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Anti-inflammatory and Antipyretic Activities of Indian Medicinal Plant *Cassia fistula* Linn. (Golden Shower) in Wistar Albino Rats

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Abstract: The study was aimed to investigate the anti-inflammatory and anti-pyretic activities of ethanolic extract of *Cassia fistula* Linn. (ELE) in experimental rats. Anti-inflammatory activity was evaluated using carrageenan induced rat paw oedema and cotton pellet granuloma models, while the antipyretic effect was evaluated using against TAB vaccine induced pyrexia. Various doses of ELE (50, 100, 250, 500 and 750 mg kg⁻¹b.wt.) were tested for its anti-inflammatory effect and the results were compared with standard drugs (diclofenac and indomethacin). Results indicate that the ELE significantly inhibited both the carrageenan-induced hind paw oedema and cotton-pellet granuloma in a dose dependant manner. ELE at 250 and 500 mg kg⁻¹b.wt., reduced TAB vaccine induced pyrexia in rats after 60 min, whereas at 750 mg kg⁻¹b.wt., it reduced the vaccine induced elevated body temperature post 30 min of its administration. The results suggest that there exists a potential benefit in utilizing *Cassia fistula* Linn. in treating conditions associated with inflammation and fever. These properties can be attributed to the presence of phyto constituents present in ELE and the exact mechanism needs to be elucidated.

Key words: *Cassia fistula*, inflammation, carrageenan, cotton-pellet, TAB-vaccine, ethanolic leaf extract, inflammatory mediators

INTRODUCTION

The special significance of conserving the traditional medicinal plants stems from the major cultural, livelihood or economic roles that they play in many people's lives. Continuing discovery on the efficacy of these plants and their active principles against several disorders has been facilitated by the recent development of new bioassay methods. These naturally occurring bioactive compounds are mostly secondary metabolites which are nowadays being used as medicines, dietary supplements and other useful commercial products (Balunas and Kinghorn, 2005). Crude herbs have long been and continue to be the basis of many traditional medicines worldwide. In Asia, these therapies include Traditional Chinese medicine (TCM) Japanese Chinese medicine (kampo), Korean Chinese medicine, jamu (Indonesia) and ayurvedic medicine (India) and in Europe, phytotherapy and homeopathy are widely used for the treatment of several diseases (Verpoorte *et al.*, 1999; Gomez-Galera *et al.*, 2007). For thousands of years, these natural plant products have

been utilized for human healthcare in the form of drugs, antioxidants, flavors, fragrances, dyes, insecticides and pheromones. However, during the last century, the use of synthetic drugs led to a decline in the use of plant-derived compounds, so that at one time it was believed by many that the synthetic drugs would perhaps completely replace the use of traditional plant-derived medicines. However, in recent years, a resurgence of the use of herbal drugs has once again been witnessed, firstly because the synthetic drugs have been found to be hazardous in many cases and secondly because there is growing awareness that the plant-derived medicines have none of the side effects that are so common in the case of synthetic drugs (Joshi *et al.*, 2004).

Cassia fistula Linn. (Leguminosae) is an ornamental plant widely cultivated throughout India and commonly called as Sarakonrai in Tamil. The different parts of this plant have been demonstrated to possess several medicinal values such as antibacterial (Perumal Samy *et al.*, 1998), antiparasitic (Sartorelli *et al.*,

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2009), hypoglycemic (Bhakta *et al.*, 1997), hepatoprotective (Bhakta *et al.*, 1999), acetylcholinesterase (AChE) inhibitor (Ingkaninan *et al.*, 2003), against chickengunya vector (Govindarajan, 2009), hypocholesterolaemic (El-Saadany *et al.*, 1991) and antidiabetic properties (Esposito Avella *et al.*, 1991). Based on the ancient practices and traditional uses of this plant, the present study was designed to investigate the anti-inflammatory and antipyretic activity of the ethanolic leaf extract of *Cassia fistula* Linn. (ELE) and its results are reported hereunder.

MATERIALS AND METHODS

Animals: Healthy Wistar albino rats of either sex weighing between 190±10 g purchased in the year of 2003 from Tamil Nadu Veterinary and Animal Sciences University, Chennai, were used for this study. Animals were housed in poly propylene cages and were provided certified rodent pellet diet and water *ad libitum*. They were maintained at 25°C with 12 h light and dark cycle. All animal experiments were performed in accordance with the strict guidelines prescribed by the Institutional Animal Ethical Committee (IAEC) after getting necessary approval.

Chemicals: Carrageenan was purchased from Sigma-Aldrich, USA. Polysaccharide typhoid vaccine (TAB vaccine) was purchased from Bharat Biotech International Ltd., Hyderabad. Diclofenac and Indomethacin were obtained as gratis from The Madras Pharmaceuticals, Chennai, India. All the other chemicals used were of analytical grade and purchased locally.

Plant collection and extraction: Fresh leaves of *Cassia fistula* Linn. were collected from Tamil Nadu Medicinal Plant Farm and Herbal Medical Corporation Limited (TAMPCOL), Chennai, India. The plant and its leaves were authenticated by Dr. S. Narayanappa, Chief Botanist, TAMPCOL. Voucher specimens of leaves were deposited in the herbarium of Botanical Survey of India (BSI), Coimbatore (Herbarium No. BSI/C.F./001/2002). Immediately after collection, the leaves were washed to remove all the external dirt and unwanted materials, shade dried for 72 h and crushed into a coarse powder. Hundred grams of the powdered leaves were subjected to soxhlet extraction using 95% ethanol. This ethanolic soxhlet extract was evaporated to dryness at 50°C over water bath. The yield of ELE was around 15 to 17% and was used for further biochemical studies.

Phytochemical screening of ELE: The ELE was subjected to standard phytochemical screening for flavonoids (Sodium hydroxide, ferric chloride and lead acetate test), glycosides (Molisch, Benedict's and Fehling's test), Alkaloids (Dragendorff's, Wagner's and Mayer's test), Tannins (Lead acetate and ferric chloride test) and saponins (Foam and Libermann's test) as described by Harborne (1973).

Experimental design: The acute and chronic anti-inflammatory activities of ELE were performed by employing carrageenan-induced hind-paw oedema and cotton-pellet granuloma methods respectively using wistar albino rats.

Evaluation of acute anti-inflammatory activity of ELE: Hind-paw oedema was induced in rats by injecting 0.1 mL of carrageenan (1%; w/v) dissolved in distilled water on to the sub-plantar region of the right hind-paw (Winter *et al.*, 1962). Rats were divided into 8 groups each comprising of 6 animals. The experimental design was as follows:

Group I rats served as controls and were treated with saline 30 min prior to carrageenan administration. Group II and III were administered Diclofenac and indomethacin orally at doses of 25 and 10 mg kg⁻¹ b.wt., respectively, 30 min before carrageenan administration. Group IV-VIII were administered ELE orally at the doses of 50, 100, 250, 500 and 750 mg kg⁻¹ b.wt., respectively, 30 min prior to administration of carrageenan. Paw oedema was expressed as the increase in paw volume (mm) after carrageenan injection. The volume of the injected and the contra-lateral paws were measured at 1, 2, 4, 8 and 24 h after induction of inflammation, using plethysmometer.

Evaluation of chronic anti-inflammatory activity of ELE: Pellets of sterile density cotton (30 mg) were used for implantation in the rats. Under thiopentathol anesthesia (10 mg kg⁻¹ b.wt., i.p.), two cotton pellets were implanted sub-cutaneously in the groin region of rats, one on each side, after making a ventral mid-line incision. The wounds were sutured and the animals were allowed to recover during which free access of food and water was provided (Freeman *et al.*, 1982). In this model, the animals were divided into 8 groups, each comprising of 6 animals. The experimental designs are as follows:

Group I rats served as control were administered saline orally. Group II and III were administered diclofenac and indomethacin orally at a concentration of 25 and 10 mg kg⁻¹ b.wt., respectively. Group IV-VIII were administered with ELE at a dose of 50, 100, 250, 500 and 750 mg kg⁻¹ b.wt., orally respectively. ELE administration was started 24 h after cotton-pellet implantation and was continued for 7 consecutive days. On 8th day, all the

animals were sacrificed and the cotton-pellets were removed. The cotton-pellet granuloma was made free from exogenous tissues and were incubated at 37°C for 24 h and subsequently dried at 60°C for 24 h. The increment of dry weights in pellets was taken as the measurement of granuloma formation (Winter and Porter, 1957).

Evaluation of anti-pyretic activity of ELE: Pyrexia was induced by sub-cutaneous injection of TAB vaccine and the anti-pyretic effect of test drugs were analyzed as described by Pendse *et al.* (1977). The TAB-vaccine is a sterile suspension, containing 1×10^9 *Salmonella typhi* and 7.5×10^8 *Salmonella paratyphi* A and B organisms/mL in vials. Sixty rats of either sex were injected TAB vaccine at a dose of 0.1 mL/100 g b.wt. (i.p) to induce pyrexia. Animals with increased the rectal temperature of 1.5°C after TAB vaccine administration were selected for the experiment. The pyrexia induced rats were divided into 7 groups, each comprising of 6 animals at random. Group I rats administered with saline orally, served as control. Group II rats were administered with aspirin at a concentration of 100 mg kg⁻¹ b.wt., orally. Group III-VII were orally administered with ELE at a dose of 50, 100, 250, 500 and 750 mg kg⁻¹ b.wt., respectively. The rectal temperatures of all these groups were measured using a thermometer, at an interval of every 30 min up to 4 h for the evaluation of anti-pyretic activity.

Statistical analysis: The data obtained was subjected to One way ANOVA and Tukey's multiple comparison test was performed using SPSS statistical package (Version 7.5). Values are expressed as Mean ±SE p-value <0.05 was considered significant.

RESULTS

The ELE was subjected to acute toxicity evaluation in rats before the aimed experiments were started. A dose of 2500 mg kg⁻¹ b.wt. was orally administered and observed for up to 72 h to determine its safety efficacy in rats. Rats did not show any signs or symptoms of toxicity for up to 72 h when compared with saline treated control. Based to this observation a dose of 50, 100, 250, 500 and 750 mg kg⁻¹ b.wt., were chosen for further pharmacological evaluations of ELE. The phytochemical analysis of ELE showed positive for flavanoids, glycosides, alkaloids, tannins and saponnins (Table 1).

Effect of ELE treatment on carrageenan induced hind-paw oedema volume: The acute anti-inflammatory effect of ELE treatment is graphed in Fig. 1. The result showed an increase in the paw oedema volume in

Table 1: Phytochemical analysis of ELE

Test	Test methods	Test results
Tests for flavonoids	Sodium hydroxide test	+
	Ferric chloride test	+
	Lead acetate test	+
Tests for glycosides	Molisch test	+
	Benedict's test	+
	Fehling's test	+
Tests for alkaloids	Dragendorff's test	+
	Wagner's test	+
	Mayer's test	+
Tests for tannins	Lead acetate test	+
	Ferric chloride test	+
Tests for saponins	Foam test	+
	Libermann test	+

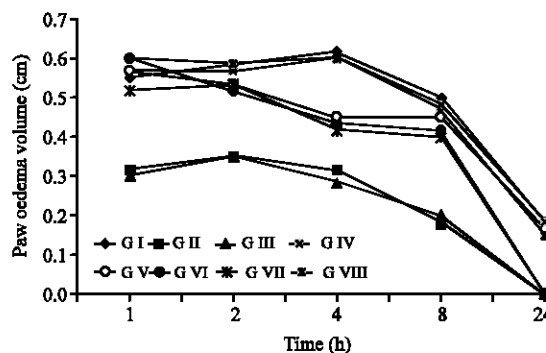


Fig. 1: Effects of ELE on anti-inflammatory activity challenged against carrageenan-induced acute inflammation was observed in control (saline treated), Standard drugs (Diclofenac (25 mg kg⁻¹ b.wt.), Indomethacin (10mg kg⁻¹ b.wt.) and different doses of ELE extracts. Values are presented as Mean±SEM for 6 rats in each group. Multiple comparisons between treatment groups were performed by Tukey's test

control rats (Group I), 1 h post administration, indicating the onset of inflammation, which reached its peak at 4 h and gradually reduced at 8 h up to 24 h. Oedema volume did not revert back to normalcy even 24 h, after carrageenan treatment in saline treated control rats. On the contrary, administration of Diclofenac (Group II) and indomethacin (Group III) showed a highly significant decrease (p<0.001) in paw oedema volume from 1, 2, 4 and 8 h after carrageenan administration and reverted back to normal at 24 h after carrageenan treatment. Administration of ELE at 250, 500 and 750 mg kg⁻¹ b.wt. (Group VI-VIII, respectively) caused a dose-dependent decrease in oedema volume from 4, 8 and 24 h after administration of carrageenan while there was no significant reduction in oedema volume at low doses of ELE (Group IV and V). At higher doses of ELE, the paw volume returned towards normalcy at 24 h (Group VII and VIII) and was comparable with the standard drug treated rats (Group II and III; Fig. 1).

Table 2: Effect of ELE treatment on cotton pellet granuloma induced inflammation

Groups (n = 6)	Treatment	Granuloma weight (mg)	
		Wet weight	Dry weight
I	Control	290.00±6.55	69.96±1.56
II	Diclofenac	140.00±2.85a***	29.99±0.71a***
III	Indomethacin	131.00±2.96a***	25.99±0.64a***b*
IV	ELE (50 mg kg ⁻¹)	200.00±3.61a,b,c***	40.99±0.74a,b,c***
V	ELE (100 mg kg ⁻¹)	188.00±3.89a,b,c***	37.99±0.77a,b,c***
VI	ELE (250 mg kg ⁻¹)	175.00± 3.17a,b,c***	34.99±0.63a,c***b**
VII	ELE (500 mg kg ⁻¹)	155.00±3.21a***c**	31.00 ± 0.54a***c**
VIII	ELE (750 mg kg ⁻¹)	141.99±3.23 a***b	28.00 ± 0.63a***

Effects of ELE on anti-inflammatory activity challenged against the measurement of granulomatous tissues developed by the implantation of cotton-pellet was observed in control (saline treated), standard drugs (Diclofenac (25 mg kg⁻¹ b.wt.); indomethacin (10 mg kg⁻¹ b.wt.) and different doses of ELE extracts were showed anti-pyretic activity. Values are presented as Mean±SEM for 6 rats in each group. Multiple comparisons between treatment groups were performed by Tukey's test. a: Compared with control rats (Group I); b: Compared with Diclofenac treated rats (Group II); c: Compared with indomethacin treated rats (Group III). ***p<0.001, **p<0.01, *p<0.05

Effect of ELE treatment on cotton pellet granuloma induced inflammation: An increase in both the wet and dry weight of granuloma indicates the onset of chronic inflammation in animals. Seven days after implantation of cotton-pellets, the wet and dry weight was significantly increased in control rats (Group I). Group II and III caused a 50% reduction in both the wet and dry weight of cotton-pellet granuloma when compared to the control and indicated the marked anti-inflammatory effect of diclofenac and indomethacin. Oral administration of ELE for seven days at a dosage range of 50 to 750 mg kg⁻¹ b.wt. (Group IV to VIII), caused a dose-dependent decrease in both the wet and dry weight of cotton-pellet granuloma. At higher dose administration of ELE Group VII and VIII, showed almost 50% reduction in the granuloma weight, which was same as that of diclofenac and indomethacin treatment (Table 2).

Effect of ELE administration against TAB vaccine induced pyrexia: The baseline rectal temperature of untreated rats was in the range of 36.76 to 37.0°C. Four hour after administration of TAB vaccine, the rectal temperature was elevated by 1.00 to 1.5°C from the base line temperature in all the groups, indicating the onset of fever. The TAB vaccine-induced fever was significantly reduced in aspirin administered (Group II) rats and the body temperature was normalize between 3 to 4 h after onset of fever. The fever was significantly reduced in ELE administration at 500 and 750 mg kg⁻¹ b.wt. (Group VI and VII) and the body temperature was normalize at 4 h, but in low dose administration showed that there was no appreciable fall in temperature on Group III-V (Fig. 2) up to 4 h.

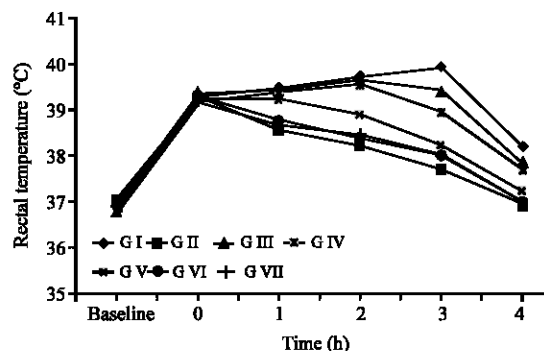


Fig. 2: Effects of ELE on anti-pyretic activity challenged against TAB vaccine-induced pyrexia was observed in control (saline treated), Standard drug (Aspirin 100 mg kg⁻¹ b.wt.) and different doses of ELE extracts were showed anti-pyretic activity. Values are presented as Mean±SEM for 6 rats in each group. Multiple comparisons between treatment groups were performed by Tukey's test

DISCUSSION

Plants form the main ingredients of medicines in traditional systems of healing and have been the source of inspiration for several major pharmaceutical drugs. The medicinal uses of plants grade into their uses for other purposes, as for food, cleaning and personal care. Plants are used in medicine to maintain and augment health-physically, mentally and spiritually-as well as to treat specific conditions and ailments. Ayurveda, Siddha, Unani and Folk (tribal) medicines are the major systems of indigenous medicines. Among these systems, Ayurveda is most developed and widely practiced in India. *Cassia fistula* Linn. is frequently indexed in Ayurveda, Siddha and other traditional systems of medicine in India for use in therapeutic purposes in human.

The toxicity assessment of ELE showed that it did not produced any abnormal effects on the animals which were treated with a dose of 2500 mg kg⁻¹ b.wt. Followed by the toxicity assessment, ELE was subject to evaluation of its pharmacological activities like anti-inflammatory and antipyretic activities against inflammation and pyrexia. The ELE at low dose administration (50 and 100 mg kg⁻¹ b.wt.) did not show any significant reduction in paw oedema volume in rats at all the time periods of study. The carrageenan-induced paw oedema model in rats is known to be sensitive to cyclooxygenase (COX) inhibitors and has been used to evaluate the effect of non-steroidal anti-inflammatory agents (Rao *et al.*, 2005). It is also suitable for assessing the anti-oedematous effect of natural products and is believed to be biphasic (Adedapo *et al.*,

2008). The present investigation showed significant dose-dependant decrease in paw oedema after 4 h of carrageenan administration on higher dose administration of ELE (250, 500 and 750 mg kg⁻¹ b.wt.). The carrageenan-induced inflammation constitutes of two phases. The first phase of 1 h involves the release of serotonin and histamine while the second phase of the next 1 h is mediated by prostaglandin (PG), interleukins (IL) and increased accumulation of polymorpho nuclear cells in to the inflammatory area (Vinegar *et al.*, 1987; Perianayagam *et al.*, 2006). It is said that the activation of polymorpho nuclear cells cause the release of lysosomal enzymes and liberation of reactive free radicals such as O₂⁻ and H₂O₂⁻ which destroy connective tissues, resulting in paw oedema (Mazzon *et al.*, 2001). Therefore, the result of this study supports the use of the plant in folklore medicine for the management of acute inflammation. The suppression of paw oedema in the last phase during ELE administration could probably be due to inhibition in the release of early mediators such as histamine, serotonin and kinins (Amresha *et al.*, 2007) as well as cyclooxygenase (Seibert *et al.*, 1994).

Cotton-pellet-induced granuloma formation is an established inflammatory reaction and can serve as sub-chronic and chronic inflammatory models (Spector, 1969) and it is employed to assess the transductive and proliferative components of chronic inflammation. The fluid absorbed by the cotton-pellet greatly influence the wet weight of granuloma and the dry weight is well correlated with the amount of granulomatous tissue formed (Panthong *et al.*, 2004). ELE administration caused a dose-dependant decrease in both the dry and wet weight of cotton-pellet granuloma in rats, indicating its chronic anti-inflammatory activity. At higher doses (750 mg kg⁻¹ b.wt.), ELE produced an anti-inflammatory effect, which was comparable with the standard drugs which showed a 50% reduction in both the dry and wet weight of cotton-pellet granuloma, indicating the chronic anti-inflammatory activity of these drugs (Suleyman *et al.*, 2003). It is said that these NSAID decrease the size of granuloma by inhibiting the generation of collagen fiber and suppressing mucopolysaccharides (Procida *et al.*, 1971; Ionac *et al.*, 1996). The phytoconstituents present in ELE might be involved in decreasing the dry and wet weight of granuloma which can attributed to their ability to inhibit the formation of fibroblast, the synthesis of collagen and mucopolysaccharides, which are natural proliferative agents of granuloma formation. This observation is in agreement with the previous report (Arrigoni-Martellie, 1977).

On the other hand, induction of COX-2 enzyme was shown to increase inflammation and this effect was

attributed to the larger scale release of prostanoids (Gadient and Patterson, 1999). In the light of these reports, it is likely that both indomethacin and diclofenac could have reduced the paw oedema in rats by preventing or inhibiting the expression of COX-2 enzymes and consequent release of PG. In the present study, the demonstration of rapid decrease in wet and dry weight of ELE administered at higher doses, which is comparable to the standard drugs indomethacin and diclofenac treated rats, is the clear indication of anti-inflammatory activity of ELE, it could be suggested that ELE might interfere with PG synthesis by unknown mechanism to reduce the inflammation stress in the experimental rats.

Fever may be the result of infection or one of the sequelae to tissue damage, inflammation, graft rejection or other diseased states (Devi *et al.*, 2003). Regulation of body temperature requires a delicate balance between the production and loss of heat. The elevation of temperature in the pre-optic zone of frontal area of hypothalamus above the thermal-set point of 37°C is believed to be the cause for pyrexia (Mackowiak, 1998). It is hypothesized that production of PG at this thermoregulatory centre initiates the onset of pyrexia and that the synthesis of PGE series is believed to act as the mediator of pyrogen fever (Milton and Wendlandt, 1971; Feldberg and Saxena, 1971; Feldberg *et al.*, 1973; Dey *et al.*, 1974). The ability of ELE to reduce the experimentally elevated body temperature shows that ELE possesses significant antipyretic effect on TAB vaccine induced pyrexia. The reduction in TAB vaccine induced fever by ELE might be due to its influence on the prostaglandin biosynthesis since it is involved in the regulation of body temperature (Dascombe, 1985). In general, it is believed that several mediators and multiple processes play a vital role in the pathogenesis of fever. Inhibition of any of these mediators is said to bring about anti-pyresis and as to how they interfere with PG synthesis is not clearly established (Akio *et al.*, 1988). The result of this study confirmed that ELE could be beneficial in the management of inflammations, pains and fever. These activities may be due, in part, to the presence of phytochemicals such as glycosides, alkaloids, tannins, flavonoids, steroids and/or terpenes.

The available anti-inflammatory and anti-pyretic drugs (steroidal and nonsteroidal) present a wide range of side effects for which the major reason is nonselective inhibition of cyclooxygenase I (COX I) and cyclooxygenase II (COX II) (Vane and Botting, 1995). Several studies are being directed to find a selective COX II inhibitor or compounds acting with other mechanisms and little side effects. The results from the present study show that ELE exhibited activities in various degrees against experimentally induced inflammation and fever. By

activating the cyclooxygenase, the levels of prostaglandin, especially PGE₂, increases markedly and its production provokes inflammation, pain and fever (Dannhardt and Kiefer, 2001). Fever induction studies in rodents have shown that expression of COX-2 enzyme in the vasculature of the brain is the cause for onset of fever (Matsumura *et al.*, 1998; Li *et al.*, 1999; Vellucci and Parrott, 1998). Therefore, we assume that some active metabolites present in ELE could have played a role in inhibiting cyclooxygenase activity. Phytochemicals such as flavonoids, steroids, glycosides, alkaloids, saponins and anthraquinones have been reported to exhibit both acute, chronic anti-inflammatory and anti-pyretic activity in rats (Tariq *et al.*, 1989; Panthong *et al.*, 2004; Ebrahimzadeh *et al.*, 2006) and present study also reports the presence of these phytochemicals in the ELE of *Cassia fistula* Linn. Further studies are underway to identify the active principle responsible for the anti-inflammatory and anti-pyretic activities of ELE and to study its mechanism of action.

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