

ANALGESIC AND ANTI - INFLAMMATORY ACTIVITY OF SAM COMPOUNDS IN EXPERIMENTAL ANIMALS

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ABSTRACT

Pain and inflammation are the common signs of tissue injuries, traumatic injuries, sprains, arthritis, gout etc. Many analgesics & Non – Steroidal Anti-inflammatory Drugs (NSAIDs) are available in the market used for the clinical treatment of inflammatory diseases. Most of them are known to produce untoward effects on a long run. *Ayurveda* explains a range of effective herbs which deals effectively with pain and inflammation. Hence polyherbal formulations named ‘SAM’ compounds (SAM 011, 011A & 011B) were taken for the current study to experiment & establish their analgesic and anti – inflammatory activity in rats and mice using three different preliminary models. Acetic acid induced writhing in mice, Eddys hot plate induced thermal pain for analgesic and Carrageenan induced rat paw oedema for anti-inflammatory study were selected for this preliminary screening. The results of the acetic acid induced model revealed that at a dose of 7.8 mg/kg p.o; the protective effect of SAM011 was 78.68% (P<0.05) when compared to SAM011A and SAM011B having 42.10% (P<0.05) and 65.51% (P<0.05) respectively. The results of the hot plate model revealed that at the same dose the percentage of protection of SAM011 was found to be 91.50% (P<0.5) compared to SAM011A and SAM011B each having percentage of protection of 75% (P<0.5) respectively. The results of the carrageenan induced oedema model revealed that at a dose of 270 mg/kg p.o; the percentage of protection of SAM011 was 60% (P<0.01) compared to SAM011A and SAM011B having percentage of protection of 40% (P<0.05) and 46.66% (P<0.05) respectively. From the above results it can be concluded that SAM011 has shown significant analgesic and anti – inflammatory activity compared to SAM011A & SAM011B respectively on three preliminary screening models of Analgesia & Inflammation.

Keywords: Analgesic, Anti-inflammatory, SAM Compound.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as analgesic or antipyretic agents for

the clinical treatment of inflammatory diseases. These agents exhibit an inhibitory action on the

cyclooxygenase that catalyzes the biosynthesis of prostaglandins and thromboxane from arachidonic acid. It has been also reported that reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical and peroxynitrite participate in the process of inflammation in various tissues [1]. In skin, ROS can be produced not only by chemical ionization and/or UV radiation but also enzymatically by polymorphonuclear leukocytes that infiltrate the sites of infection [2]. In both cases, the excessively produced ROS can injure cellular biomolecules such as nucleic acids, proteins, carbohydrates and lipids, causing cellular and tissue damage, which in turn augments the state of inflammation [3,4]. Although the synthesis of leukotrienes and prostaglandins has been reported to be involved in arachidonic acid [5], it has been assumed that ROS also play an important role in the edema formation in these models. As evidence in support of this hypothesis, several antioxidative compounds have been reported to show anti-inflammatory action either on arachidonic acid-induced ear edema or on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema [6].

In addition to their role in acute inflammation, ROS may also contribute to several chronic cutaneous inflammatory diseases such as psoriasis, atopic dermatitis, and contact dermatitis [7]. In a chronological sequence of reactions, various cytokines, which participate in the pathogenesis of inflammatory reactions, are produced. Therefore, compounds that have scavenging activities toward these radicals and/or suppressive activities on lipid peroxidation may be expected to have therapeutic potentials for several inflammatory diseases [1]. Cyclooxygenase products are well known to play an important role in pain, and it has been reported that extracellular calcium is involved in the formation of prostaglandins [8,9]. Prostaglandins have been reported to act as a Ca^{2+} ionophore, through L-type voltage-sensitive calcium channels in brain synaptosomes [10]. Peripheral sensory stimulation has

been reported to induce prostaglandin release from the cerebral cortex [11].

Most clinically important medicines belong to steroidal or non-steroidal anti-inflammatory chemical therapeutics for treatment of inflammation related diseases. Though these have potent activity, long-term administration is required for treatment of chronic disease. Furthermore, these drugs have various and severe adverse effects. Therefore, the present study has planned to carry out the SAM compounds of Ayurvedic products for analgesic and anti-inflammatory activity in experimental animals.

MATERIALS AND METHODS:

Collection of sample:

Sample of coded drug "SAM011", "SAM011A" and "SAM 011B" were collected from sponsor Sriveda Sattva Private Limited, 21st KM, Kanakapura road, Udayapura, Bangalore-560082.

Experimental Animals

Adult wistar albino rats (150-200 g) and swiss albino mice (25-30 g) of either sex were obtained from Sri Raghavendra Enterprises, Bangalore, India. Maintained under standard in-house conditions and they were given a standard pellet diet and water *ad libitum*. All experiments were carried out in accordance with the guidelines laid down by the Institutional Animal Ethical Committee (IAEC/ABMRCP/2014-2015/11).

Acute Oral Toxicity study

Test drugs 'SAM011', 'SAM011A' and 'SAM011B' were screened for acute oral toxicity study. The study was performed according to OECD 425 guidelines. The test formulations were made in to fine suspension with vehicle (gum acacia) with suitable concentrations. All the animals were subjected to overnight fasting before the day of dosing. The rats were weighed and the dose was calculated in reference to the body weight. The animals were distributed into five groups. Animals were dosed constant dose volume (1 ml/ 100g body

weight) and administered single dose orally at a dose of 175, 550, 2000 mg/kg body weight by using oral feeding needle sleeved on to disposable syringe.

Analgesic activity

Acetic acid induced writhing in mice

Swiss albino mice were randomly divided into five groups consisting of six animals per group. Group-I (Control) received 1% w/v of CMC (1 ml/kg, p.o.). Group II, III and IV received SAM011, SAM011A and SAM011B respectively. Group-V was treated with standard drug Diclofenac sodium (10 mg/kg, p.o.); after 30 min each mice received 1% v/v of acetic acid (0.1 ml/10 gm, i.p). The number of writhing as abdominal constriction, trunk twisting, and hind limb extension was cumulatively counted every 10 min over a period of 20 min immediately after the acetic acid injection. The analgesic activity was expressed as percentage of inhibition of writhing.

Eddys hot plate induced thermal pain

The mice were placed on hot-plate maintained at $55^{\circ}\text{C} \pm 1^{\circ}\text{C}$ and the time between placement of the mouse on the platform and licking of the paws or jumping was recorded as the hot-plate latency. Mice with baseline latency higher than 10 second were eliminated from the study. Twenty-four hours later Group-I (Control) received 1% w/v of CMC (1 ml/kg, p.o.). Group II, III and IV received SAM011, SAM011A and SAM011B respectively. Group-V was treated with standard drug Diclofenac sodium (10 mg/kg, p.o.). Reaction time was measured after 30 min of drug administration.

Anti-inflammatory activity

Carrageenan induced rat paw oedema

The albino rats were randomly divided into five groups consisting of six animals per group. Group-I

(Control) received 1% w/v of CMC (1 ml/kg, p.o.). Group II, III and IV received SAM011, SAM011A and SAM011B respectively. Group-V was treated with standard drug Diclofenac sodium (10 mg/kg, p.o.). Subsequently 30 min after above treatment, 0.1 ml of 1% w/v of carrageenan was injected subcutaneously into the planter region of right hind paw to induce oedema. The paw volume was measured at 0, 2, 3, 4, 6 and 24 h after carrageenan administration using plethysmometer and percentage of inflammation was calculated.

Statistical analysis

Values were expressed in mean \pm S.E.M. The data were analyzed by one way ANOVA followed by Student's 't' test. P values lower than 0.05 were considered as statistically significant and those of $p < 0.01$ and $P < 0.001$ were highly significant.

RESULTS:

Acute Oral Toxicity study

Physical and behavioral examination:

There were no physical and behavioral changes-except observation of mild analgesia at 2000mg/kg in all the treated animals on day one at 1,2,3,4 hour intervals after dosing and thereafter once daily for 14 consecutive days. Thus the data obtained from the study on single dose administration of coded drugs SAM011, SAM011A and SAM011B oral administration up to 14 days of observation period does not result in any physical and behavioral changes. Parameters observed before and after the administration of the test substance are shown in Table 1.

Mortality:

All the animals belonging to the treated group survived throughout the 14 days observation period after dosing.

Table 1: Sign and symptoms during gross behavioral study

Signs & symptoms	Head (175mg/kg)		Neck (550mg/kg)		Back (2000mg/kg)		Base of tail (2000mg/kg)		No mark (2000mg/kg)	
	Before	After	Before	After	Before	After	Before	After	Before	After
General impression	N	N	N	N	N	N	N	N	N	N
Increased motor activity	A	A	A	A	A	A	A	A	A	A
Convulsion	Tonic	A	A	A	A	A	A	A	A	A
	Clonic	A	A	A	A	A	A	A	A	A
Straubs reaction	A	A	A	A	A	A	A	A	A	A
Muscle spasm	A	A	A	A	A	A	A	A	A	A
Catatonnia	A	A	A	A	A	A	A	A	A	A
Opisthotonus	A	A	A	A	A	A	A	A	A	A
Hyperaesthesia	A	A	A	A	A	A	A	A	A	A
Decreased motor activity	A	A	A	A	A	A	A	A	A	A
Muscle relaxation	A	A	A	A	A	A	A	A	A	A
Anaesthesia	A	A	A	A	A	A	A	A	A	A
Arching and rolling	A	A	A	A	A	A	A	A	A	A
Lacrimation	A	A	A	A	A	A	A	A	A	A
Diarrhoea	A	A	A	A	A	A	A	A	A	A
Writhing	A	A	A	A	A	A	A	A	A	A
Salivation	Viscid	A	A	A	A	A	A	A	A	A
	watery	A	A	A	A	A	A	A	A	A
Resira tion	Stimulation	A	A	A	A	A	A	A	A	A
	Depression	A	A	A	A	A	A	A	A	A
	Failure	A	A	A	A	A	A	A	A	A
Skin colour	Blanching	A	A	A	A	A	A	A	A	A
	Cyanosis	A	A	A	A	A	A	A	A	A
	Vasodilatation	A	A	A	A	A	A	A	A	A
Grip strength	N	N	N	N	N	N	N	N	N	N
Visual placing response	N	N	N	N	N	N	N	N	N	N
Tail pinch response	N	N	N	N	N	N	N	N	N	N
Auditory response	N	N	N	N	N	N	N	N	N	N
mucus membrane	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N

N= Normal, A = Absent.

Acetic acid induced writhing in mice

The results revealed that SAM011 significantly reduced writhing induced by 1% v/v of acetic acid at a dose of 7.8 mg/kg, *p.o.* (Table 2). The significant protective effect with SAM011 was 78.68 % (P <0.05) reduction observed in early phase compared

with control. The significant protective effect with SAM011A and SAM011B were 42.10% (P <0.05) and 65.51 % (P < 0.05) reduction respectively. Diclofenac (10 mg/kg, *p.o.*) had 89.73 % (P < 0.01) inhibition acting as analgesic.

Table 2: Effect of SAM011, 011A, 011B and Diclofenac on writhing induced by acetic acid

Group	Dose (mg/kg,p.o)	No. of Writhing			
		Early phase (0-10 min)	Percentage protection (%)	Late phase (10-20 min)	Percentage protection (%)
Control (CMC)	5 ml/kg	66.33 ± 4.91	0	106.5 ± 9.22	0
SAM011	7.8	13.5 ± 3.69**	78.68	38.5 ± 8.00**	63.84
SAM011A	7.8	36.6 ± 6.93**	42.10	53.5 ± 9.74**	49.76
SAM011B	7.8	21.83 ± .02**	65.51	47.67 ± .64**	55.23
Diclofenac	10	6.5 ± 4.20**	89.73	35.33 ± .06**	66.82

Data were presented as mean ± S.E.M. Statistical differences between control and treated groups were tested by one way ANOVA followed by Student's t-test. The differences were considered significant at $P < 0.05$, $P < 0.01$.

Eddys hot plate induced thermal pain

The results of the hotplate test (Table 3) revealed that the reaction time for the mice was significantly increased from 2.0 to 3.83 seconds (SAM011) at dose of 7.8 mg/kg, p.o. with protection found to be 91.50% ($P < 0.5$) at 30 min. Pretreatment with SAM011A (7.8 mg/kg, p.o.) and SAM011B (7.8

mg/kg, p.o.) increased reaction time from 2.0 to 3.50 seconds and 2.0 to 3.50 seconds respectively with percentage protection found to be 75% ($P < 0.5$) at 30 min. Diclofenac (10 mg/kg, p.o.) significantly showed maximum protective effect of 100% ($P < 0.01$) at 30 min compared to control.

Table 3: Effect of SAM011, 011A, 011B and Diclofenac on pain induced by hotplate

Group	Dose (mg/kg,p.o)	Jump response (At 30 min)	Percentage protection	Jump response (At 60 min)	Percentage protection
Control (CMC)	5 ml/kg	2.0 ± 0.36	0	2.0 ± 0.25	0
SAM011	7.8	3.83 ± 0.54*	91.5	3.16 ± 0.40	58
SAM011A	7.8	3.5 ± 0.34*	75	3.33 ± 0.33	66.5
SAM011B	7.8	3.5 ± 0.42*	75	3.16 ± 0.74	58
Diclofenac	10	4.0 ± 0.25**	100	3.83 ± 0.65	91.5

Data were presented as mean ± S.E.M. Statistical differences between control and treated groups were tested by one way ANOVA followed by Student's t-test. The differences were considered significant at $P < 0.05$, $P < 0.01$.

Carrageenan induced rat paw oedema

The average right paws volumes of oedema are presented in Table 4. The percentages of inhibition are reported in Table 5. For the control group, the injection of the carrageenan caused localised oedema, after 30 mins. The swelling increased progressively after 3 h to a maximum volume of 0.018 ml and remained obvious 24 hours after injection. Rats pretreated with SAM011 (270 mg/kg, p.o.), significant decreased carrageenan-induced oedema at 6 hr (0.006 ± 0.001) ml was found to be

60 % ($P < 0.01$). Whereas SAM011A (270 mg/kg, p.o.) and SAM011B (270 mg/kg, p.o.) achieved significant reduction in paw oedema at 6 hr were found to be 0.009 ± 0.002 ml (40 %, $P < 0.05$) and 0.008 ± 0.002 ml (46.66 %, $P < 0.05$) continued for 24 h (9.09 %, $P < 0.05$). Diclofenac (10 mg/kg, p.o.) attained their maximal effects at 6 hr was found to be 0.004 ± 0.001 ml (73.33 %, $P < 0.001$). Although both the SAM and Diclofenac reduced the swellings, they still remain significantly visible after 24 hours.

Table 4: Effect of SAM011, 011A, 011B and Diclofenac on carrageenan-induced oedema

Treatment	Dose (mg/kg,p.o)	Paw odema (ml)						
		0 h	1 h	2 h	3 h	4 h	6 h	24 h
Control	-	0.01 ± 0.000	0.012 ± 0.002	0.014 ± 0.002	0.018 ± 0.002	0.016 ± 0.002	0.015 ± 0.002	0.011 ± 0.001
SAM011	270	0.01 ± 0.000	0.012 ± 0.002	0.011 ± 0.002*	0.009 ± 0.002**	0.007 ± 0.002**	0.006 ± 0.001**	0.01 ± 0.007*
SAM011A	270	0.01 ± 0.000	0.012 ± 0.002	0.012 ± 0.002	0.011 ± 0.002**	0.011 ± 0.002*	0.009 ± 0.002*	0.01 ± 0.000*
SAM011B	270	0.01 ± 0.000	0.012 ± 0.001	0.012 ± 0.001	0.011 ± 0.002**	0.009 ± 0.002**	0.008 ± 0.002**	0.01 ± 0.001**
Diclofenac	10	0.01 ± 0.000	0.011 ± 0.001	0.009 ± 0.001**	0.009 ± 0.002**	0.006 ± 0.002**	0.004 ± 0.001***	0.009 ± 0.001*

Data were expressed as mean ± S.E.M. Statistical differences between control and treated groups were tested by one way ANOVA followed by Student's t-test. The differences were considered significant at P < 0.05, P < 0.01, P < 0.001.

Table 5: Percentage protection of SAM011, 011A, 011B and Diclofenac on carrageenan- induced oedema

Treatment	Dose (mg/kg,p.o)	Percentage protection (%)					
		0 h	2 h	3 h	4 h	6 h	24 h
Control	-	-	-	-	-	-	-
SAM011	270	0	21.42	50.00	56.25	60.00	9.09
SAM011A	270	0	14.28	38.88	31.25	40.00	9.09
SAM011B	270	0	14.28	38.88	43.76	46.66	9.09
Diclofenac	10	0	35.71	50.00	62.5	73.33	18.81

DISCUSSION

Medicinal plants have been an indispensable arm in ameliorating common inflammation, pain sensation as well as nociception.^[12] According to our findings, the SAM samples showed analgesic effect when assessed in chemical model of nociception in acetic acid-induced writhing test. In acetic acid-induced writhing test, a maximum analgesic effect of the SAM011 was observed. It is proposed that the acetic acid acts indirectly by inducing the release of endogenous mediators which stimulate the nociceptive neurons sensitive to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids^[13]. Acetic acid-induced abdominal constrictions are useful experimental tools in the testing of new analgesic drugs^[14] because the abdominal injection of acetic acid in mice has been attributed to the release of arachidonic acid, which results the

synthesis of prostaglandin *via* the cyclooxygenase enzyme^[15]. The special nerve endings that sense pain is very sensitive to prostaglandin. When prostaglandin is released, the nerve endings respond to it through prostaglandin E₂ receptor by picking up and transmitting the pain and injury messages to the brain and cause visceral writhing stimuli in mice^[16-18]. Therefore, it has been suggested that the inhibition of prostaglandin synthesis is remarkably an efficient analgesic mechanism in visceral pain^[19]. Since SAM011 in present study shows inhibition in acetic acid-induced pain in mice.

The significant increase in pain threshold produced by tests and standard in these models suggests involvement of central pain pathways. Pain is centrally modulated via a number of complex processes including opiate, dopaminergic descending noradrenergic and serotonergic

systems.^[20-22] The analgesic effect produced by the tests and standards may be via central mechanisms involving these receptor systems or via peripheral mechanisms involved in the inhibition of prostaglandins, leukotrienes, and other endogenous substances that are key players in pain.

Anti-inflammatory activity through carrageenan induced paw edema is a suitable test for evaluating anti-inflammatory properties for natural drugs because it shows very promising sensitivity, particularly in the acute phase of inflammation, in detecting orally active anti-inflammatory agents^[23]. Development of edema in the paw of rat after injection of carrageenan is a discrete biphasic event^[24], the initial phase of which is observed during the first hour attributed to the release of histamine and serotonin whereas the second phase of edema is due to the release of prostaglandins, protease, and lysosome^[25,26,27]. This leads to a dilation of the arterioles and venules and to an increased vascular permeability. As a consequence, fluid and plasma proteins are extravagated, and edema forms^[28]. The mediators, including histamine, 5-HT, the kinins and their complements, therefore, have become the recent focus of attention as they are the metabolites of arachidonic acid (AA). Alone or in appropriate combination, AAs are capable of producing the characteristic signs of inflammation which subsequently produces vasodilatation, hyperemia, pain, edema, and cellular filtration. SAM samples exhibit its anti-inflammatory action probably by means of either inhibiting the synthesis, release or action of inflammatory mediators like histamine, serotonin, prostaglandin, protease, and lysosome. SAM011 is sold in the name of *Sandhimitra vati* and all others are market samples taken for the study.

CONCLUSION

The non toxic nature of the coded drug SAM011 is evident from the acute oral toxicity conducted as per OECD guidelines. The normal behavior and mortality of the test animals during a period of 14 days suggests the non-toxic nature of the drug. Thus

it could be concluded that the test drug is without any toxic potential even at the dose of 2000mg/kg in animals which is equivalent to 22.4g for human being. This dose in human being is 7.4 fold higher in comparison to normal human dose of 3g per day.

All SAM compounds show analgesic in mice and anti-inflammatory activity in rats. However, SAM011 exhibit significant increase in analgesic activity by acetic acid induced and hot plate induced thermal pain compared to SAM011A and SAM011B. In addition, SAM011 achieved maximum percentage protection against carrageenan induced paw oedema compared to SAM011A and SAM011B.

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