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RESEARCH ARTICLE

ESTIMATION OF ANTIPYRETIC, PALLIATIVE AND ANTI-INFLAMMATORY POTENTIAL OF METHANOLIC EXTRACT OF *TERMINALIA CATAPPA*

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In present study, anti-inflammatory, palliative and antipyretic activities of methanolic extract of *Terminalia catappa* leaves were evaluated in standard experimental models. The results showed that the positive control (Indomethacin) significantly ($p<0.05$; $p<0.01$) decreased the paw edema at 1 h to 4 h after carrageenan injection compared to saline with 56.31% to 59.85% inhibition rate. A maximum oedema of paw volume 1.42±0.03 mm was observed in the control rats, 4 h after the carrageenan injection. Also tail flick and hot plate models revealed that methanolic extract significantly ($p<0.05$; $p<0.01$) reduced the painful stimulus. This confirmed the involvement of central and peripheral effects of the extract. The extract also possessed antipyretic potential evidenced by significant ($p<0.05$; $p<0.01$) induction of pyresis by yeast cell within 3 h. Thus, methanolic extract was found to have wide variety of pharmacological effect in the form of anti-inflammatory, palliative and antipyretic effect which proves the utility of *Terminalia catappa* in experimental pharmacology of cytokines and prostaglandins (PGs).

Key words: *Terminalia catappa*, Anti-inflammatory, Palliative, Antipyretic.

INTRODUCTION

Inflammation is the response of living tissues to injury which involves a complex array of enzyme activation, mediator release, extravasations of fluid, cell migration, tissue breakdown and repair (Vane and Botting, 1995; Perianayagam *et al* 2006). Non-steroidal anti-inflammatory drugs (NSAID) are among the most commonly prescribed drugs due to their consistent effectiveness in the treatment of pain, fever, inflammation and rheumatic disorders (Rang *et al* 2005). However, their use is associated with adverse effects at the level of digestive tract, ranging from dyspeptic symptoms, gastro-intestinal erosions and peptic ulcers to more serious complications, such as over bleeding or perforation. Therefore to overcome the toxicity of NSAID, the development of new anti-inflammatory drugs is still necessary and the natural product such as medicinal plants could lead in discovering new anti-inflammatory drugs with less undesirable effects. Medicinal plants have biological properties and now-a-days attention is being focused on the investigation of the efficacy of plant based drugs used in the traditional medicine because they are economical and relatively safe (Madaan *et al* 2011; Jain *et al* 2011; Srividya *et al* 2012; Dey *et al* 2012; Jain and Argal, 2013; Deb *et al* 2013). According to WHO, about 80% of the world population still rely mainly on herbal remedies (Muthu *et al* 2006).

Terminalia catappa is a flowering plant of the Combretaceae family. It is also known as badam widely grown in tropical regions of the world as an ornamental tree. The leaves, bark and fruits of

Terminalia catappa (*Combretaceae*) have been commonly used as a folk medicine for antidiarrhea and haemostatic purposes. The leaves of *T. catappa* have been used in Taiwan for the prevention and treatment of hepatitis and liver-related diseases (Lin and Kan, 1990). The leaves of *Terminalia catappa* contain many hydrolysable types of tannins such as punicalagin, punicalin, terflavins A and B, tergallagin, tercatain, chebulagic acid, geraniin, granatin B and corilagin (Tanaka *et al* 1986). Punicalin and punicalagin inhibited HIV replication in infected H9 lymphocytes with little cytotoxicity and also in purified HIV reverse transcriptase (Nonaka *et al* 1990). The extract of *Terminalia catappa* leaves inhibited lewis lung carcinoma cell that contributed to lung cancer (Chu *et al* 2007). The objective of the present study was to evaluate the antipyretic, palliative and anti-inflammatory activity of methanolic extract of *Terminalia catappa.*

MATERIALS AND METHODS

Plant material

Fresh leaves of *Terminalia catappa* were collected in the month of January-February from the herbal garden of Sagar Institute of Pharmaceutical Sciences (SIPS), Sagar, Madhya Pradesh. The plant was identified and authenticated from Department of Botany, Dr. H.S. Gour Vishwavidyalaya, Sagar, Madhya Pradesh. The voucher specimen of the plant was deposited at the department for future reference (Voucher specimen no. Bot./Her./B/2829).

Drug

The standard drug Indomethacin was used for anti-inflammatory study and purchased from Square Pharmaceuticals Ltd, Bangladesh. Naloxone.HCl (DuPont Pharmaceuticals Wilmington DE 1998), Paracetamol (Alkem Laboratories Private Limited, Baddi) and methanolic extract *Terminalia catappa* leaf extract were used in the study.

Preparation of methanolic extract of *Terminalia catappa*

The extraction was undertaken with 100 g of powdered plant material and 500 ml of light petroleum ether (b.p. 40-60°C) in a soxhlet apparatus for 18 h to remove the chlorophyll and lipid dewaxing. The treated material was dried and extract with methanol using soxhlet apparatus for 4 h. The extract was concentrated in vacuum using a rotary evaporator.

Animal

Healthy adult male Wistar albino rats between 2-3 months of age and weighing 180-200 g were used during study. The animals were housed individually in polypropylene cages, maintained under standard conditions (12 h light and 12 h dark cycle, 25±5°C and 40-60% humidity). The animals accessed free to feed and purified water *ad libitum* according to CPCSEA Guidelines**.** The animals were fasted for 16 h before experimentation but allowed free access to water. The experimental protocol was approved by the Institutional Animal Ethics Committee of CPCSEA (Committee for the Purpose of Control and Supervision of Experimental Animals).

Acute toxicity test

The acute toxicity of *Terminalia catappa* methanolic extract was determined in rats according to the method previously reported (El Hilaly *et al* 2004) with slight modifications. Rats fasted for 16 h were randomly divided into groups of five rats per group. Graded doses of the extract (100, 200, 400, 600 and 800 mg/kg *p.o.*) were separately administered to the rats in each of the groups by means of bulbed steel needle. All the animals were then allowed free access to food and water and observed over a period of 48h for signs of acute toxicity. The number of deaths within this period was recorded.

Anti-inflammatory study

Carrageenan induced rat hind paw edema was used as the animal model of acute inflammation (Lanhers *et al* 1991; Hossain *et al* 2011). In this experiment, the rats were divided into four groups of five animals each. Group I (Control) received 2% Tween 80 in normal saline (2 ml/kg). Group II (Positive control) received 10 mg/kg body wt. of indomethacin orally. Group III and IV received 100 and 200 mg/kg *b/w* of the extract orally respectively. Acute inflammation was induced in all the four groups by sub plantar injection of 0.05 ml of its suspension of Carrageenan with 2% Tween 80 in normal saline in the right paw of the rats 30 minutes after the oral administration of the tested materials.

The paw volume was measured with a micrometer screw gauze at 1, 2, 3 and 4 h after the administration of the drug and the extract. The percentage inhibition of inflammatory effect of the extract was calculated using the following expression:

% inhibition = $[(V_c - V_t) / V_c] \times 100$

where V_c is the average degree of inflammation by the control group and V_t is the average degree of inflammation by the test group.

Palliative activity

Tail flick method

The heat intensity of thermal stimulation (Techno Analgesiometer) was adjusted such that rats had control tail flick latency of 3-4 sec and a 10 sec cut off latency was used to prevent thermal injury. The initial reaction time was recorded in thirty animals and then they were divided into 3 groups of 5 rats each (Janssen *et al* 1963; Davies *et al* 1946). Drugs were given to the various groups as mentioned in **Table 1**. Dose of extract was selected by performing acute toxicity method in OECD Guidelines 423 (OECD Guidelines, 2001). Tail flick latency in seconds was recorded every 30 min for a duration of 3 hours after drug administration.

Table 1. Anti inflammatory effect of methanol extract of *Terminalia cattapa* (METCL) and indomethacin on carrageenan-induced oedema paw volume in male albindo Wistar rats

Group	Treatment group	Dose (mg/kg *b.w.*)	Right hind paw volume (mm)			
			1 h	2 h	3 h	4 h
I	Control	2 ml/kg (2% tween 80 in normal saline)	1.03±0.07	1.28±0.05	1.34±0.06	1.42±0.03
II	Indomethacin	10	0.45±0.03* (56.31)	0.52±0.05** (59.37)	0.51±0.04** (61.94)	0.57±0.05* (59.85)
III	METCL	100	0.75±0.04* (27.18)	0.80±0.07** (37.50)	0.79±0.06* (41.04)	0.87±0.05** (38.73)
IV	METCL	200	0.54±0.07** (47.57)	0.60±0.07* (53.12)	0.57±0.08** (57.46)	0.59±0.07** (58.45)

#Values are expressed as mean ± S.E. (n=5); *P<0.05 and **P<0.01 compared with vehicle control (ANOVA followed by Dunnet's t-test)

Hot plate method

Rats were placed on aluminum hot plate kept at 55±0.5 °C for a maximum time of 30 sec (Vaz *et al* 1997)**.** Reaction time was recorded when the animals licked or shaked one of the paws or jumped; at 0 and 15, 30 and 45 min after intraperitoneal administration of *Terminalia catappa* extract (200 mg/kg) to different groups of ten animals each. Naloxone 1mg/kg was used as the reference drugs.

Antipyretic activity

The antipyretic activity was evaluated by using Brewer's yeast induced pyrexia method in Albino rats. Fever was induced by injecting 2.0 ml/kg of 20% aqueous suspension of Brewer's yeast in normal saline and 18 h after yeast injection, the test drugs were administered. Rectal temperature was recorded by clinical thermometer at 0, 1, 2 and 3 h after drug administration. The animals were divided into 6 groups of 5 animals in each and were given the following treatment orally. Group I (control) received 1ml vehicle (2% gum acacia) only. Group II received paracetamol (30 mg/kg) as standard drug suspended in 2% gum acacia. Group III and IV received (100 and 200 mg/kg) of ethanolic extract suspended in 2% gum acacia. Before the experiment, the rats were maintained in separate cages with food *ad libitum* for 7 days and the animals with approximately constant rectal temperature (37.5 to 38.5°c) were selected for the study. The mean rectal temperature was found out for each group and compared with the value of standard drug (Mridha *et al* 2010).

Statistical analysis

All values were expressed as mean±SEM. The results analyzed for statistical significance using one-way ANOVA followed by Dunnet's 't' test with *P<0.05 and **P<0.01 were considered as significant (Kulkarni, 1997).

RESULTS

Acute toxicity test

In acute toxicity study, oral administration of graded doses (100, 200, 400, 600 and 800 mg/kg *p.o.*) of the methanol extract of *Terminalia catappa* to rats did not produce any significant changes in behaviour, breathing, salivation, lacrimation, sensory nervous system responses or gastrointestinal effects etc. during the observation period. No mortality was recorded in any group for the 14 days of administering the extract to the animals. *Terminalia catappa* was

safe upto a dose level of 800 mg/kg of body weight.

Anti-inflammatory Activity

The anti inflammatory effect of the methanolic extract of the leaves of *Terminalia catappa* using carrageenan induced oedema tests is expressed in **Table 1**. In this test, the positive control (Indomethacin) significantly ($p<0.05$; $p<0.01$) decreased the paw edema at 1 h to 4 h after carrageenan injection compared to saline with inhibition 56.31% to 59.85%. A maximum oedema paw volume of 1.42±0.03 mm was observed in the control rats, 4 h after the carrageenan injection. Rats with the extract at 200 mg/kg body weight significantly decreased ($p<0.05$; $p<0.01$) the carrageenan-induced oedema paw volume from 1 h to 4 h compared to the standard drug indomethacin at a dose of 10 mg/kg body weight.

The inhibition percentage of the oedema paw volume by the 200 mg/kg body weight of the extract was also found statistically significant when it was compared with the indomethacin treated animals at 1, 2, 3 and 4 h. The highest reduction in the paw volume by the 200 mg/kg body weight was 58.45% was comparable to that of the indomethacin (59.85%) at 4 h (**Figure 1**).

Palliative activity

The tail flick reaction time was significantly ($p<0.001$) increased in rats after *Terminalia catappa* leaf extract. Weak Palliative effect of extract was observed after 60 min of oral administration **Table 2**.

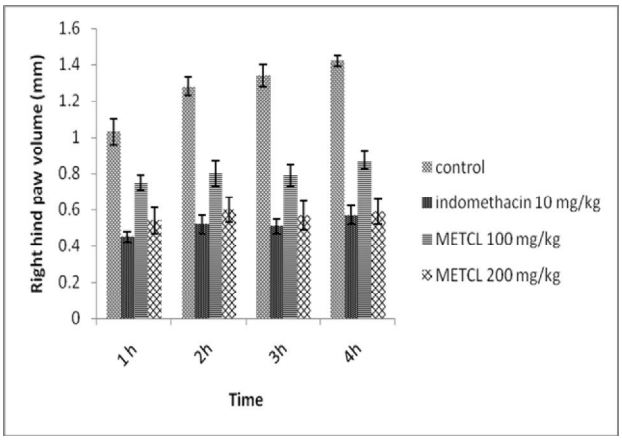

Fig. 1. Comparative assessment of anti-inflammatory effect of methanol extract of *Terminalia cattapa* (METCL) and indomethacin on carrageenan-induced oedema paw volume in male albindo Wistar rats.

The increase in tail flick reaction time at 60 min in METCL treated group was 127 %. The results of hot plate test presented in **Table 3** showed that the administration of *Terminalia catappa* leaf extract at the doses of 200 mg/kg and Naloxone (1 mg/kg) a reference drug significantly raised the pain threshold at observation time of 30 min in comparison with control ($P < 0.001$) (**Figure 2**).

Table 2. Palliative effect of methanolic extract of *Terminalia catappa* leaves (METCL) on reaction time by tail flick method

Group	Drug	Dose (mg/kg)	Control	30 min	60 min	90 min	120 min
1	METCL	200 mg	3.7±0.10	5.9±0.29**	7.5±0.12**	6.1±0.31**	4.9±0.23**
2	Naloxone	1 mg	3.0±0.14	2.3±0.12*	2.3±0.15*	2.5±0.15*	2.6±0.13
3	Naloxone + METCL	1 mg + 500 mg	3.6±0.15	4.1±0.21	4.6±0.21**	4.2±0.22*	4.3±0.31

#Values are expressed as mean ± S.E. (n=5); *P<0.05 and **P<0.01 compared with vehicle control (ANOVA followed by Dunnet's t-test)

Table 3. Palliative effect of methanolic extract of *Terminalia catappa* leaves (METCL) on the latency time by hot plate method

S. No.	Drug	Dose	0 min	15 min	30 min	45 min
1	Control	--	6.52±0.26	6.22±0.21	6.38±0.31	7.25±0.38
2	Naloxone	1 mg/kg	6.56±0.23*	11.45±0.38*	14.65±0.36**	14.79±0.81**
3	METCL	200 mg/kg	6.45±0.27**	10.10±0.30**	12.56±0.24*	12.86±0.72**

#Values are expressed as mean ± S.E. (n=5); *P<0.05 and **P<0.01 compared with vehicle control (ANOVA followed by Dunnet's t-test)

Antipyretic activity

The results of antipyretic activity of *Terminalia catappa* methanolic extract are shown in the **Table 4**. It was observed that methanolic extract at 200 mg/kg showed maximum antipyretic activity (**Figure 3**).

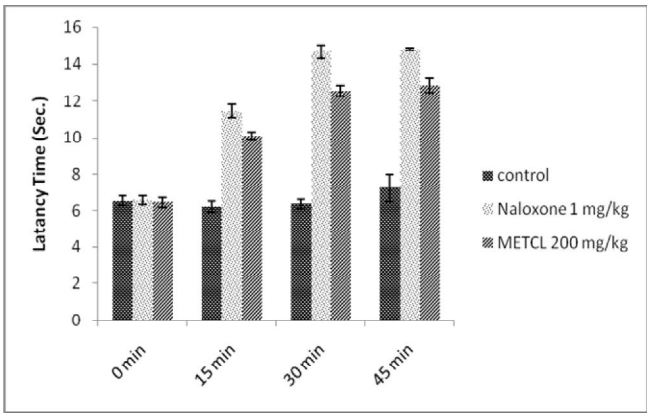

Fig. 2. Comparative assessment of palliative effect of methanolic extract of *Terminalia catappa* leaves (METCL) on the latency time by hot plate method

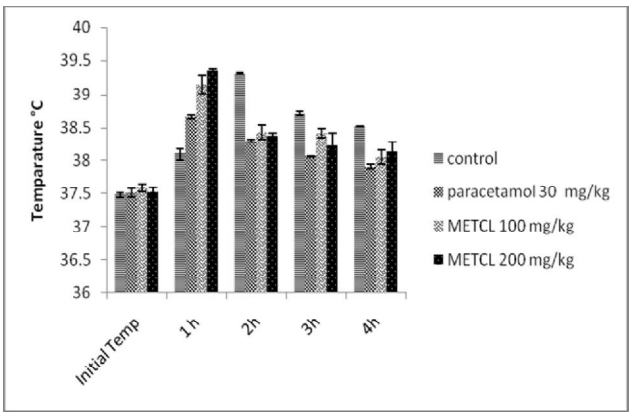

Fig. 3. Comparative assessment of antipyretic effect of methanolic extract of *Terminalia catappa* leaves (METCL) on the Yeast induced hyperthermia in albindo Wistar rats

Table 4. Antipyretic effect of methanolic extract of *Terminalia ctappa* leveas (METCL) on the yeast induced hyperthermia in albindo wistar rats

Group	Treatment	Dose (ml/kg)	Initial temp. (°C)	Rectal temperature (°C) (mean ± SEM)			
				1 h	2 h	3 h	4 h
I	Control	10	37.48±0.07	38.10±0.03	39.31±0.04	38.72±0.19	38.52±0.16
II	Paracetamol	30	37.51±0.06	38.66±0.14	38.30±0.11	38.06±0.07**	37.91±0.11
III	METCL	100	37.59±0.07	39.15±0.03	38.43±0.02	38.42±0.01*	38.05±0.03**
IV	METCL	200	37.53±0.03	39.35±0.08	38.38±0.01	38.23±0.03**	38.13±0.01**

#Values are expressed as mean±S.E. (n=6). *P<0.05 and **P<0.01 compared with vehicle control (ANOVA followed by Dunnet's t-test)

DISCUSSION

The anti-inflammatory activity was studied by carrageenan induced rat paw edema test at different doses (100 and 200 mg/kg body weight) of the methanol extract of *Terminalia catappa* leaves. Carrageenan induced oedema involves the synthesis or release of mediators at the injured site.

These mediators include prostaglandins, especially the E series, histamine, bradykinins, leukotrienes and serotonin, all of which also cause pain and fever. Inhibitions of these mediators from reaching the injured site or from bringing out their pharmacological effects normally ameliorate the inflammation and other symptoms. Development of oedema induced by carrageenan is commonly correlated with early exudative stage of inflammation (Asongalem *et al* 2004).

Carrageenan oedema is a multimediated phenomenon that liberates diversity of mediators. It is believed to be biphasic; the first phase (1 h) involves the release of serotonin and histamine while the second phase (over 1 h) is mediated by prostaglandins, the cyclooxygenase products, and the continuity between the two phases is provided by kinins (Hossain *et al* 2011). Since carrageenan induced inflammation model is a significant predictive test for anti-inflammatory agents acting by the mediators of acute inflammation (Ozaki, 1990; Mossi *et al* 1995).

The results of this study are an indication that *Terminania catappa can* be effective in acute inflammatory disorders. It is well known that most of the anti-inflammatory palliative drugs possess antipyretic activity.

Terminalia catappa Linn. revealed weak antipyretic effect at low dose *i.e.* 100 ml/kg *b.w.* but at higher dose *i.e.* 200 ml/kg *b.w.*, it produced marked antipyretic effect in brewel yeast induced fibril rats.

In general, anti-inflammatory drugs produce their antipyretic action through inhibition of prostaglandin synthesis within the hypothalamus (Clark and Cumby, 1975). Although there is no direct evidence of T*erminalia catappa* to interfere with prostaglandin synthesis in hypothalamus, but it can be supported by a related study in which *D. odorifera* extract was found to inhibit prostaglandin by synthesis (Goda *et al* 1992).

CONCLUSION

From the results, it is concluded that the extract from *Terminalia catappa* possessed both peripheral and central palliative activity along with marked antipyretic and anti-inflammatory activity in rats. Moreover, present study provokes the traditional use of *Terminalia catappa* for the purpose of various ailments like palliative, anti-inflammatory and antipyretic.

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REFERENCE

Asongalem EA, Foyet HS, Ekobo S, Dimo T, Kamtchouing P. Antiinflammatory, lack of central analgesia and antipyretic properties of Acanthus montanus (Ness) T. Anderson. *J. Ethnopharmacol.* 2004;95(1):63-8. [DOI: 10.1016/j.jep.2004.06.014]

Chu S-C, Yang S-F, Liu S-J, Kuo W-H, Chang Y-Z, Hsieh Y-S. In vitro and in vivo antimetastatic effects of Terminalia catappa L. leaves on lung cancer cells. *Food Chem. Toxicol.* 2007;45(7):1194-201. [DOI: 10.1016/j.fct.2006.12.028]

Clark WG, Cumby HR. The antipyretic effect of indomethacin. *J. Physiol.* 1975;248(3):625-38.

Davies OL, Raventos J, Walpole AL. A method for the evaluation of analgesic activity using rats. *Br. J. Pharmacol. Chemother.* 1946;1(4):255-64.

Deb L, Bhattacharjee C, Shetty SR, Dutta A. Evaluation of anti-diabetic potential of the *Syzygium cuminii* (linn) skeels by reverse pharmacological approaches. *Bull. Pharm. Res.* 2013;3(3):135-45.

Dey TK, Emran TB, Saha D, Rahman MA, Zahid Hosen SM, Chowdhury N. Antioxidant activity of ethanolic extract of *Cassia hirsuta* (L.) leaves. *Bull. Pharm. Res.* 2012;2(2):78-82.

El Hilaly J, Israili ZH, Lyoussi B. Acute and chronic toxicological studies of *Ajuga iva* in experimental animals. *J. Ethnopharmacol.* 2004;91(1):43-50. [DOI: 10.1016/j.jep.2003.11.009]

Goda Y, Kiuchi F, Shibuya M, Sankawa U. Inhibition of prostaglandin biosynthesis from Dalbergia odorifera. *Chem. Pharm. Bull. (Tokyo)* 1992;40(9):2452-7.

Hossain H, Moniruzzaman S, Nimmi I, Kawsar H, Hossain A, Islam A, Jahan IA. Anti-inflammatory and antioxidant activities of the ethanolic extract of *Ceriops decandra* (Griff.) Ding Hou bark. *Orient. Pharm. Exp. Med.* 2011; 11(4):215-20. [DOI: 10.1007/s13596-011-0037-z]

Jain RA, Agarwal RC, Pandey A, Jain R. Evaluation of *Argemone mexicana* fruits extract using micronucleus assay in mouse bone marrow cells. *Bull. Pharm. Res.* 2011; 1(2):22-4.

Jain S, Argal A. Effect of a polyherbal formulation on glycolic acid-induced urolithiasis in rats. *Bull. Pharm. Res.* 2013; 3(1):40-3.

Janssen PAJ, Niemegeers CJE, Dony JG. The inhibitory effect of fentanyl and other morphine-like analgesics on the warrn water induced tail withdrawl reflex in rats. *Arzneimittelforschung* 1963;13:502-7.

Kulkarni SK. Handbook of Experimental Pharmacology, 1st edition, Vallabh Prakashan, Delhi: 1997.

Lanhers MC, Fleurentin J, Dorfman P, Mortier F, Pelt JM. Analgesic, antipyretic and anti-inflammatory properties of *Euphorbia hirta*. *Planta Med.*1991;57(3):225-31. [DOI: 10.1055/s-2006-960079]

Lin C-C, Kan W-S. Medicinal plants used for the treatment of hepatitis in Taiwan. *Am. J. Chin. Med.* 1990;18(1-2):35-43. [DOI: 10.1142/S0192415X9000006X]

Madaan R, Bansal G, Sharma A. New phenolic glycosides from roots of *Actaea spicata* Linneaus. *Bull. Pharm. Res.* 2011;1(1):11-4.

Mossai JS, Rafatullah S, Galal AM, Al-Yahya MA. Pharmacological studies of *Rhus retinorrhaea*. *Int. J. Pharmacog.* 1995;33(3):242-6.

Mridha D, Saha D, Beura S. *Int. J. Pharmacol. Biol. Sci.* 2010;4:67.

Muthu C, Ayyanar M, Raja N, Ignacimuthu S. Medicinal plants used by traditional healers in Kancheepuram district of Tamil Nadu, India. *J. Ethnobiol. Ethnomed.* 2006;2:43. [DOI: 10.1186/1746-4269-2-43]

Nonaka G-i, Nishioka I, Nishizawa M, Yamagishi T, Kashiwada Y, Dutschman GE, Bodner AJ, Kilkuskie RE, Cheng Y-C, Lee K-H. Anti-Aids agents, 2: Inhibitory effects of tannins on HIV reverse transcriptase and HIV replication in H9 lymphocyte cells. *J. Nat. Prod.* 1990; 53(3):587-95. [DOI: 10.1021/np50069a008]

OECD Guidance Document on Acute Oral Toxicity. Environmental Health and Safety Monograph Series on Testing and Assessment No 24, 2001.

Ozaki Y. Antiinflammatory effects of Curcuma xanthorrhiza Roxb, and its active principles. *Chem. Pharm. Bull. (Tokyo)* 1990;38(4):1045-8. [DOI: 10.1248/cpb.38.1045]

Perianayagam JB, Sharma SK, Pillai KK. Anti-inflammatory activity of Trichodesma indicum root extract in experimental animals. *J. Ethnopharmacol.* 2006;104(3): 410-4. [DOI: 10.1016/j.jep.2005.08.077]

Rang HP, Dale M, Ritter J, Moore P. Pharmacology, Elsevier, New Delhi; 2005: 666.

Srividya AR, Dhanabal SP, Yadav AK, Sathish Kumar MN, Vishnuvarthan VJ. Phytopreventive antihyperlipidemic activity of *Curcuma zedoaria*. *Bull. Pharm. Res.* 2012; 2(1):22-5.

Tanaka T, Nonaka G-I, Nishioka I. Tannins and related compounds. XLII. Isolation and characterization of four new hydrolyzable tannins, terflavins A and B, tergallagin and tercatain from leaves of Terminalia catappa L. *Chem. Pharm. Bull.* 1986;34(3):1039-49. [DOI: 10.1248/cpb.34.1039]

Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. *Inflamm. Res.* 1995;44(1):1-10. [DOI: 10.1007/BF01630479]

Vaz ZR, Mata LV, Calixto JB. Analgesic effect of the herbal medicine catuama in thermal and chemical models of nociception in mice. *Phytother. Res.* 1997;11(2):101-6. [DOI: 10.1002/(SICI)1099-1573(199703)11:2<101::AID-PTR28>3.0.CO;2-U]

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