

Analgesic, Anti-pyretic and Anti-inflammatory Activity of Dietary Sesame Oil in Experimental Animal Models

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Abstract: Background: Inflammation and pain were associated with most of the life threatening diseases. Treatment for these conditions by available drugs producing promising therapeutic effect with more unwanted effects. To avoid this problem search of newer and alternative therapy is getting important. Sesame oil is one of the best nutrients with more therapeutic option. **The context and purpose of the study:** The present research was undertaken to find out the analgesic, antipyretic and anti-inflammatory activity of sesame oil (5, 10 mL kg⁻¹ b.wt.) in experimental animals. **Results:** Antipyretic activity was determined by yeast induced pyrexia in rats. Sesame oil produced significant antipyretic (p<0.001) when compared with paracetamol. Analgesic and anti-inflammatory activity in few experimental models tested. Incomparable analgesic activity was found in the hot plate, acetic acid induced writhing and formalin induced pain model and it shows dose dependent activity also. In acetic acid induced writhing test the maximum percentage inhibition activity (45%) was produced by 10 mL treated mice. **Conclusion:** These initial findings confirm its therapeutic value against various pain and inflammatory diseases.

Key words: Sesame oil, anti-inflammatory, pain, analgesics, dietary nutrition, carrageenan

INTRODUCTION

Inflammation is a defensive reaction of the local microcirculation to tissue injury arising from cell damages due to mechanical trauma, chemical, physical and thermal injury, antigen antibody reactions and infections. The signs and symptoms of inflammation include redness, swelling, heat, pain and loss of function of the affected area (Ferrero-Miliani *et al.*, 2007). Pain is an unpleasant sensation that is a consequence of complex neurochemical processes in the central and peripheral nervous systems. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are used in management of mild to moderate and severe pains respectively. These drugs have serious limitations due to their side effects (Mycek *et al.*, 2006). Most of the drugs used presently for the management of pain and inflammation possess some side and toxic effects (Ahmad *et al.*, 1992). It is therefore, inevitable to search for new, less toxic and more effective antiinflammatory and analgesic agents.

From ancient time globally the peoples were using the sesame oil as dietary source. Sesame oil is known dietary source having putative antioxidant property (Gauthaman and Saleem, 2009). Sesame oil, derived from

the seeds of plant species of *Sesamum indicum* belongs to family Pedaliaceae, consists of various fatty acids and nonfat antioxidants, including tocopherol, sesamin, sesamol and sesamol (Fukuda, 1990). It helps regulate the body's immune and auto immune system balance. It inhibits a set of regulating compounds which cause inflammation, clotting and other immune imbalances that contribute to disorders such as heart disease and autoimmune joint disorders. Consumption of sesame oil as dietary source may help to enhance antioxidant defense system in humans (Gauthaman and Saleem, 2009). Sesame seeds and oil have long been categorized as traditional health food in India and other East Asian countries. Sesame oil has been found to contain considerable amounts of the sesame lignans: sesamin, episesamin and sesamol. The lignans present in sesame oil are thought to be responsible for many of its unique chemical and physiological properties, including its antioxidant and antihypertensive properties (Sankar *et al.*, 2006). Up to our knowledge no one is reported the anti-inflammatory and analgesic activity of sesame oil. So, the present research was undertaken to find out the analgesic, antipyretic and anti-inflammatory activity of sesame oil by using experimental animals.

MATERIALS AND METHODS

Animals: Wistar albino rats weighing about 150-200 g and Swiss albino mice weighing about 25-30 g were obtained from institute animal center, ANCP, Rajampet and used in the experiments. The protocol was approved by the Institute's Animal Ethical Committee. Animals were kept in animal house at an ambient temperature of 25°C and 45-55% relative humidity with 12 h each of dark and light cycles. Animals were fed pellet diet and water ad-libitum. A CPCSEA guideline for laboratory animal facility (IJP 2003; 35: 257-274) was followed.

Drugs: Sesame oil and other drugs were used for this study were procured from local market.

Test for antipyretic activity

Yeast-induced pyrexia: Twenty four male Wistar albino rats were divided into 4 groups of 6 rats each and fasted for 24 h but allowed water *ad libitum*. At zero hour, the basal temperature of the rats was taken using digital clinical thermometer. Thereafter, each animal was administered subcutaneously with 15% w/v aqueous suspension of yeast at a volume of 10 mL kg⁻¹. Nineteen h after yeast injection, the rectal temperature was recorded again and animal showing a rise in temperature of <0.6°C was discarded (Mukherjee *et al.*, 2002). There after, treatment was carried out as follows: The first group was given 10 mL kg⁻¹ of Normal saline orally and served as control, groups 2 received sesame oil 5 mL kg⁻¹ p.o., groups 3 received sesame oil 10 mL kg⁻¹ p.o. and groups 4 received Paracetamol 10 mg kg⁻¹ i.p. Rectal temperatures were then recorded at 20, 22, 24 h (T°C) after yeast injection.

Test for anti-nociceptive study

Acetic acid induced writhing reaction in mice: The acetic acid induced writhing test in mice as described by Koster *et al.* (1959) was employed. Twenty four Swiss albino mice were divided into 4 groups of 6 mice each. The first group was given 10 mL kg⁻¹ of normal saline orally and served as control, group 2 received sesame oil 5 mL kg⁻¹ p.o., group 3 received sesame oil 10 mL kg⁻¹ p.o. and group 4 received Diclofenac sodium 10 mg kg⁻¹ i.p. Thirty minutes later, mice in all the groups were treated with Acetic acid (0.6% v/v, 1 mL per 100 g body weight i.p.). Five minutes after acetic acid injection mice were placed in individual cage and the number of abdominal contractions was counted for each mouse for a period of 10 min. Percentage inhibition of writhing was calculated using the formula:

$$\text{Inhibition (\%)} = \frac{\text{Mean No. of writhings (control)} - \text{Mean No. of writhings (test)}}{\text{Mean No. of writhing (control)}} \times 100$$

Formalin-induced paw licking in mice: Twenty four Swiss albino mice were divided into 4 groups of 6 mice each. The first group was given 10 mL kg⁻¹ of Normal saline i.p. and served as control, group 2 received sesame oil 5 mL kg⁻¹ p.o., group 3 received sesame oil 10 mL kg⁻¹ p.o. and group 4 received Diclofenac sodium 10 mg kg⁻¹ i.p. Thirty minutes later, mice in all the groups were treated with Acetic acid (0.6% v/v, 1 mL per 100 g body weight i.p.). The animals were fasted for 24 h and pretreated with sesame oil and Diclofenac sodium in respective doses before being challenged with buffered formalin. Twenty microlitres of 2.5% formalin solution (0.9% of formaldehyde) made up in phosphate buffer solution (PBS, concentration NaCl -137 mM, KCl 2.7 mM and phosphate buffer 10 mM) was injected subcutaneously under the surface of the right hind paw of each mice and the responses were observed for 15 and 30 min. The control animals were given 10 mL kg⁻¹ of saline orally. The amount of time spent licking the injected paw was timed and was indicative of pain. The first phase of the analgesic activity normally peaked at 5 min after formalin injection and the second phase 15-30 min after formalin injection, representing the neurogenic and inflammatory pain responses, respectively.

Thermally-induced pain in mice: The effect of the sesame oil on hot plate-induced pain was investigated in mice. The hot plate test was used to measure the response latencies according to the method of Vaz *et al.* (1996). Twenty four Swiss albino mice were divided into 4 groups of 6 mice each. The first group was given 10 mL kg⁻¹ of Normal saline orally and served as control, group 2 received sesame oil 5 mL kg⁻¹ p.o., group 3 received sesame oil 10 mL kg⁻¹ p.o. and group 4 received Diclofenac sodium 10 mg kg⁻¹ i.p. Thirty minutes later, mice in all the groups were treated with acetic acid (0.6% v/v, 1 mL per 100 g body weight i.p.). The animals were fasted for 24 h but allowed water ad libitum before used in the experiment. The animals were fasted for 24 h and pretreated with sesame oil and Diclofenac sodium in respective doses 30 min prior to the placement on the hot plate. In these experiments, the hot plate was maintained at 55±1°C. Animals were placed into a glass beaker of 50 cm diameter on the heated surface and the time between placement and shaking or licking of the paws or jumping was recorded as the index of response latency. An automatic 15s cut-off was used to prevent tissue damaged.

Test for anti-inflammatory activity

Anti-inflammatory activity by carrageenan induced rat paw edema method: Anti-inflammatory activity was assessed by the method described by Winter *et al.* (1962). Twenty four male Wistar albino rats were divided into 4 groups of 6 rats each and fasted for 24 h but allowed water *ad libitum*. The first group was given 10 mL kg⁻¹ of normal saline orally and served as control, group 2 received sesame oil 5 mL kg⁻¹ p.o., group 3 received sesame oil 10 mL kg⁻¹ p.o. and group 4 received Diclofenac sodium 10 mg kg⁻¹ i.p. Subsequently 1 h after treatment; 0.1 mL of 1% suspension of carrageenan in normal saline was injected into the subplanter region of left hind paw to induce edema. The paw volume was measured initially at 0, 1, 2, 3 and 4 h after carrageenan injection using plythismograph. The difference between the initial and subsequent values gave the actual edema volume which was compared with control. The inhibition of inflammation was calculated using the formula:

$$\% \text{ inhibition} = 100 \frac{V_c - V_t}{V_c}$$

where, V_c represents edema volume in control and V_t edema volume in group treated with test.

Formalin induced arthritis in rats: Twenty four male Wistar albino rats were divided into 4 groups of 6 rats each and fasted for 24 h but allowed water *ad libitum*. The rats were treated up to 10 days as per treatment protocol follows: The first group was given 10 mL kg⁻¹ of normal saline orally and served as control, group 2 received sesame oil 5 mL kg⁻¹ p.o., group 3 received sesame oil 10 mL kg⁻¹ p.o. and group 4 received Diclofenac sodium 10 mg kg⁻¹ i.p. Formalin (0.1 mL of 2% solution) was injected in the subplantar tissue of the right hind paw on 1st and 3rd day (Seyle, 1949). The paw volume was measured at daily using plethysmometer. The mean increase in the paw volume of all the groups over a period of 10 days was calculated and compared. The percentage inhibition of edema is calculated using following formula:

$$\text{Percentage inhibition of edema} = \frac{V_c - V_t}{V_c} \times 100$$

where, V_t and V_c are the volume of edema in control and drug treated rats

Statistical analysis: Data analysis was carried out using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison tests by using Graphpad prism version 5.01. p<0.05 was considered statistically significant.

RESULTS

Antipyretic activity: The result of antipyretic activity of sesame oil was present in Fig. 1. There was a progressive reduction in rectal temperature in sesame oil treated and paracetamol treated rats. At 24th h (T24) we found that a significant (p<0.001) reduction in rectal temperature in all the treatment groups when compared with 19th h (T19).

Thermally (Hot plate) induced pain in mice: The effect of the sesame oil on hot plate induced pain is shown in Table 1. Mice pretreated with sesame oil (5, 10 mL kg⁻¹, p.o.) demonstrated a dose-dependent increase in latency of response in the hot plate test. The increase in the latency of response (analgesic effect) were statistically significant (p<0.001) and were incomparable to that of the standard drug, Diclofenac sodium (10 mg kg⁻¹). Particularly at 180 min sesame oil treated rats at the dose of 5 mL kg⁻¹ was retained the activity when compared with the dose of 10 mL kg⁻¹.

Formalin induced hind paw licking in mice: The result of the effect of the sesame oil against formalin induced hind paw licking in mice is shown in Table 2. The sesame oil (5, 10 mL kg⁻¹) pretreated animals showed a significant (p<0.01, 0.001) dose-related reduction of hind paw licking caused by formalin when compared to control and were incomparable to that of the standard drug, Diclofenac sodium (10 mg kg⁻¹). Sesame oil treated with the dose of 10 mL kg⁻¹ shows better activity when compared with other groups.

Acetic acid induced writhing in mice: The result of the effect of the sesame oil against acetic acid induced writhing in mice is shown in Table 3. The sesame oil (5, 10 mL kg⁻¹) dose dependently reduced acetic acid

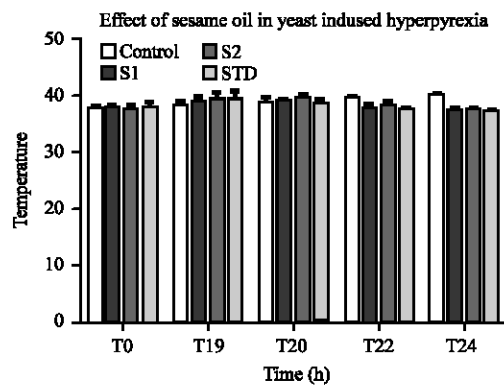


Fig. 1: Antipyretic effect of sesame oil

Table 1: Analgesic activity of sesame oil in thermally induced pain in mice

Treatment	Basal reaction time in seconds in every time period (min)					
	0	30	60	120	180	240
Control saline 10 mL kg ⁻¹ p.o.	4.5±0.33	3.5±0.33	3.2±0.07	4.5±0.33	3.2±0.07	3.5±0.33
Sesame oil 5 mL kg ⁻¹ p.o.	4.5±0.33	4.5±0.33 ^{ns}	6.5±0.33 ^{***}	10.5±0.33 ^{***}	10.0±1.36 ^{***}	4.3±0.91 ^{ns}
Sesame oil 10 mL kg ⁻¹ p.o.	3.2±0.07	4.5±0.33 ^{ns}	6.1±0.64 ^{**}	10.83±0.57 ^{***}	6.5±0.33 [*]	5.5±0.33 ^{ns}
Diclofenac sodium 10 mg kg ⁻¹ i.p.	3.5±0.33	9.4±1.45 ^{***}	10.0±0.68 ^{***}	10.5±1.02 ^{***}	14.0±0.68 ^{***}	4.0±0.68 ^{ns}

Values are expressed as Mean±SEM. *p<0.05, **p<0.01 and ***p<0.001 when compared with control. ns: Non significant

Table 2: Analgesic activity of sesame oil in formalin induced pain in mice

Treatment	No. of paw licking (min)	
	0-5	15-30
Control saline 10 mL kg ⁻¹ p.o.	29.67±0.14	13.25±0.42
Sesame oil 5 mL kg ⁻¹ p.o.	21.75±0.44	7.75±0.32 ^{**}
Sesame oil 10 mL kg ⁻¹ p.o.	18.75±0.44	1.25±0.33 ^{***}
Diclofenac sodium 10 mg kg ⁻¹ i.p.	24.25±0.44	9.25±0.44 ^{**}

Values are expressed as Mean±SEM. **p<0.01 and ***p<0.001 when compared with control

Table 3: Analgesic activity of sesame oil in acetic acid induced writhing response in mice

Treatment	No. of writhing	Percentage inhibition
Control saline 10 mL kg ⁻¹ p.o.	13.67±0.49	----
Sesame oil 5 mL kg ⁻¹ p.o.	8.83±0.79 [*]	35
Sesame oil 10 mL kg ⁻¹ p.o.	7.83±0.79 [*]	43
Diclofenac sodium 10 mg kg ⁻¹ i.p.	7.16±0.47 [*]	48

Values are expressed as Mean±SEM. *p<0.0001 when compared with control

induced abdominal constrictions and stretching of hind limbs. The reduction was significant (p<0.0001) when compared to control. The effect of the extract was comparable to that of the standard drug, Diclofenac sodium (10 mg kg⁻¹).

Carrageenan induced paw edema in rats: The result of the effect of sesame oil on carrageenan-induced oedema is shown in Table 4. The sesame oil exerted a significant (p<0.001) anti-inflammatory effect at the dose of 5, 10 mL kg⁻¹ and was incomparable to that of the standard drug, Diclofenac sodium (10 mg kg⁻¹). The percentage inhibition activity of sesame oil (5, 10 mL kg⁻¹) and Diclofenac sodium 10 mg kg⁻¹ were found to be 63, 55 and 68%, respectively.

Formalin induced arthritis in rats: The result of the effect of sesame oil on formalin induced arthritis in rats is shown in Table 5. The sesame oil exerted a significant anti-inflammatory effect on 10th day at the dose of 5, 10 mL kg⁻¹ (p<0.001, p<0.05) and was comparable (p<0.01) to that of the standard drug, Diclofenac sodium (10 mg kg⁻¹). The percentage inhibition activity of sesame oil (5, 10 mL kg⁻¹) and Diclofenac sodium 10 mg kg⁻¹ were found to be 52, 35 and 42%, respectively.

DISCUSSION

In the present study, the analgesic, antipyretic and anti-inflammatory activity of sesame oil has been established.

Indeed, Non-steroidal Anti-Inflammatory Drugs (NSAID), like paracetamol exert their antipyretic action by largely inhibiting prostaglandin (E-type) production in hypothalamus (Rang *et al.*, 1999). Sesame oil at two different doses (5, 10 mL kg⁻¹) demonstrated effective antipyretic activity as evident in the inhibition of the elevation in the yeast induced hyperpyrexia model (Fig. 1). The antipyretic action of the extract may be possibly be through inhibition of prostaglandin production, leading to suppression of elevated plasma level, especially since the extract had been shown to possess analgesic and anti-inflammatory activities that we discussed below.

In addition, the classification of analgesic drugs is usually based on their mechanism of action either on the central nervous system or on the peripheral nervous system (Swingle *et al.*, 2000). With respect to the writhing test the research group of Derardt *et al.* (1980), described the quantification of prostaglandins by radio immune assay in the peritoneal exudates of rats, obtained after intra peritoneal injection of acetic acid. They found high levels of prostaglandins, PGE2 and PGF2 alpha during the first 30 min after acetic acid injection. Nevertheless, it was found that the intra peritoneal administration of acetic acid induces the liberation not only of prostaglandins but also of the sympathetic nervous system mediators (Hokanson, 1978; Duarte *et al.*, 1988). Thus, the results obtained for the writhing test using acetic acid (Table 3) are similar to those obtained from the oedematogenic test using carrageenan (Table 4, 5). Therefore, anti-inflammatory substances may also be involved in the peripheral analgesic activity.

Experimental evidence obtained in this study indicates that the sesame oil reduced acetic acid induced writhes and formalin induced paw licking in mice. Similarly, it significantly delayed the reaction time of animals to the heat stimulus. Acetic acid causes inflammatory pain by inducing capillary permeability (Amico-Roxas *et al.*, 1984), formalin exhibits neurogenic and inflammatory pain (Vaz *et al.*, 1996, 1997) while hot

Table 4: Anti-inflammatory activity of sesame oil in carrageenan induced paw edema

Treatment	Paw edema in mL					Percentage of inhibition of edema at 4th h
	0 h	1 h	2 h	3 h	4 h	
Control saline 10 mL kg ⁻¹ p.o.	0.25±0.06	0.36±0.02	0.43±0.01	0.52±0.02	0.56±0.02	----
Sesame oil 5 mL kg ⁻¹ p.o.	0.35±0.02	0.51±0.04**	0.60±0.01	0.29±0.01***	0.21±0.01***	63
Sesame oil 10 mL kg ⁻¹ p.o.	0.25±0.02	0.29±0.02*	0.30±0.04*	0.26±0.04***	0.25±0.02***	55
Diclofenac sodium 10 mg kg ⁻¹ i.p.	0.21±0.01	0.32±0.01 ^{ns}	0.35±0.02*	0.25±0.02***	0.18±0.01***	68

Values are expressed as Mean±SEM. *p<0.05, **p<0.01 and ***p<0.001 when compared with control. ns: Non significant

Table 5: Anti-inflammatory activity of sesame oil in formalin induced arthritis in rats

Treatment	Paw edema in mL in each day										Percentage of inhibition over 10 days
	1	2	3	4	5	6	7	8	9	10	
Control saline 10 mL kg ⁻¹ p.o.	0.40±0.01	0.45±0.02	0.40±0.06	0.45±0.02	0.31±0.01	0.25±0.02	0.35±0.02	0.31±0.02	0.31±0.02	0.31±0.02	----
Sesame oil 5 mL kg ⁻¹ p.o.	0.31±0.01	0.25±0.02	0.35±0.02 ^{ns}	0.60±0.04**	0.51±0.01	0.21±0.01 ^{ns}	0.21±0.01***	0.15±0.02***	0.15±0.02***	0.15±0.02***	52
Sesame oil 10 mL kg ⁻¹ p.o.	0.21±0.01	0.30±0.04**	0.25±0.02*	0.35±0.02*	0.30±0.04*	0.30±0.04*	0.35±0.02 ^{ns}	0.35±0.02 ^{ns}	0.25±0.02 ^{ns}	0.20±0.02*	35
Diclofenac sodium 10 mg kg ⁻¹ i.p.	0.31±0.01	0.31±0.01**	0.31±0.01 ^{ns}	0.31±0.01**	0.35±0.02 ^{ns}	0.35±0.02*	0.31±0.01 ^{ns}	0.23±0.02*	0.23±0.02*	0.18±0.02**	42

Values are expressed as Mean±SEM. *p<0.05, **p<0.01 and ***p<0.001 when compared with control. ns: Non significant

plate-induced pain indicates narcotic involvement (Besra *et al.*, 1996). The sesame oil seems to act centrally just like NSAIDs. The central action of the sesame oil is further supported by its ability to inhibit both phases of formalin induced paw licking which is a characteristic of drugs (such as narcotics) that act centrally (Santos *et al.*, 1994). Furthermore, the sesame oil may have exerted its action through other mechanisms of antinociception thereby leading to the observed analgesic effect. The sesame oil further demonstrated central action by increasing the reaction time to heat. This indicates the involvement of narcotic or opiod receptors.

The sesame oil at two different doses (5, 10 mL kg⁻¹) were found to significantly inhibit the carrageenan induced rat paw edema, a test which has significant predictive value for anti-inflammatory agents acting by inhibiting the mediators of acute inflammation (Mossa *et al.*, 1995). Carrageenan-induced edema has been commonly used as an experimental animal model for acute inflammation and is believed to be biphasic. The early phase (1-2 h) of the carrageenan model is mainly mediated by histamine, serotonin and increased synthesis of prostaglandins in the damaged tissue surroundings. The late phase is sustained by prostaglandin release and mediated by bradykinin, leukotrienes, polymorphonuclear cells and prostaglandins produced by tissue macrophages (Antonio and Brito, 1998; Gupta *et al.*, 2006). The significant inhibitory activity shown by the sesame oil over a period of 4 h in carrageenan- induced inflammation was quite similar to that exhibited by the group treated with Diclofenac sodium. The highest percentage inhibition activity was

found in the dose of 5 mL kg⁻¹ with the mean percentage inhibition of 63% after 4 h of sesame oil administration. These results indicate that the sesame oil acts in later phases in dose dependent manner, probably involving arachidonic acid metabolites which produce an edema dependent neutrophils mobilization (Just *et al.*, 1998). The formalin induced arthritis is a simple animal model of sub-chronic inflammation. Formalin administered on 1st and 3rd day produces overgrowth of fibroblast and causes arthritis which is inhibited by NSAIDs. In this study sesame oil also showed significant protection against formalin induced arthritis when compared with standard Diclofenac sodium. The percentage inhibition activity over 10th day of treatment of sesame oil (5, 10 mL kg⁻¹) was found to be 52 and 35%, respectively. This effect is comparable with the standard drug which produces the percentage inhibition activity of 42%.

In several researches it has been found that sesamin (Sesame oil lignan) inhibits Δ5 desaturase activity, resulting in accumulation of dihomolinolenic acid which displaces arachidonic acid and consequently decreases the formation of proinflammatory 2-series prostaglandin (PGE₂) (Jeng and Hou, 2005). Therefore, sesame oil may have a therapeutic potential supplementation for pain and inflammatory diseases due to presence of active principle sesamin lignans.

CONCLUSION

From this present research it has been concluded that sesame oil as dietary supplement produced significant analgesic, antipyretic and anti-inflammatory activity.

Present study indicates that inclusion of sesame oil in diet may be useful for an alternative choice for various inflammatory diseases.

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