa has been employed locally for treating quite a number of ailments, including oligospermia, fever, inflammation and peptic ulcers.

Series of chemical studies had been carried out on *Strophanthus sarmentosus* (Euw et al., 1954, Fechtig et al., 1960) but no investigations has been reported about its pharmacological properties. The dearth of information on the scientific evaluation of this plant therefore, necessitated the present study, which was designed to evaluate the analgesic, anti-inflammatory and antipyretic activities of the ethanolic extract of the dried root, in order to explore the claims made by the indigenes, as well as elucidating its possible mechanisms of action, using different relevant standard experimental models.

MATERIALS AND METHODS

Plant material

The fresh roots of SMS were purchased from a local market in Mushin area of Lagos State, Nigeria. The plant was identified and authenticated by Dr. A. Adekunle of the Department of Botany and Microbiology, Faculty of Science, University of Lagos, Nigeria.

Experimental animals

Wistar rats (120-150 g) and Swiss albino mice (15-20 g) of either sex obtained from the Laboratory Animal Centre, University of Lagos, were employed in this study. They were all maintained under standard environmental conditions and fed on standard chow (Neimeth Livestock Feeds, PLC, Ikeja-Lagos, Nigeria), and given water *ad-lib*.

Extraction of plant

Pieces of the fresh plant roots were dried in shade for three weeks until a constant weight was obtained and thereafter ground into a coarse powder using a domestic blender. A known weight was extracted in absolute ethanol using the Soxhlet apparatus. The resultant extract was dried in an oven set at 40 °C and the residue weighed to determine the percentage yield.

One hundred gram (100 g) per ml of the dark brown extract with chocolate aroma gave a pH of 6.8.

Acute toxicity test

Toxicity of the plant extract was determined using the method of Miller and Tainter (1944). Mice were fasted for 12 h and administered orally different doses of the extract up to 4 g kg⁻¹ and control mice given 10 ml kg⁻¹ distilled water. Intraperitoneal route was also employed in the investigation with doses of 50-200 mg kg⁻¹ administered to six groups of mice (n=5).

All the treated animals were closely observed for toxic symptoms and behavioural changes for the first 2 h after administration and mortality recorded within 24 h. LD₅₀ was estimated using the log-dose vs probit plot analysis.

Preliminary phytochemical analysis

Presence of various compounds like alkaloids, saponins, tannins, phlobatannins, anthraquinones and simple sugars was evaluated using simple chemical tests outlined by (Odebiyi and Sofowora, 1978).

Test for Analgesia

Analgesic potential of the plant extract was assessed using two laboratory models as follows:

Mouse writhing test

Twenty five mice were randomly divided into groups of five animals each. Doses of 50-200 mg kg⁻¹ SMS were administered to the three groups while the remaining two groups received distilled water 10 ml kg⁻¹, acetylsalicylic acid (ASA) 150 mg kg⁻¹, and piroxicam 0.5 mg kg⁻¹ respectively (Koster et al., 1959; Salawu et al., 2008). All treatments were made through the oral route, and 30 min thereafter, 10 ml kg⁻¹ 0.6% acetic acid solution in normal saline was injected intraperitoneally. The number of writhes/stretches was counted for 30 min.

Hot plate model

Study was based on the method of (Hosseinzadeh et al., 2000). The hot plate at 55 ± 0.2 °C and the animals were placed into the Perspex cylinder on the heated surface and the time (sec) to discomfort reaction (licking paws or jumping) was recorded as response latency, prior to and 30, 60 and 120 min after oral administration of doses of the test agents-

Table 1: Effect of Ethanolic root extract of SMS on acetic acid-induced writhes in mice.

Drug/Dose (mg/kg)	No. of writhes \pm SEM /30 min	% Inhibition
Control	30.5 \pm 4.21	-
SMS 50	18.2 \pm 1.85*	40.3
SMS 100	12.0 \pm 1.36*	60.7
SMS 200	8.0 \pm 1.22*	72.8
ASA 150	10.2 \pm 1.00*	66.6
PXC 0.5	2.5 \pm 0.51*	91.8

* Significantly different from the control at $p < 0.05$

ASA=Acetylsalicylic acid

PXC=Piroxicam

10 ml kg^{-1} distilled water (control), 50, 100 and 200 mg kg^{-1} SMS and 5 mg kg^{-1} morphine sulphate (s.c). A latency period of 20 sec was defined as complete analgesia and the measurement was terminated if it exceeded the latency period in order to avoid injury.

Test for anti-inflammatory activity

Carrageenan-induced rat paw oedema

Similar doses of SMS used above were also employed in this study. The control group received distilled water 10 ml kg^{-1} while the standard drug indomethacin 10 mg kg^{-1} was given via oral cannulation. An hour after, oedema was induced in rats by injection of 0.1 ml freshly prepared carrageenan (1 % w/v in normal saline) into the sub-plantar tissue of the right hand paw of the rats (Winter et al., 1962; Agbaje et al., 200; Owoyele et al., 2008). The linear paw circumference was measured using the cotton thread method (Bamgbose and Noamesi, 1981). Measurements were made immediately (0 h) before injection of carrageenan and at 1 h interval for 5 h. The paw swelling at each time was calculated as the difference between the linear circumference at time C_t and at zero hour C_0 .

Xylene-induced ear oedema

Mice were allotted to five groups of 5 animals each. The animals were treated orally with the extract in doses of 50, 100 and 200 mg kg^{-1} ; dexamethasone, the standard drug (1 mg kg^{-1}) and distilled water (10 ml kg^{-1}) for the control group. One hour after therapy, oedema was induced in each mouse by applying a drop of xylene to the inner surface of the right ear. Three hours afterwards, the animals were humanely sacrificed and both ears cut-off to approximately equal size and weighed. The mean difference between the right and left ears were determined for each group and recorded as an indication of inflammation (Jumping et al., 2005).

Antipyretic effect

D-amphetamine-induced pyrexia

Rats were randomly divided into five groups of six animals each and their basal temperature was measured rectally using a digital thermometer. After three different readings, fever was induced by administering 5 mg kg^{-1} D-amphetamine i.p. Thirty minutes post-induction, the rectal temperature was measured and recorded and thereafter monitored every hour until appreciable rise in temperature (≥ 2 $^{\circ}\text{C}$) was observed.

Graded doses of the extract, 50-200 mg kg^{-1} were orally administered to three groups of rats while the remaining two received distilled water (10 ml kg^{-1}) and acetaminophen (150 mg kg^{-1}) respectively via the same route.

Rats were restrained for the recording of their rectal temperatures at interval of 1 h for the next 3 h.

Klebsiella pneumonia-induced pyrexia

The above procedure was repeated but induction of pyrexia was through the inoculation of 10^6 - 10^8 inoculum of *K. pneumonia* suspended in 0.9% normal saline

Statistical analysis

Data were expressed as \pm standard error of the mean (SEM). Student's t-test was used to determine the differences between groups and p values less than 0.05 were considered as indicative of significance.

RESULTS

Acute toxicity

LD₅₀ values were respectively interpolated as 2187.8 mg kg^{-1} and 549.5 mg kg^{-1} . Apart from mortality, the extract caused a reduction in motor activity, sedation

Table 2: Effect of SMS on thermally induced pain stimulus

Drug/Dose (mg/kg)	Time (min) / % Protection			
	0	30	60	90
Control	3.60±0.15	3.24±0.08	2.94±0.11	3.05±0.19
SMS 50	4.88±0.52	5.10±0.47 (4.5)	5.38±0.61* (10.25)	4.26±0.49
SMS 100	4.01±0.38	5.84±0.57* (40.1)	5.63±0.29* (45.6)	4.26±0.38 (6.23)
SMS 200	3.22±0.17	4.51±0.30* (40.4)	5.44±.38* (68.9)	5.05±0.53* (56.83)
Morphine 5	3.15±0.23	8.20±0.15* (71.4)	10.00±0.00* (96.0)	11.00±0.00* (98.4)

Results represent mean reaction time ± SEM; * Significant protection compared to control (p<0.05); % protection in parenthesis.

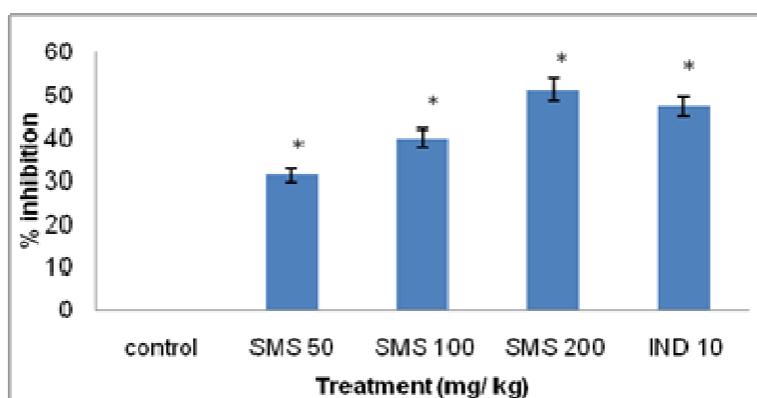


Figure 1: Percentage inhibition of test agents on carrageenan induced rat paw oedema 3hr post induction. Data represented as ± S.E.M. (n = 5) *p<0.05 as compared with the control group.

and increased respiratory rate.

Analgesic effect

Acetic-acid-induced mouse writhing test

A dose-dependent reduction in the number of writhes was produced by oral doses (50, 100, and 200 mg kg⁻¹) of the extract (Table 1 above). The highest dose of the herbal drug produced the most significant (p<0.05) effect, which superseded that of ASA but much less than piroxicam.

Hot plate test

Effect of SMS was observed to be dose dependent, but the peak activity was recorded 2 h post- drug therapy. However, the standard drug morphine offered a better protection against pain due to therm-

al stimulus (Table 2 above).

Anti-inflammatory activity

Carrageenan-induced rat paw oedema

Carrageenan induced a progressive swelling of the rat paw that reached the maximum (3.07± 0.12) after 3 h. The extract (50, 100 and 200 mg kg⁻¹), produced dose-dependent inhibition of the induced oedema with the greatest percentage inhibition of 51.2% effect observed at the dose of 200 mg kg⁻¹ (Figure.1 above). The standard drug indomethacin (10 mg kg⁻¹) produced 47.5 % inhibition.

Xylene-induced ear oedema

SMS in the various doses administered reduced the

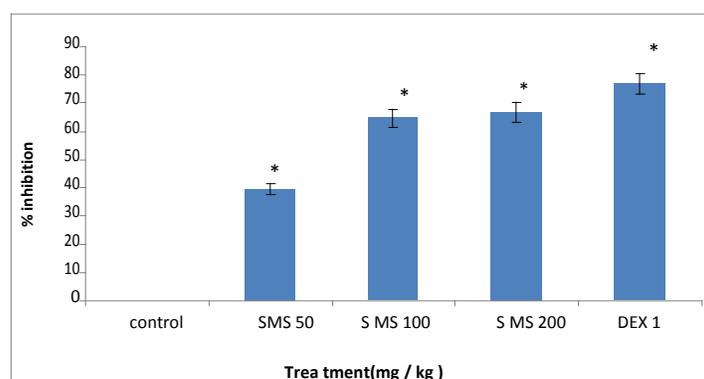


Figure 2: Percentage inhibition of test agents on xylene-induced mouse ear oedema. Data represented as \pm S.E.M. (n = 5) *p<0.05 as compared with the control group

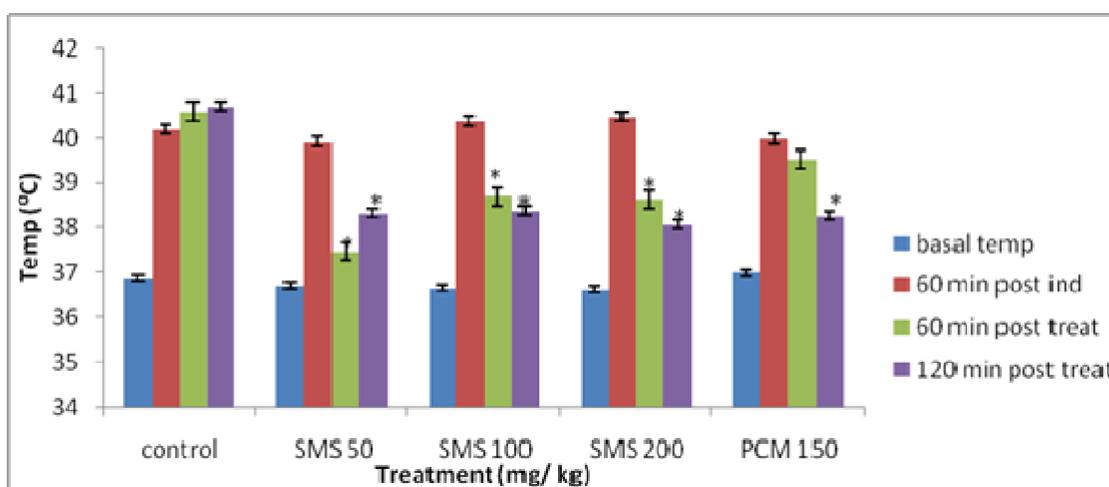


Figure 3: Effects of test agents on d-amphetamine induced pyrexia. Data represented as \pm S.E.M. (n = 5) *p<0.05 as compared with the control group

oedema-induced through topical application of xylene to the mouse ear. However, dexamethasone (1 mg kg^{-1}) produced a greater effect than the plant drug (Figure.2 below).

Antipyretic effect

D-amphetamine-induced pyrexia

The hyperthermic temperature was obtained at 1 h after the administration of D-amphetamine. The extract showed significant ($p<0.05$) and dose-dependent reduction of pyrexia. The time of onset of action of the herbal drug was observed to be faster than the standard drug and highest dose of SMS given produced a better antipyretic effect than acetaminophen (PCM) (Figure. 3 below). Neither drug could return body temperature to the basal level throughout the period of study.

Klebsiella pneumonia-induced pyrexia

The hyperthermic temperature was obtained one hour after the inoculation of pyrogen. The extract showed significant ($p<0.05$) and dose dependent reduction in the elevated body temperature (Figure. 4 below). Antipyretic effect of the highest dose of SMS compared well with PCM.

DISCUSSION

The aim of the present work was to validate the ethnobotanical uses of the root extract of SMS as an antipyretic, analgesic and anti-inflammatory agent. Inflammation is body's response to disturbed homeostasis caused by infection, injury or trauma and resulting in systemic and local effects.

In living animal tissues, inflammatory processes involve the release of several mediators including

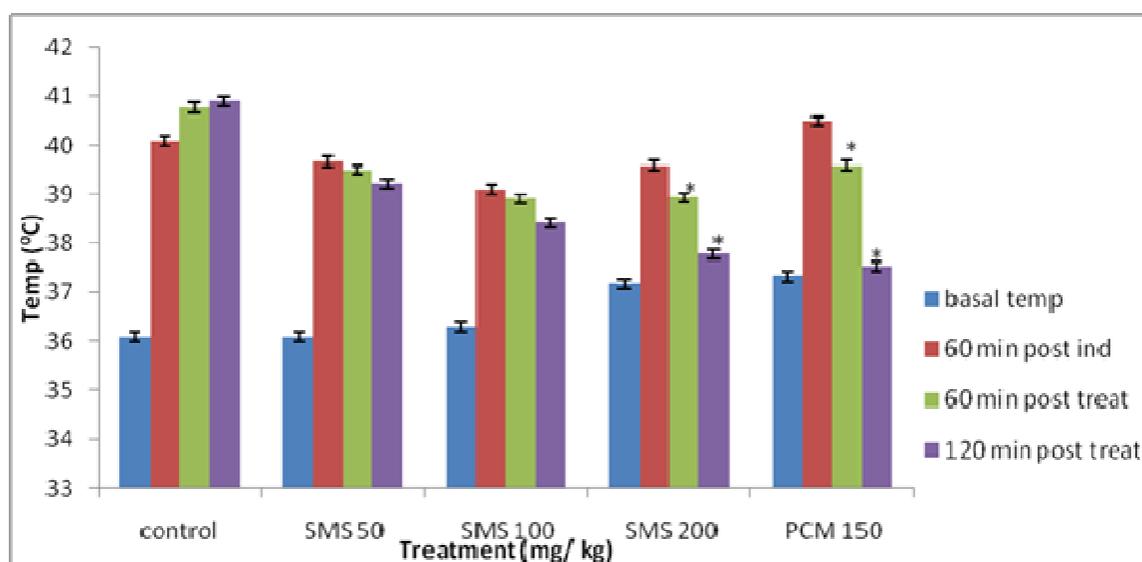


Figure 4: Effects of test agents on Klebsiella-induced pyrexia. Data represented as \pm S.E.M. ($n = 5$) $*p < 0.05$ as compared with the control group

prostaglandins, histamine, thermo-attractants, cytokines, proteinases, as well as substances that regulate adhesion of molecules and the processes of cell migration, activation and degranulation (Hollander et al., 2003; Ganesh et al., 2008).

Carrageenan-induced rat paw oedema is a suitable test for evaluating anti-inflammatory drugs and has frequently been used to assess the anti-oedematous effect of natural products (Panthong et al., 2003). Carrageenan is known to be devoid of apparent systemic effects and it is non-antigenic (Chakraborty et al., 2004) but offers a reproducible model for anti-inflammatory agent evaluation. Development of oedema in the paw of the rat after injecting the phlogistic agent is believed to be a biphasic mechanism (Vinegar et al., 1969; Patra et al., 2009), of which the first 1-2 h is due to the release of histamine or serotonin, while the second phase of oedema formation is due to the released prostaglandins/ protease and lysosome which peak at 3 h (Britto and Antonio, 1998; Saha et al., 2007; Agbaje and Adeneye, 2008). Pre-treatment of rats with the extract ($50-200 \text{ mg kg}^{-1}$) significantly inhibited the paw oedema induced by carrageenan when compared with the control group (Figure 1) and 200 mg kg^{-1} produced a better efficacy than the indomethacin-treated group. The mechanism of anti-inflammatory activity of SMS could be speculated to be through the inhibition of one or more of the released inflammatory mediators.

The xylene model usually investigates the role of phospholipase A₂ (PLA₂) in the pathophysiology of inflammation (Lin et al., 1992). Dexamethasone was used as the standard drug since the xylene-induced ear oedema is less sensitive to non-steroidal anti-inflammatory agents than steroidal anti-inflammatory drugs (Zaninir et al., 1992). A similar trend of oedema

inhibition recorded in the xylene-induced group (Figure 2), suggests the possible interaction of SMS with PLA₂ in its anti-inflammatory mechanism.

Pyrexia could be induced by tissue damage, inflammation, infections, malignancy and other disease-states. The infected or damaged tissue initiates the enhanced formation of pro-inflammatory mediators (cytokines e.g. interleukins and TNF- α), which increase the synthesis of prostaglandin E₂ near the pre-optic hypothalamic area, thereby triggering the hypothalamus to elevate body temperature (Spacer and Breder, 1994). Most of the antipyretics inhibit cyclooxygenase-2 expression, thus inhibiting PGE₂ biosynthesis and consequently reduce the elevated body temperature. The abdominal constriction response induced by acetic acid is a sensitive procedure to establish peripherally acting analgesics (Gene et al., 1998). Generally, acetic acid produces pain by liberating endogenous substances such as serotonin, histamine, prostaglandins, bradykinins and substance P, which stimulate nerve endings and local peritoneal receptors are involved in the abdominal constriction response (Bentley et al.,

1983). Usually, most anti-inflammatory drugs, especially the non-steroidal possess both analgesic and antipyretic properties; the significant reduction in acetic acid-induced writhes by the ethanolic extract of SMS, suggests that the analgesic effect may be peripherally mediated via the inhibition of synthesis and release of PGs and other endogenous substances (Salawu et al., 2008). The herbal drug at a dose of 200 mg kg^{-1} produced a better protection than acetylsalicylic acid, but less than piroxicam. The significant increase in pain threshold produced by SMS in the hot plate model suggests the involvement of central pain pathways. Pain is centrally modulated via a number of complex

processes including opiate, dopaminergic, descending noradrenergic and serotonergic systems (Pasero et al., 1999, Salawu et al., 2008). It is well established that thermal nociceptive tests are more sensitive to opioid μ -agonists (Abbott, 1988, Agbaje et al., 2008). The present study showed that SMS acts via both central and peripheral pathways, although a greater percentage inhibition was recorded in the hot plate model than in the acetic acid induced analgesia.

Unlike in the Klebsiella-induced pyrexia model, which involves the cyclooxygenase mechanism, the herbal drug produced a significant reduction in pyrexia induced with D-amphetamine compared with the standard drug PCM employed (Figures 3 and 4).

Amphetamine is an indirectly-acting sympathomimetic agent and the SMS effect at all doses administered suggests a possible antagonistic effect on endogenous catecholamines in the central adrenergic neurons. Further studies are required to establish the latter speculation.

The therapeutic benefits of traditional remedies are often attributed to a combination of active constituents (Chindo et al., 2003). For instance, flavonoids are known to target PGs involved in late phase of acute inflammation and pain perception (Rajnarayan et al., 2001) and they have therefore been linked with analgesic, anti-inflammatory and antipyretic activities (Mutalik et al., 2003, Venkatesh et al., 2003). It is not surprising therefore to have observed the three activities in SMS, since it contains flavonoids.

In conclusion, the ability of ethanolic extract of dried root of SMS to suppress abdominal writhes, increase reaction time in hot plate test, suppress both carrageenan induced and xylene induced inflammation, temperature induced by D-amphetamine and *K. pneumonia* indicates that the extract possesses analgesic, anti-inflammatory and antipyretic activities, acting through both central and peripheral pathways. The LD₅₀ obtained evidenced the relative safety of the herbal drug, coupled with its almost neutral pH of 6.8, which are both advantageous, compared with the most currently used drugs, especially, the NSAIDs.

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