Analgesic and Antipyretic Activity of Tri-Sa-Maw Recipe

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Background: *Tri-sa-maw recipe is composed of equal proportions of the three fruits including Terminalia chebula Retz., Terminalia sp. and Terminalia bellirica Roxb. In Southeast Asia, these fruits are used as both food and medicine. In Thai traditional medicine, Tri-sa-maw recipe is well known for treating fever, expectorant, periodic maintenance, and tight stomach relief.*
Objective: *To study anti-inflammatory, analgesic and antipyretic activities of Tri-sa-maw recipe in experimental animals.*
Material and Method: *The anti-inflammatory study was conducted by two experimental models; ethyl phenylpropiolate-induced ear edema and carrageenin-induced paw edema. For analgesic activity, the pain was induced by acetic acid or heat. In addition, yeast-induced hyperthermia was performed for the study of antipyretic activity.*
Results: *The results showed that Tri-sa-maw recipe extract reduced ear edema of rat induced by EPP but did not inhibit acute inflammation in the carrageenin-induced paw edema. However, the extract at the doses of 300-1,200 mg/kg was able to inhibit the acetic acid-induced writhing response, but not the heat-induced pain. This result suggests the peripheral effect of its analgesic activity, which inhibits the biosynthesis, and/or release of some pain mediators. Finally, oral administration of the extract at the dose of 1,200 mg/kg body weight effectively reduced the hyperthermia, which possibly is due to the inhibition of prostaglandins.*
Conclusion: *The present study has clearly demonstrated both analgesic and antipyretic activities of Tri-sa-maw recipe.*

Keywords: *Tri-sa-maw recipe, Anti-inflammatory activity, Analgesic activity, Antipyretic activity*

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Tri-sa-maw recipe is composed of equal proportions of the three fruits including *Terminalia chebula* Retz., *Terminalia sp.* and *Terminalia bellirica* Roxb. In Southeast Asia, these fruits are used as both food and medicine. In Thai traditional medicine, Tri-sa-maw recipe is well known for treating fever, expectorant, periodic maintenance, and tight stomach relief. *T. chebula, T. bellirica* and *Terminalia sp.* are plants belonging to the family of Combretaceae[1]. *T. chebula* or Sa-Maw-Thai has several pharmacological activities in both in vitro and in vivo tests, such as antioxidant[2,3] and antibacterial[4]. *T. bellirica* or Sa-Maw-Phi Phek showed antibacterial[5], antifungal[6], antioxidant[7] and anti-HIV-1 reverse transcriptase[8]. However, the anti-inflammatory, analgesic and antipyretic activities of these plant ingredients have never been studied. The aim of the present study is therefore to determine the anti-inflammatory, analgesic and antipyretic activities of Tri-sa-maw recipe in experimental animals.

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Material and Method

Plant materials and extraction method

The fruits of *T. chebula, T. bellerica* and *Terminalia sp.* were identified by Associate Professor Dr. Noppamas Soonthornchareonnon, Department of Pharmacognosy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand. The voucher specimen has been kept at the Faculty of Pharmacy, Mahidol University, Bangkok, Thailand.

Each plant material was dried in hot air oven at 50°C, ground into a fine powder and sifted through a sieve (No. 100). Tri-sa-maw recipe was prepared by Thai-China Flavours and Fragrnces Industry Co., Ltd. The quality control of raw materials and the water extract of Tri-sa-maw recipe was followed by Thai Herbal Pharmacopoeia including organoleptic examination, % loss on drying, extractive values, total ash and acid

insoluble ash[9]. The chemical constituents in raw materials and the water extract of Tri-sa-maw recipe were also studied using thin layer chromatography (TLC) following the method of Farnswort[10].

Experimental animals

Male ICR albino mice (30-40 g) and male Sprague Dawley rats (40-60 g, 100-120 g, 200-250 g) were obtained from the National Laboratory Animal Center, Nakorn Pathom, Thailand. The animals were housed in a temperature-controlled room (25±1°C) and provided with standardized pelleted feed and clean drinking water *ad libitum*. The protocol of animal study was approved by the Animal Ethics Committee of Faculty of Medicine, Thammasat University, Pathumthani, Thailand (AE013/2013).

Ethyl phenylpropiolate (EPP)-induced ear edema in rats[11]

Male rats (40-60 g) were subjected to topical application of EPP (1 mg/20 mcl/ear) to the inner and outer surface of both ears to produce the ear edema. The water extract of Tri-sa-maw recipe (4 mg/ear), phenylbutazone (1 mg/ear) and vehicle (the mixture of dimethylsulfoxide and acetone, 1:1) were applied in the same manner in a volume of 20 mcl prior to the irritant. The edema thickness was measured with digital vernier calipers at 0, 15, 30, 60, and 120 min after EPP induction.

Carrageenin-induced paw edema in rats[12]

Five groups of male rats (100-120 g) containing six animals per group orally received distilled water (control, 2 ml/kg), the water extract of Tri-sa-maw recipe (300, 600 and 1,200 mg/kg), or aspirin (300 mg/kg). One hour after oral administration of test substance, acute inflammation was produced by an intradermal injection of carrageenin (1% in normal saline solution, NSS) into the plantar surface of the right hind paw of the rat. The paw edema volume was measured using a plethysmometer (model 7140, Ugo Basile, Italy) before and at 0, 1, 3 and 5 hours after carrageenin injection.

Acetic acid-induced writhing response[13]

Male mice weighing 30-40 g were divided into five groups of six animals. The control group received distilled water (2 ml/kg). Test group received the extract of Tri-sa-maw recipe (300, 600 and 1,200 mg/kg) or aspirin (300 mg/kg). The writhing response was induced by injection of 0.75% acetic acid aqueous solution in a volume of 0.1 ml/10 g body weight into the peritoneal cavity after administration of each test substance for 1 hour. The number of writhes, the response consisting of contraction of an abdominal wall, pelvic rotation followed by hind limb extension, was counted during continuous observation for 15 min beginning from 5 min after acetic acid injection. The number of writhes in each test group was compared with that of the control group and the percentage of inhibition was calculated.

Tail-flick test[14]

Male rats (100-120 g) were divided into five groups of six animals orally received distilled water (control group, 2 ml/kg), the extract of Tri-sa-maw recipe (300, 600 and 1,200 mg/kg), or aspirin (300 mg/kg). The spinal reflex was induced by placing the tail of rat (3 cm from tip) on a flush mounted photocell window of the tail-flick apparatus (model 7360, Ugo Basile, Italy). Heat was applied by the infrared lamp (50 W bulb) mounted in a reflector. A pedal switch was depressed, the infrared lamp turned on and a timer started. When the rat felt pain and moved (flicked) its tail away from the heat, this automatically stopped the timer and switched off the lamp. The reaction time was presented on a digital display. The voltage was adjusted to give a normal reaction time of 2-4 sec. The cut-off time of 10 sec was a maximum time for the rat that did not move its tail away from the heat to avoid tissue damage. The reaction time was determined before and at 1, 2, and 3 h after each test substance administration. The reaction time of each group was compared with its baseline.

Antipyretic activity[15]

Male rats (200-250 g) were injected subcutaneously of 1 ml/100 g body weight of 25% brewer's yeast. Rectal temperatures were recorded using a twelve channel electric thermometer (LETICA, model TMP 812 RS, Panlab SL, Spain) at the initial and 18th h after yeast injection. Those animals which showed a rise in rectal temperature of more than 1°C were selected for testing the substance. Then, the rectal temperatures of animals were recorded at 30 min interval for 2 h following drug treatment.

Statistical analysis

Results were expressed as mean ± standard error of mean (SEM). Statistical significance was determined by one-way analysis of variance (ANOVA) and Dunnett test. The *p*-values less than 0.05 were considered significant.

Results and Discussion

The EPP-induced ear edema model was a

standard assay for screening and evaluating the anti-inflammatory activity of the extract[11]. EPP causes acute inflammatory response by inducing pro-inflammatory mediator releases (e.g., histamine, serotonin, kinins, and PGs)[16] which cause vascular changes, including vasodilatation, and increasing in vascular permeability leading to ear edema formation[17,21]. Table 1 shows the inhibitory effect of the Tri-sa-maw recipe on EPP-induced ear edema. Tri-sa-maw recipe (4 mg/ear) and phenylbutazone (1 mg/ear) were able to reduce the edema thickness at all assessment times. The results revealed a promising anti-inflammatory effect of the Tri-sa-maw recipe in this model. Thus, the possible mechanism of action of Tri-sa-maw recipe may elicit via the inhibitions of the production and/or the activity of these pro-inflammatory mediators.

The carrageenin-induced hind paw edema model was used to evaluate the acute anti-inflammatory activity of the extract. This model is a well-known test that is sensitive to COX inhibitors[12]. The injection of carrageenin into the plantar surface of hind paw causes acute inflammatory response leading to biphasic phase of paw edema. The first phase (0-2.5 h after carrageenin injection) results from concomitant release of histamine, serotonin, and kinins, whereas the second phase (2.5-6 h) is correlated with elevated production of inducible COX-2, PGs, oxygen-derived free radicals, as well as the local neutrophil infiltration and activation[18-23]. Unfortunately, the extract of the Tri-sa-maw recipe at doses of 300, 600 and 1,200 mg/kg did not inhibit acute inflammation in the carrageenin-induced paw edema at all assessment times when compared with that of the control group. The data were summarized in Table 2.

In the analgesic tests, acetic acid-induced writhing response and tail-flick test models were measured for evaluation of nociceptive pain and physiologic pain. Acetic acid-induced writhing response model is a screening test of both centrally and peripherally acting analgesic activity. Acetic acid is an irritant, which causes the synthesis and release of pro-inflammatory mediators (e.g., bradykinin, serotonin, histamine, PGs, and substance P) that provoke pain nerve endings (nociceptors)[13,24,25]. As shown in Table 3, the Tri-sa-maw recipe (300, 600, 1,200 mg/kg) and

Table 1. Effect of Tri-sa-maw recipe on EPP-induced ear edema

Time	Edema thickness (μm) (% inhibition)		
	Control	Phenylbutazone 1 mg/ear	Tri-sa-maw recipe 4 mg/ear
15 min	100.00±0.00	31.67±5.43* (68.33%)	21.67±1.67* (78.33%)
30 min	166.67±4.22	56.67±3.33* (66.00%)	83.33±8.03* (50.00%)
60 min	183.33±3.33	73.33±4.22* (60.00%)	123.33±6.15* (32.73%)
120 min	166.67±4.22	76.67±2.11* (54.00%)	120.00±7.30* (28.00%)

Values are expressed as mean ± SEM (n = 6)
* Significantly different from the control group, $p<0.05$

Table 2. Effect of Tri-sa-maw recipe on carrageenin-induced hind paw edema

Group	Dose (mg/kg)	1 h		3 h		5 h	
		EV (ml)	EI (%)	EV (ml)	EI (%)	EV (ml)	EI (%)
Control	-	0.29±0.01	-	0.55±0.12	-	0.68±0.09	-
Aspirin	300	0.14±0.03*	51.72	0.15±0.05*	72.73	0.16±0.06*	76.47
Tri-sa-maw	300	0.20±0.02	31.03	0.57±0.10	-3.64	0.59±0.05	13.23
	600	0.22±0.03	24.14	0.60±0.09	-9.09	0.61±0.05	10.29
	1,200	0.24±0.03	17.24	0.35±0.06	36.36	0.57±0.06	16.18

Values are expressed as mean ± SEM (n = 6)
* Significantly different from the control group, $p<0.05$
EV = edema volume; EI = edema inhibition

aspirin (300 mg/kg) exhibited a significant inhibitory effect on acetic acid-induced writhing response. The tail-flick test is widely used for assessment of analgesic activity through central mechanism at the spinal cord level[14,26]. The flick of tail results from the reflex arc in the spinal cord that is modulated via a descending pathway mechanism[24]. The effect of the Tri-sa-maw recipe is shown in Table 4. Tri-sa-maw did not increase the tail flick time when compared to that of the control group. The results of analgesic tests suggest that the inhibitions of peripheral pro-inflammatory mediator production and/or activity may be the main possible mechanisms of action of the Tri-sa-maw recipe.

Antipyretic activity of the extract was determined using the yeast-induced hyperthermia model. High body temperature involves the production of pro-inflammatory cytokines such as IL-1β, IL-6, IFN-α and TNF-α, which enter the hypothalamic circulation and stimulate the release of local PGs, resetting the hypothalamic thermal set point[27]. The results in this study showed that aspirin (300 mg/kg) and Tri-sa-maw (1,200 mg/kg) significantly reduced the body temperature. The data are summarized in Table 5.

In the present study, the Tri-sa-maw recipe extract did not inhibit acute inflammation in the carrageenan-induced paw edema. The extract was able to inhibit the acetic acid-induced writhing response, but not the heat-induced pain. This result suggests the peripheral effect of its analgesic activity may involve the inhibitions of the biosynthesis and/or release of some pain mediators. Finally, oral administration of the extract at a dose of 1,200 mg/kg body weight effectively reduced the hyperthermia, which might be due to the inhibition of prostaglandins. In conclusion, the present study has clearly demonstrated both analgesic and antipyretic activities of the Tri-sa-maw recipe.

Acknowledgement

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Potential conflicts of interest

None.

Table 3. Effect of Tri-sa-maw recipe on acetic acid-induced writhing response

Group	Dose (mg/kg)	Number of writhes	% inhibition
Control	-	25.17±0.60	-
Aspirin	300	9.17±0.48*	63.58
Tri-sa-maw	300	12.33±0.49*	51.00
	600	10.33±0.42*	58.94
	1,200	7.17±0.65*	71.53

Values are expressed as mean ± SEM (n = 6)
* Significantly different from the control group, $p<0.05$

Table 4. Effect of Tri-sa-maw recipe on tail-flick test

Group	Dose (mg/kg)	Reaction time (sec)			
		Baseline	1 h	2 h	3 h
Control	-	2.87±0.20	3.18±0.42	3.33±0.61	3.30±0.44
Codeine	120	2.82±0.20	4.70±0.36*	5.80±0.43*	5.18±0.45
Aspirin	300	2.78±0.13	3.27±0.65	3.18±0.60	3.30±0.75
Tri-sa-maw	300	2.75±0.16	3.00±0.33	3.33±0.24	3.30±0.40
	600	2.92±0.16	3.43±0.39	3.35±0.32	3.37±0.30
	1,200	2.88±0.31	3.40±0.32	3.37±0.47	3.35±0.35

Values are expressed as mean ± SEM (n = 6)
* Significantly different from the control group, $p<0.05$

Table 5. Effect of Tri-sa-maw recipe on yeast-induced hyperthermia

Group	Dose (mg/kg)	Baseline	18 h after yeast injection	Rectal temperature (°C)			
				30 min	60 min	90 min	120 min
Control	-	37.53±0.11	39.35±0.14	39.22±0.12	39.13±0.15	39.03±0.18	39.10±0.15
Aspirin	10	37.75±0.18	39.02±0.17	38.55±0.10	38.10±0.12*	37.75±0.20*	37.47±0.20*
Tri-sa-maw	300	37.80±0.11	39.18±0.19	39.30±0.72	39.12±0.15	38.98±0.17	38.77±0.24
	600	37.85±0.11	39.15±0.14	38.90±0.67	38.82±0.15	38.67±0.17	38.45±0.17
	1,200	37.72±0.06	39.17±0.11	38.60±0.44	38.33±0.29*	38.18±0.27*	38.03±0.18*

Values are expressed as mean ± SEM (n = 6)
* Significantly different from the control group, $p<0.05$

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ฤทธิ์ระงับปวดและ ลดไข้ของตำรับยาตรีสมอ

อุรารัตน์ แน่นหนา, กาญจนา ใจจ้อย, นพมาศ สุนทรเจริญนนท์, สีวบูรณ์ สิริรัฐวงศ์

ภูมิหลัง: *ตำรับยาตรีสมอ ประกอบด้วยผลของสมอไทย (Terminalia chebula Retz.) ผลสมอเทศ (Terminalia sp.) และผลสมอพิเภก (Terminalia bellirica Roxb.) ในสัดส่วนที่เท่ากัน ในกลุ่มประเทศเอเชียตะวันออกเฉียงใต้ ผลของสมอ ทั้งสามนี้ใช้เป็นทั้งอาหารและยาในตำรับยาไทยโบราณ ตำรับยาตรีสมอมีสรรพคุณในการลดไข้ ขับเสมหะ บำรุงร่างกายและบรรเทาอาการปวดแน่นท้อง*

วัตถุประสงค์: *เพื่อศึกษาฤทธิ์ต้านการอักเสบ ระงับปวดและลดไข้ของตำรับยาตรีสมอในสัตว์ทดลอง*

วัสดุและวิธีการ: *ศึกษาฤทธิ์ต้านการอักเสบโดยใช้ 2 แบบจำลองการอักเสบ คือ การใช้สารเอทิลฟีนิลโพรพิโอเลท (ethylphenylpropiolate, EPP) เหนี่ยวนำให้เกิดการบวมของใบหูและการใช้สารคาราจีนิน (carrageenin) เหนี่ยวนำทำให้เกิดการบวมบริเวณอุ้งเท้า สำหรับการศึกษาฤทธิ์ระงับปวดจะเหนี่ยวนำความเจ็บปวดโดยใช้กรดแอซีติกหรือความร้อน นอกจากนี้การใช้ยีสต์เหนี่ยวนำให้เกิดไข้จะใช้สำหรับศึกษาฤทธิ์ลดไข้*

ผลการศึกษา: *ผลการศึกษาพบว่าสารสกัดตำรับยาตรีสมอมีฤทธิ์ลดการบวมของหูหนูในแบบจำลองที่เหนี่ยวนำด้วย EPP แต่สารสกัดตำรับยาตรีสมอไม่มีฤทธิ์ต้านอักเสบแบบเฉียบพลันจากการทดลองโดยใช้สารคาราจีนินเหนี่ยวนำการบวมของอุ้งเท้าหนู แต่อย่างไรก็ตามสารสกัดตำรับยาตรีสมอขนาด 300-1,200 มิลลิกรัม/กิโลกรัมน้ำหนักตัว สามารถยับยั้งการบิดลำตัวและเหยียดขาหลังของหนูจากการใช้กรดแอซีติกได้ แต่ไม่สามารถลดปวดจากการใช้ความร้อนเหนี่ยวนำให้เกิดอาการปวดได้ สรุปได้ว่าฤทธิ์ระงับปวดของสารสกัด ตำรับยาตรีสมอมีกลไกผ่านทางระบบประสาทส่วนปลาย โดยเป็นผลจากการยับยั้งการสังเคราะห์และหรือการหลั่งสารสื่อกลางที่ทำให้เกิดอาการปวดบางชนิด นอกจากนี้การให้สารสกัดตำรับยาตรีสมอขนาด 1,200 มิลลิกรัม/กิโลกรัมน้ำหนักตัว ทางปากพบว่าสามารถลดไข้ได้ ซึ่งกลไกอาจเกิดจากการยับยั้งสารสื่อกลาง พรอสตาแกรนดิน (prostaglandins; PGs)*

สรุป: *การศึกษาครั้งนี้แสดงให้เห็นอย่างชัดเจนว่าตำรับยาตรีสมอมีทั้งฤทธิ์ระงับปวดและฤทธิ์ลดไข้*