Original Article

Evaluation of the analgesic, antipyretic and anti-inflammatory activities of the extracts from the pericarp of *Garcinia mangostana* Linn. in experimental animals

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Abstract

The effects of the ethanol and dichloromethane extracts from the pericarp of *Garcinia mangostana* Linn. (*G. mangostana*) on nociceptive response using writhing and hot plate tests in mice and the antipyretic activity in yeast-induced fever in rats, were examined. Anti-inflammatory activity using carrageenin-induced paw edema in rats was also investigated. The ethanol extract (400, 800 mg/kg, p.o.) significantly suppressed the writhings induced by acetic acid. The dichloromethane extract (200, 400 and 800 mg/kg, p.o.) also decreased acetic acid-induced writhing in mice. Neither the ethanol extract nor dichloromethane extract had significant effects on antinociceptive response in the hot plate test. No significant effects on yeast-induced fever were observed after oral administration of the ethanol and dichloromethane extracts in rats. Either oral administration (800 mg/kg) of the ethanol extract or dichloromethane extract significantly decreased the rat paw edema induced by carrageenin. These results suggest that the ethanol and dichloromethane extracts from the fruit hull of *G. mangostana* possess analgesic and anti-inflammatory actions but no antipyretic action and one mechanism of action of the anti-inflammatory activity of the extracts may involve in cyclooxygenase (COX) inhibition.

Keywords: *Garcinia mangostana*, pericarp, extract, analgesic, antipyretic, anti-inflammatory

1. Introduction

Garcinia mangostana Linn. (*G. mangostana*), commonly known as mangosteen, family Guttiferae, is a tropical evergreen tree. Its origin is in Southeast Asia. It is known in Thai as "Mangkhut". The edible fruit is deep reddish purple when ripe. In Asia, it is known as the "Queen of Fruits" due to its pleasant flavor (Morton, 1987). The fruit hull of mangosteen has been used for a long time in Southeast Asia as a traditional medicine for skin infection, wounds, dysentery and diarrhea (Morton, 1987).

Several isolation and identification of compounds from *G. mangostana* have been reported. For examples, many xanthones e.g., mangostin or α-mangostin, β-mangostin, γ-mangostin and gartanin (Gopalakrishnan and Balaganesan, 2000), were isolated and identified. Mangostenones C, D, and E, prenylated xanthones, methoxy-β-mangostin and geranylated biphenyl derivative, 3-hydroxy-4-geranyl-5-methoxybiphenyl, were isolated from the young fruit of *G. mangostana* (Suksamrarn *et al.*, 2006; Dharmaratne *et al.*, 2005). Diprenylated xanthone (mangoxanthone) and benzophenone (3′,6-dihydroxy-2,4,4′-trimethoxybenzophenone) were isolated from the acetone extract of the heartwood of *G. mangostana* (Nguyen *et al.*, 2005).

Many pharmacological activities from the pericarp of *G. mangostana* have been studied. Several xanthones e.g.,

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mangostin have antibacterial (Dharmaratne *et al.*, 2005), antifungal (Gopalakrishnan *et al.*, 1997), antiplasmodial (Mahabusarakam *et al.*, 2006), antioxidant (Weecharangsan *et al.*, 2006), antitumor (Suksamrarn *et al.*, 2006), anti-HIV activities (Chen *et al.*, 1996); and are histamine and serotonin receptor antagonists (Chairungsrilerd *et al.*, 1998a,b) as well as vasorelaxant (Furukawa *et al.*, 1997).

This study aimed to investigate analgesic and anti-pyretic activities of the ethanol and dichloromethane extracts from the pericarp of *G. mangostana* using writhing and hot plate tests in mice and yeast-induced fever in rats, respectively. The anti-inflammatory effect was also tested using carrageenin-induced paw edema in rats.

2. Materials and Methods

2.1 Plant material and chemicals

The fresh rind of *G. mangostana* Linn. (Guttiferae) was collected in October, 2004 from Chumphon Province, Thailand. The voucher specimen (number: SKP 083071301) was kept at the Herbarium of the Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand.

The following drugs and AR grade of chemicals were used: morphine sulfate, brewer's yeast, carrageenin lambda (Sigma Chem. Co., St. Louis, U.S.A.), aspirin and tween 80 (Srichand United Dispensary Co., Ltd., Bangkok, Thailand), sodium chloride (Carlo Erba, Germanny), acetic acid (AR grade, J.T., Baker Inc., Phillipsburg, U.S.A.), propylene glycol (Vidhyasom Co., Ltd., Bangkok, Thailand), ethanol and dichloromethane (Merck KGaA, Germany).

2.2 Preparation of the extracts from the fruit rind of *G. mangostana*

The small pieces of the rind of *G. mangostana* were dried at 50°C, powdered and extracted with ethanol. For the ethanolic extract, dried ground rind of *G. mangostana* was macerated for seven days with 95% ethanol. The maceration was done three times, then concentrated to dryness under reduced pressure. The dichloromethane extract was obtained by partition the ethanol extract dissolved in ethanol between dichloromethane and water. The lower part was collected as dichloromethane extract. The separation was done three times, then combined. All the extracts were filtered, concentrated and freeze dried. The percentage yields of the ethanol and dichloromethane extracts were 17.73 % w/w and 7.12 % w/w, respectively. The ethanol extract and dichloromethane extract were quantitatively analyzed by a reverse phase HPLC with Hypersil BDS C18 column®, 125 x 4 mm. The mobile phase was 100 % acetonitrile : 0.2 % formic acid (70:30) using a UV detector at the wave length of 240 nm. The major component was α-mangostin. The amounts of α-mangostin in ethanol extract and dichloromethane extract were 16.91 % w/w and 45.74 % w/w, respectively. The stan-

dard α-mangostin (96.5%) was purchased from Chromadex INC, USA. The ethanol extract and dichloromethane extract were qualitative analyzed for other components. At least one more compound was shown in the chromatograms. This compound was γ-mangostin. The authentic compound was kindly provided by Associate Professor Dr.Sunit Suksamrarn, Department of Chemistry, Srinakharinwirot University, Thailand. The ethanol and dichloromethane extracts were dissolved in a cosolvent (containing propylene glycol : tween 80 : water = 4:1:4) and used as the test extracts. All doses were expressed in terms of crude extract (mg/kg body weight).

2.3 Animals

All animals were obtained from the Southern Laboratory Animal Facility, Prince of Songkla University, Hat Yai, Songkhla, Thailand. The animals used in this study were male Swiss albino mice, weighing 30-38 g and Wistar rats with the weight ranging from 150-210 g. The animals were housed for at least one week in the laboratory animal room prior to testing. Housing conditions were thermostatically maintained at 23-24°C with a 12 :12 light-dark cycle. Food and water were given *ad libitum* unless otherwise specified. All experimental protocols were approved by the Animal Ethics Committee, Prince of Songkla University (No 0521.11/ 330).

2.4 Antinociceptive activities

2.4.1 Writhing test

Writhing behavior was tested, in which 0.6% acetic acid solution (10 ml/kg body weight) was injected intraperitoneally and the number of writhing and stretching was counted over a 20 min period as previously reported (Koster *et al.*,1959; Hendershot and Forsaith, 1959). The extracts (200, 400 and 800 mg/kg), a reference analgesic drug, aspirin (200 mg/kg), or cosolvent were orally administered 30 min before the intraperitoneal injection of acetic acid.

2.4.2 Hot plate test

The hot plate test was carried out according to the method described by Woolfe and MacDonald (1944). Mice were placed on a hot plate maintained at 55°C ± 1°C. Latency of nociceptive response such as licking of a hind limb or jumping was measured. Starting thirty minutes after oral administration of the test agents (200, 400, 800 mg/kg) except morphine sulfate (10 mg/kg, 15 min after subcutaneous administration), the nociceptive response was measured every 15 min over a 60 min period. The cut-off time was 45 s. Only the mice that showed nociceptive responses within 15 s were used for the experiments.

2.5 Antipyretic activity

Antipyretic activity of the extracts was measured the method described by Adams *et al.* with some modification (1968). Male Wistar rats were fasted overnight with water *ad libitum* before the experiments. Pyrexia was induced by subcutaneously injecting 20% (W/V) brewer's yeast suspension (10 ml/kg) into the animal's dorsal region. Seventeen hours after the injection, the rectal temperature of each rat was measured using a digital thermometer (SK-1250 MC, Sato Keiryoki Mfg. Co., Ltd., Japan). Only the rats that showed an increase in the temperature of at least 0.7°C were used for the following experiments. The test extracts (200, 400, 800 mg/kg), aspirin (200 mg/kg) or cosolvent was administered orally and the temperature was measured at 1, 2, 3, 4, and 5 hours after the drug administration.

2.6 Anti-inflammatory activity

According to the method described by Winter *et al.* (1962), the initial right hind paw volume of the rat was measured using a plethysmometer (Ugo Basile) and then 0.1 ml of 1% (w/v) carrageenin in 0.9% sodium chloride was subcutaneously injected into the subplantar region of the right hind paw. The volume of the right hind paw was measured at 1, 2, 3, 4 and 5 hours after the carrageenin injection and the paw volume was determined. The cosolvent, the extract (200, 400, 800 mg/kg) or aspirin (200 mg/kg) was orally administered 30 min before the carrageenin injection.

2.7 Statistical analysis

Data are expressed as mean±SEM and were analyzed statistically by one-way ANOVA, followed by Dunnett's test. A difference was considered significant at $p < 0.05$.

3. Results

3.1 Effects of the ethanol and dichloromethane extracts of *G. mangostana* and aspirin on acetic acid-induced writhing in mice

Oral administration of the ethanol extract from the fruit hull of *G. mangostana* (200, 400, 800 mg/kg) dose dependently reduced the number of writhing and stretching induced by 0.6% acetic acid (i.p.) in mice. At the dose of 200, 400 and 800 mg/kg, it inhibited the writhing by 24%, 37% and 62%, respectively. Similarly, the dichloromethane extract of *G. mangostana* rind significantly suppressed the writhings induced by acetic acid (0.6%, i.p.) after oral administration (200, 400 and 800 mg/kg) in mice. It decreased the writhing at the dose of 200, 400 and 800 mg/kg by 29%, 31% and 33%, respectively. The reference drug, aspirin (200 mg/kg), also produced a significant protective effect towards the acetic acid induced pain by 80% inhibition (Figure 1).
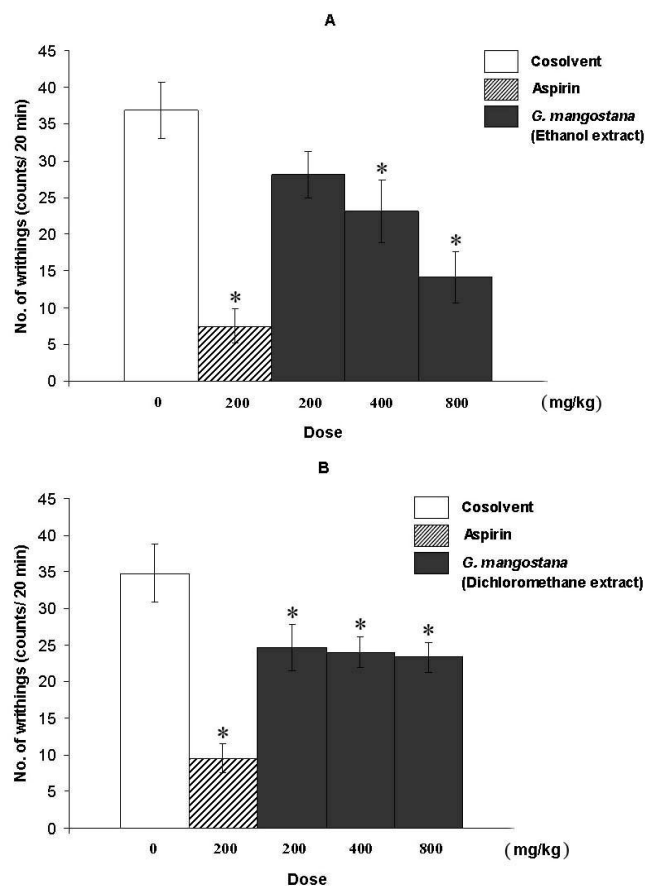

Figure 1. Effects of ethanol (A) and dichloromethane (B) extracts of *G. mangostana* and aspirin on acetic acid-induced writhing in mice. The ethanol and dichloromethane extracts of *G. mangostana* were orally administered. Then 30 min later, 0.6% acetic acid solution (10 ml/kg) was intraperitoneally injected into mice. Immediately after injection, the number of writhings was counted over a 20-min period. Each datum represents the mean ± S.E.M. from 10 mice. *$p < 0.05$ compared to the control group (Dunnett's test).

3.2 Effects of the ethanol and dichloromethane extracts of *G. mangostana*, aspirin and morphine on nociceptive response induced by heat in mice

The extracts of *G. mangostana* pericarp (200, 400 and 800 mg/kg, p.o.) and aspirin (200 mg/kg, p.o.) did not significantly exert protective effect on heat-induced pain in mice. By contrast, the centrally acting analgesic drug, morphine sulfate (10 mg/kg, s.c.) markedly increased pain latency (Table 1).

3.3 Effects of the ethanol and dichloromethane extracts of *G. mangostana* and aspirin on brewer's yeast-induced fever in rats

The ethanol and dichloromethane extracts of *G. mangostana* (200, 400 and 800 mg/kg, p.o.) did not show

Table 1. Effects of the ethanol and dichloromethane extracts of *G. mangostana*, aspirin and morphine on nociceptive response induced by heat in mice.

Drug	Dose (mg/kg, p.o.)	Latency of nociceptive response (sec) at			
		15 min	30 min	45 min	60 min
Cosolvent	-	14.4±1.4	14.0±2.0	15.9±1.6	15.2±1.3
Aspirin	200	14.2±1.2	13.5±1.0	14.8±1.5	15.0±1.0
Morphine (s.c.)	10	42.9±1.9*	45.0±0.0*	44.9±0.1*	41.4±2.6*
G. mangostana	200	15.2±1.4	17.1±2.0	14.1±2.1	16.8±1.1
(ethanol)	400	16.0±1.3	14.6±1.5	16.1±1.6	14.2±1.4
	800	18.9±1.8	14.1±1.6	13.1±1.5	14.0±1.9
Cosolvent	-	13.2±1.2	12.1±1.3	12.8±0.9	12.3±1.1
Aspirin	200	12.0±0.9	12.6±1.7	12.1±1.3	14.8±1.2
Morphine (s.c.)	10	32.9±3.6*	39.3±3.5*	36.3±3.0*	37.6±3.2*
G. mangostana	200	14.4±1.7	16.2±1.3	13.5±1.3	16.6±1.1
(dichloromethane)	400	16.9±2.0	14.3±2.1	12.7±1.7	14.4±2.1
	800	14.6±2.0	13.6±1.8	13.3±1.9	15.1±2.0

Beginning at 30 min after oral administration of the test agents (or 15 min after morphine injection, s.c.), the nociceptive response was measured every 15 min over a 60-min period. Each datum represents the latency of nociceptive responses (sec) ± S.E.M. (n= 10) * p< 0.01 compared with the control group (Dunnett's test).

any significant effect on yeast-induced fever in rats while the reference drug, aspirin, suppressed fever induced by yeast in rats (Table 2).

3.4 Effects of the ethanol and dichloromethane extracts of *G. mangostana* and aspirin on carrageenin-induced paw edema in rats

Oral administration of the ethanol extract at the dose of 800 mg/kg significantly suppressed the paw edema at 1, 3, 4 and 5 hours after the carrageenin injection in rats (Figure 2-A). The dichloromethane extract (800 mg/kg) also significantly decreased the carrageenin-induced paw edema at 1, 2, 3, 4 and 5 hours after the carrageenin injection in rats (Figure 2-B). Aspirin (200 mg/kg), the standard drug, also reduced the paw edema in this test (Figure 2).

4. Discussion

The results demonstrate that the ethanol and dichloromethane extracts obtained from the fruit hull of *G. mangostana* exhibited analgesic and anti-inflammatory activities.

The writhing test is generally used for screening of antinociceptive effect (Koster *et al.*, 1959; Hendershot and Forsaith, 1959). The ethanol and dichloromethane extracts of *G. mangostana* showed significant inhibition on acetic acid-induced writhing response. The reference drug, aspirin (200 mg/kg), also produced significant protective effect towards the acetic acid-induced pain in mice. In comparison, both of the ethanol and dichloromethane extracts were less

potent than those of the aspirin on nociceptive response in mice. It is possible that the active compound (s) contained in the extracts of *G. mangostana* (α-mangostin and/or γ-mangostin) possesses the antinociceptive effect.

Pain induced by thermal stimuli is known to be selective to centrally but not peripherally acting analgesic drugs (Chau, 1989). In the present study, morphine, a centrally acting analgesic drug, produced an inhibitory effect on the nociceptive response in the hot plate test, while all the extracts from the pericarp of *G. mangostana* and aspirin failed to affect the responses. Another study of the analgesic activity of mangostin and its derivatives, xanthones from the rind fruit of *G. mangostana* was also reported by using a tail flick model, but none of these compounds exhibited analgesic effect in rats tested by the radiant heat method (Shankaranarayan *et al.*, 1979). Thus, it is suggested that the apparent antinociceptive activity of the extracts may be mediated through the peripheral mechanism.

Neither the ethanol nor the dichloromethane extracts of *G. mangostana* showed significant effect on yeast-induced fever in rats while the reference drug, aspirin, suppressed the fever by inhibiting the synthesis of prostaglandin E2 (Dascombe, 1985; Vane, 1987). None of the mangostin and its derivatives from the fruit rind of *G. mangostana* showed any antipyretic effect in the similar model (Shankaranarayan *et al.*, 1979).

In the present study, the ethanol and dichloromethane extracts of the fruit rind of *G. mangostana* at the dose of 800 mg/kg significantly suppressed the paw edema induced by carrageenin in rats and they were less potent than that of the aspirin (200 mg/kg). α-Mangostin and its derivatives from
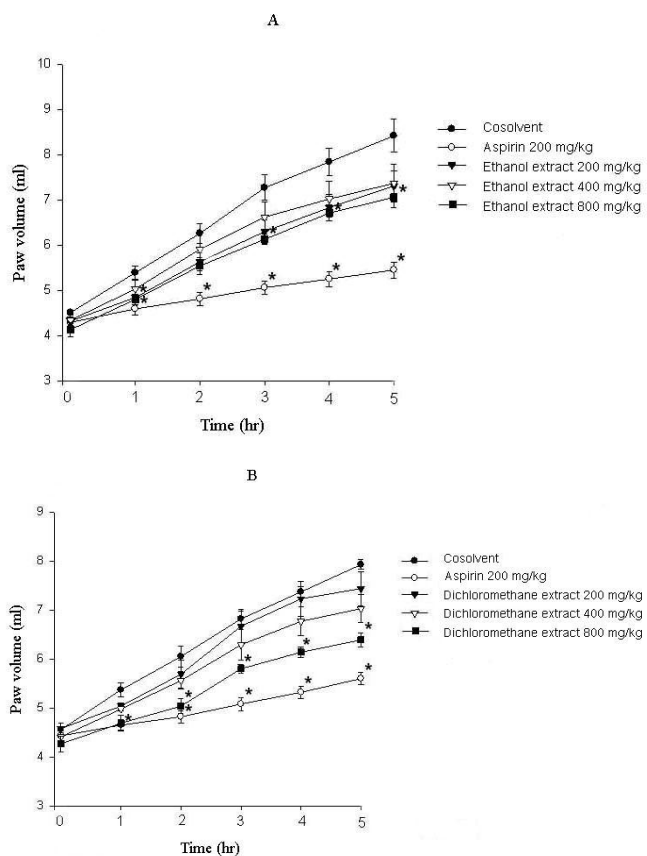
Figure 2. Effects of ethanol (A) and dichloromethane (B) extracts of *G. mangostana* and aspirin on carrageenin-induced paw edema in rats. The initial hind paw volume of the rat was determined volumetrically. Thirty minutes after the test agent was administered (p.o.), 1% carrageenin in saline was subcutaneously injected in a volume of 0.1 ml into the right hind paw at time 0 hr and the paw volume was measured at 1 hr intervals for 5 hr. Each point represents the mean $\pm$ S.E.M. of 6 rats. *$p<0.05$, compared to the cosolvent group (Dunnett's test).

the fruit rind of *G. mangostana* also produced anti-inflammatory activity in rats tested by carrageenin-induced paw edema, cotton pellet implantation and granuloma pouch techniques (Shankaranarayan *et al.*, 1979). As it has been reported that ethanolic extract from the fruit rind of *G. mangostana* inhibited A23187-induced prostaglandin E_2 synthesis in C6 rat glioma cells (Nakatani *et al.*, 2002a), it is possible that one mechanism of action on the anti-inflammatory activity of the extracts may involve in cyclooxygenase (COX) inhibition and some xanthones contained in the extracts may involve in the anti-inflammatory activity but not α-mangostin which was inactive in COX-1 and COX-2 assays at the dose of 24.36 μM while aspirin exhibited IC_{50} for COX-1 and COX-2 assays at 22.20-27.75 μM and 49.96-55.51 μM, respectively (Data were provided by National Center for Genetic Engineering and Biotechnology (BIOTEC), Thailand, using radioimmunoassay method). γ-Mangostin, a tetraoxygenated diprenylated xanthone contained in

mangosteen competitively inhibited COX activity in an enzyme assay *in vitro* (Nakatani *et al.*, 2002b). Furthermore, it also inhibited rat carragenin-induced paw edema and decreased lipopolysaccharide-induced COX-2 gene expression in C6 rat glioma cells (Nakatani *et al.*, 2004). As already mentioned in the preparation of the extracts, besides the α-mangostin, the extracts also contained γ-mangostin. Though the extracts contained γ-mangostin as a small proportion compared with the α-mangostin, it could play an important role in anti-inflammatory activity of the extracts. Therefore, to control the quality of the extracts, the quantity of both compounds should be analyzed.

Both extracts from the fruit hull of *G. mangostana* exhibited analgesic and anti-inflammatory effects but there was no antipyretic effect. In addition to COX inhibition, other mechanism (s) of the active substance (s) from the pericarp of *G. mangostana* cannot be excluded. However, further studies would be needed to clarify the mechanism (s) of the extracts of *G. mangostana*.

Based on these results, we conclude that the ethanol and dichloromethane extracts of the fruit rind of *G. mangostana* possess analgesic and anti-inflammatory activities but no antipyretic effect and one mechanism of action on the anti-inflammatory activity of the extracts may involve in COX inhibition.

Acknowledgement

References

Adams, S.S., Hebborn, P. and Nicholson, J.S. 1968. Some aspects of the pharmacology of ibufenac, a non-steroidal anti-inflammatory agent. The Journal of Pharmacy and Pharmacology. 20, 305-312.

Chairungsrilerd, N., Furukawa, K-I., Ohta, T., Nozoe, S. and Ohizumi, Y. 1998a. γ-mangostin, a novel type of 5-hydroxytryptamine 2A receptor antagonist. Naunyn-Schmiedeberg's Archives of Pharmacology. 357, 25-31.

Chairungsrilerd, N., Furukawa, K-I., Tadano, T., Kisara, K. and Ohizumi, Y. 1998b. Effect of γ-mangostin through the inhibition of 5-hydroxytryptamine$_{2A}$ receptors in 5-fluoro-a-methyltryptamine-induced head-twitch responses of mice. British Journal of Pharmacology. 123, 855-862.

Chau, T. 1989. Pharmacology methods in the control of inflammation. *In*: Modern Methods in Pharmacology, Vol. V, Alan. R. Liss., Inc., New York, pp. 195-212.

Chen, S.X., Wan, M. and Loh, B.N. 1996. Active constituents against HIV-1 protease from *Garcinia mangostana*. Planta Medica. 62, 381-382.

Table 2. Effects of the ethanol and dichloromethane extracts of *G. mangostana* and aspirin on brewer's yeast-induced fever in rats.

Drug	Dose (mg/kg, p.o.)	Rectal temperature ($^{\circ}$C)						
		-17 hr	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr
Cosolvent	-	36.2±0.1	37.1±0.1	37.2±0.1	37.0±0.1	37.0±0.1	36.8±0.1	36.7±0.1
Aspirin	200	36.4±0.1	37.2±0.0	36.5±0.1*	36.1±0.1*	36.1±0.1*	35.9±0.1*	35.9±0.1*
G. mamgostana	200	36.5±0.0	37.2±0.0	36.8±0.1	36.7±0.1	36.6±0.1	36.5±0.1	36.4±0.1
(ethanol)	400	36.4±0.1	37.2±0.0	36.8±0.1	36.7±0.1	36.5±0.1	36.3±0.1	36.3±0.1
	800	36.4±0.1	37.4±0.1	37.2±0.2	37.0±0.2	36.6±0.2	36.6±0.2	36.6±0.2
Cosolvent	-	36.8±0.1	37.6±0.1	37.5±0.1	37.3±0.1	37.1±0.1	37.0±0.1	36.9±0.1
Aspirin	200	36.7±0.1	37.4±0.1	36.9±0.1*	36.7±0.1*	36.4±0.1*	36.3±0.1*	36.3±0.1*
G. mamgostana	200	36.8±0.1	37.6±0.1	37.4±0.1	37.3±0.1	37.1±0.1	37.1±0.1	37.0±0.1
(dichloromethane)	400	36.6±0.1	37.4±0.1	37.2±0.1	37.1±0.1	36.9±0.1	36.8±0.1	36.7±0.1
	800	36.8±0.1	37.6±0.1	37.4±0.1	37.2±0.1	37.1±0.1	36.9±0.1	36.9±0.1

Twenty percent of yeast suspension was subcutaneously injected into the dorsum region of rats. Seventeen hours after injection, the rectal temperature was measured (time 0) and then the drugs were orally administered. The temperature was again measured at 1, 2, 3, 4 and 5 hr after drug administration. Each datum represents the mean rectal temperature ($^{\circ}$C) ± S.E.M. (n = 7-8) *$p < 0.05$, compared with the control group (Dunnett's test).

Dascombe, M.J. 1985. The pharmacology of fever. Progress in Neurobiology. 25, 327-373.

Dharmaratne, H.R., Piyasena, K.G. and Tennakoon, S.B. 2005. A geranylated biphenyl derivative from *Garcinia mangostana*. Natural Product Research. 19, 239-243.

Furukawa, K., Chairungsrilerd, N., Ohta, T., Nozoe, S. and Ohizumi, Y. 1997. Novel types of receptor antagonists from the medicinal plant *Garcinia mangostana*. Nippon Yakurigaku Zasshi 110 Suppl 1, 153P-158P [Abstract].

Gopalakrishnan, G., Banumathi, B. and Suresh, G. 1997. Evaluation of the antifungal activity of natural xanthones from *Garcinia mangostana* and their synthetic derivatives. Journal of Natural Products. 60, 519-524.

Gopalakrishnan, G. and Balaganesan, B. 2000. Two novel xanthones from *Garcinia mangostana*. Fitoterapia 71, 607-609.

Hendershot, L.C. and Forsaith, J. 1959. Antagonism of the frequency of phenylquinone-induced writhing in the mouse by weak analgesics and nonanalgesics. The Journal of Pharmacology and Experimental Therapeutics 125, 237-240.

Koster, R., Anderson, M. and de Beer, E.J. 1959. Acetic acid for analgesic screening. Federation Proceedings. 18, 412.

Mahabusarakam, W., Kuaha, K., Wilairat, P. and Taylor, W.C. 2006. Prenylated xanthones as potential antiplasmodial substances. Planta Medica. 72, 912-916.

Morton, J. 1987. Mangosteen. *In*: Fruits of warm climates, p. 301-304, Available at: URL: http://www.hort.purdue.edu/newcrop/morton/mangosteen.html. Ac-

cessed April 14, 2007.

Nakatani, K., Atsumi, M., Arakawa, T., Oosawa, K., Shimura, S., Nakahata, N. and Ohizumi, Y. 2002a. Inhibitions of histamine release and prostaglandin E$_2$ synthesis by mangosteen, a Thai medicinal plant. Biological and Pharmaceutical Bulletin. 25, 1137-1141.

Nakatani, K., Nakahata, N., Arakawa, T., Yasuda, H. and Ohizumi, Y. 2002b. Inhibition of cyclooxygenase and prostaglandin E$_2$ synthesis by γ-mangostin, a xanthone derivative in mangosteen, in C6 rat glioma cells. Biochemical Pharmacology. 63, 73-79.

Nakatani, K., Yamakuni, T., Kondo, N., Arakawa, T., Oosawa, K., Shimura, S., Inoue, H. and Ohizumi, Y. 2004. γ-mangostin inhibits inhibitor-kB kinase activity and decreases lipopolysaccharide-induced cyclooxygenase-2 gene expression in C6 rat glioma cells. Molecular Pharmacology. 66, 667-674.

Nguyen, L.H., Venkatraman, G., Sim, K.Y. and Harrison, L.J. 2005. Xanthones and benzophenones from *Garcinia griffithii* and *Garcinia mangostana*. Phytochemistry 66, 1718-1723.

Shankaranarayan, D., Gopalakrishnan, C. And Kameswaran, L. 1979. Pharmacological profile of mangostin and its derivatives. Archives Internationales de Pharmacodynamie et de Therapie. 239, 257-269.

Suksamrarn, S., Komutiban, O., Ratananukul, P., Chimnoi, N., Lartpornmatulee, N. and Suksamrarn, A. 2006. Cytotoxic prenylated xanthones from the young fruit of *Garcinia mangostana*. Chemical and Pharmaceutical Bulletin. 54, 301-305.

Vane, J. 1987. The evolution of non-steroidal anti-inflammatory drugs and their mechanisms of action. Drugs 33 Suppl 1, 18-27.

Weecharangsan, W., Opanasopit, P., Sukma, M., Ngawhirun-pat, T., Sotanaphun, U. and Siripong, P. 2006. Antio-xidative and neuroprotective activities of extracts from the fruit hull of mangosteen (*Garcinia mangostana* Linn.). Medical Principles and Practice. 15, 281-287.

Winter, C.A. Risley, E.A. and Nuss, G.W. 1962. Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. Proceedings of the Society for Experimental Biology and Medicine. 111, 544-547.

Woolfe, G. and MacDonald, A.D. 1944. The evaluation of the analgesic action of pethidine hydrochloride (Demerol). The Journal of Pharmacology and Experimental Therapeutics. 80, 300-330.