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Antipyretic Effect of Mitragynine and Crude Methanolic Extract of *Mitragyna speciosa* Korth. in Mice

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ABSTRACT

Mitragyna speciosa Korth., also known as *ketum* or *kratom*, is a tropical plant native to Southeast Asia. Mitragynine is its major active alkaloid. It is traditionally used as treatment for various conditions, including fever. The crude extract of *M. speciosa* leaves has been proven to have anti-inflammatory and analgesic properties. In general, *M. speciosa* induces a dose-dependent effect, inducing a stimulant effect at low dose and an opioid-like effect at a high dose. This study was conducted to determine the antipyretic effect of mitragynine and methanolic extract of *M. speciosa* (MSM) using mice as an *in vivo* pyretic model. Eighty mice were divided into 8 groups: 6 treatment groups (mitragynine: 5, 10, and 20 mg/kg; MSM: 50, 100, and 200 mg/kg) and 2 control groups (20% Tween 80 in 0.9% NaCl; ketoprofen 1 mg/kg). Eighteen hours after induction of pyrexia by inoculation of yeast, rectal temperature was measured every half an hour for 5 hours. Compared to the negative control group, all groups treated with either mitragynine or MSM had significant reduction of rectal temperature at different points of time. The positive control group treated with ketoprofen had significant ($P < 0.001$) reduction of pyrexia from 0.5 to 5.0 hours after dosing. At 200 mg/kg, MSM has led to the opioid-like effect of hypothermia, possibly due to its synergistic effect with other compounds such as 7-hydroxymitragynine or mitragynine pseudoindoxyl. This article discusses concerns pertaining to toxicity of mitragynine and MSM, and possible involvement of cyclooxygenase and microsomal prostaglandin E2 synthase pathways. In conclusion, mitragynine and MSM possess dose-dependent antipyretic properties in mice.

Keywords: *Mitragyna speciosa*, mitragynine, mice, pyrexia

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INTRODUCTION

Mitragyna speciosa Korth., also known as *ketum* or *kratom*, is a plant found in tropical and subtropical Asia (such as Thailand, Indonesia, and Malaysia), East and West Africa, and India (Ahmad & Aziz, 2012). In Malaysia, it is widely distributed across the northern half of Peninsular Malaysia and Selangor (Idayu et al., 2011). More than 40 different alkaloids have been identified in the plant (Meireles et al., 2019). Mitragynine is regarded as the major alkaloid of the whole leaf, amounting to about 66.2% (Gibbons & Arunotayanun, 2013).

Asian workers use the leaves of *M. speciosa* for their stimulant effects (Saingam et al., 2013). The stimulant effect enhances the workers' tolerance to endure heavy work and also relieves muscle strains. In Thailand and Malaysia, it is also used traditionally as treatment for fever (pyrexia), diarrhea, opium addiction, diabetes, and helminthiasis (Ahmad & Aziz, 2012). The leaves have been used to treat opium withdrawal syndrome and are considered as an alternative to methadone or other opioids (Prozialeck, 2016). Administration of *M. speciosa* usually results in dose-dependent effects. An opioid-like effect predominates at high doses, whereas administration at lower doses typically results in stimulant-like effects.

Fever, or pyrexia, is an increase in body temperature above the normal range triggered by the presence of pyrogens. It can be caused by many infectious (e.g., bacterial, viral, parasitic diseases) or noninfectious (e.g., trauma, thrombosis, cancer) medical conditions. Hence, fever is the most common primary complaint in medical practices (Celebi et al., 2009). For humans, most antipyretic drugs are available as nonprescription drugs, including aspirin, acetaminophen, ibuprofen, ketoprofen, and naproxen. Although these antipyretic drugs are considered safe, adverse side effects have been reported that affect the gastrointestinal tract, kidney, and liver (Plaisance, 2000).

Scientifically, it has been shown that mitragynine and the crude methanolic extract of *M. speciosa* (MSM) provide anti-inflammatory and antinociceptive properties by affecting the supraspinal opioid receptors (Meireles et al., 2019; Mossadeq et al., 2009). Most analgesic and anti-inflammatory drugs are known to possess antipyretic activity (Srinivasan et al., 2003). Since *M. speciosa* has been used traditionally as a treatment for fever, it is possible that it possesses an antipyretic effect. However, there is no scientific report available pertaining to such an effect of the crude extract of *M. speciosa* and mitragynine. Such information could be important for human or veterinary therapeutic uses in the future. This study was conducted to validate the traditional claim of the antipyretic effect of MSM and mitragynine using an *in vivo* pyretic mice model. Subsequently, the effective doses, onset of action, and duration of action related to the antipyretic effect were determined.

MATERIALS AND METHODS

Preparation of Mitragynine and MSM

The study was conducted in 2010. MSM was obtained from freeze-dried stock of a previous study (Mossadeq et al., 2009). The pure compound of mitragynine (Chromadex Inc., CA, USA) was purchased from Chemtron Biotechnology Sdn. Bhd. (Kuala Lumpur, Malaysia). Each substance was prepared in 20% Tween 80 in 0.9% NaCl (T-80-NaCl) (Idayu et al., 2011). This was achieved by dissolving them in 20 mL Tween 80 using a sonicator. The resulting solution was then mixed with 80 mL of 0.9% NaCl and stirred using a magnetic stirrer to produce a homogenous solution.

Animals

A total of 80 female BALB/c mice weighing between 20 and 25 g were obtained from the Animal Resource Unit, Faculty of Veterinary Medicine, Universiti Putra Malaysia. The animals were acclimatized for 2 weeks and kept in a standard cage at a stocking density of 8 mice per cage. They were housed in a laboratory animal facility with a 12-h light-dark cycle. The mice were brought to the laboratory and were acclimatized to the laboratory environment for 48 hours (h) prior to the experiment. All experimental procedures were approved by the Animal Care and Use Committee, Faculty of Veterinary Medicine, Universiti Putra Malaysia (FPV/AUP/FYP/009/2010).

Experimental Design and Antipyretic Effect

Evaluation of the antipyretic effect was conducted as previously described (Zakaria et al., 2008), with minor modifications. The basal temperature of all mice was measured using a digital thermometer by inserting a thermistor probe 1 cm into the rectum. Subsequently, the mice were induced into pyrexia by subcutaneous inoculation of 30% (w/v) suspension of Brewer's yeast in 0.9% NaCl at a dose of 10 mL/kg. Eighteen h after induction of pyrexia, rectal temperature was recorded. Because all 80 mice had more than 0.5°C rise in rectal temperature, they were all subjected to the experiments. They were randomly divided into 8 groups. Groups 1, 2, and 3 were administered 5, 10, or 20 mg/kg mitragynine intraperitoneally (i.p.), respectively. Groups 4, 5, and 6 were administered 50, 100, and 200 MSM i.p., respectively. The different doses of mitragynine and MSM were based on a previous study that evaluated the antinociceptive properties of these substances (Sabetghadam et al., 2010). Group 7 was administered ketoprofen 1 mg/kg i.p. as positive control, and mice of Group 8 were administered T-80-NaCl i.p. as a negative control. Rectal temperature was immediately measured after the treatment and every 30 minutes thereafter, for a total period of 5 h. Percentage of temperature reduction was calculated using the following formula:

$$\text{Percentage of temperature reduction} = \frac{(\text{yeast} - \text{induced pyrexia} - \text{post treatment temperature})}{\text{yeast} - \text{induced pyrexia}} \times 100$$

Statistical Analysis

The mean change in the rectal temperature for each mouse was calculated. General linear model repeated measure analysis of variance (ANOVA) was used to analyze data separately between the groups treated with mitragynine and the groups treated with MSM. Results were expressed as mean ± standard error of the mean (SEM). One-way ANOVA followed by posthoc analysis was used to compare data of the treatment and negative control groups at each point of time. All data were analyzed to observe different degrees of statistical significance ($P < 0.05$, $P < 0.01$, $P < 0.001$).

RESULTS

Mauchly's test of sphericity, multivariate test, and test within subject from repeated measure ANOVA showed a significant ($P < 0.001$) relationship between change in rectal temperature, time, treatment, and interaction between time and treatment. In between subjects, the rectal temperature was found to be significantly affected by the different types of treatment administered, while within subjects, the rectal temperature was significantly affected by the time.

Induction of pyrexia in negative control mice of Group 8 resulted in elevation of rectal temperature to 38°C. This pyretic state persisted throughout the 5 h duration, with the highest rectal temperature of 38.67°C recorded at 1.0 h. In general, mice of all treatment groups showed significant reduction of rectal temperature compared to negative control mice of Group 8 at different points of time (Figures 1 and 2). Positive control mice of Group 7 showed significant ($P < 0.001$) difference in rectal temperature from 0.5 to 5.0 h compared to negative control mice of Group 8 (Figure 1). The same group had a significant reduction in rectal temperature between 0.5 and 1.0 h, and between 3.5 and 5.0 h compared to Group 8 (Tables 1 and 2). The lowest rectal temperature achieved in the positive control mice of Group 7 treated with ketoprofen was 36.65°C at 5.0 h.

Mitragynine administered at a dose of 5 mg/kg in Group 1 mice resulted in significant reduction in rectal temperature between 1.0 and 4.5 h. On the other hand, mice treated with mitragynine (10 mg/kg) in Group 2 showed significant reduction in rectal temperature between 1.0 and 5.0 h. Administration of mitragynine at a dose of 20 mg/kg in mice of Group 3 led to a highly significant ($P < 0.001$) reduction of rectal temperature between 0.5 and 5.0 h.

Mice of Group 4 administered with MSM at a dose of 50 mg/kg showed statistically significant ($P < 0.05$, $P < 0.01$, $P < 0.001$) reductions of rectal temperature between 2.5 and 5.0 h. Mice of Group 5 treated with MSM at a dose of 100 mg/kg had a significant ($P < 0.05$, $P < 0.01$, $P < 0.001$) reduction in rectal temperature at 0.5 h and between 2.0 and 5.0 h. Mice of Group 6 treated with MSM at a dose of 200 mg/kg had a significant ($P < 0.001$) reduction in rectal temperature between 0.5 and 5.0 h.

The administration of ketoprofen in mice of Group 7 resulted in the highest percentage of inhibition of pyrexia (Figures 1 and 2) at 5.0 h. Among all the doses of mitragynine

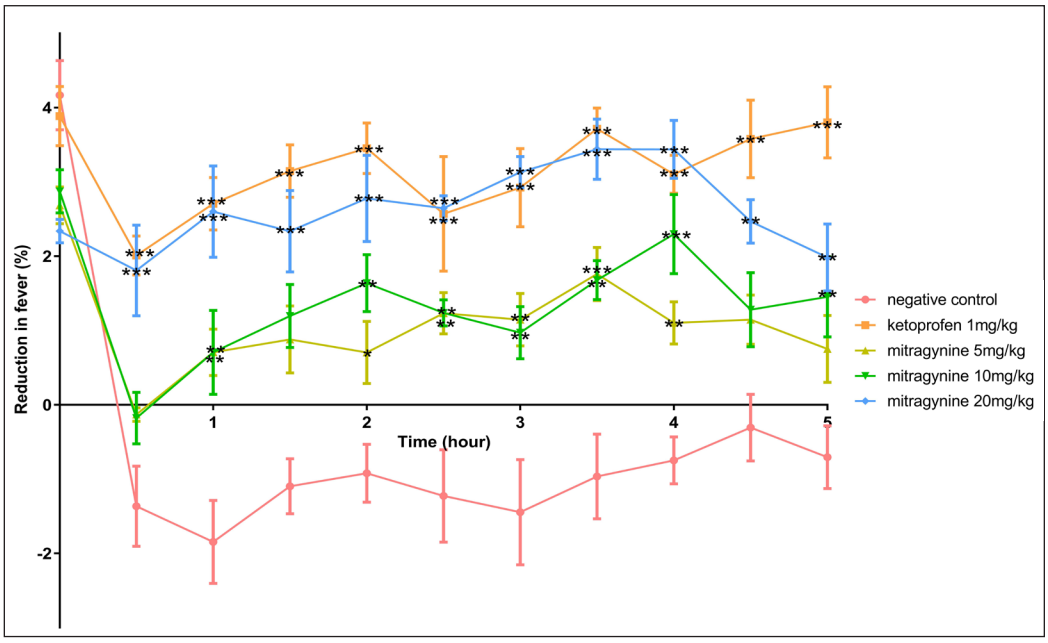

Figure 1. Percentage reduction of fever with mitragynine administered intraperitoneally in Brewer's yeast-induced pyrexia in mice. (*P < 0.05, **P < 0.01, and ***P < 0.001 compared to the negative control)

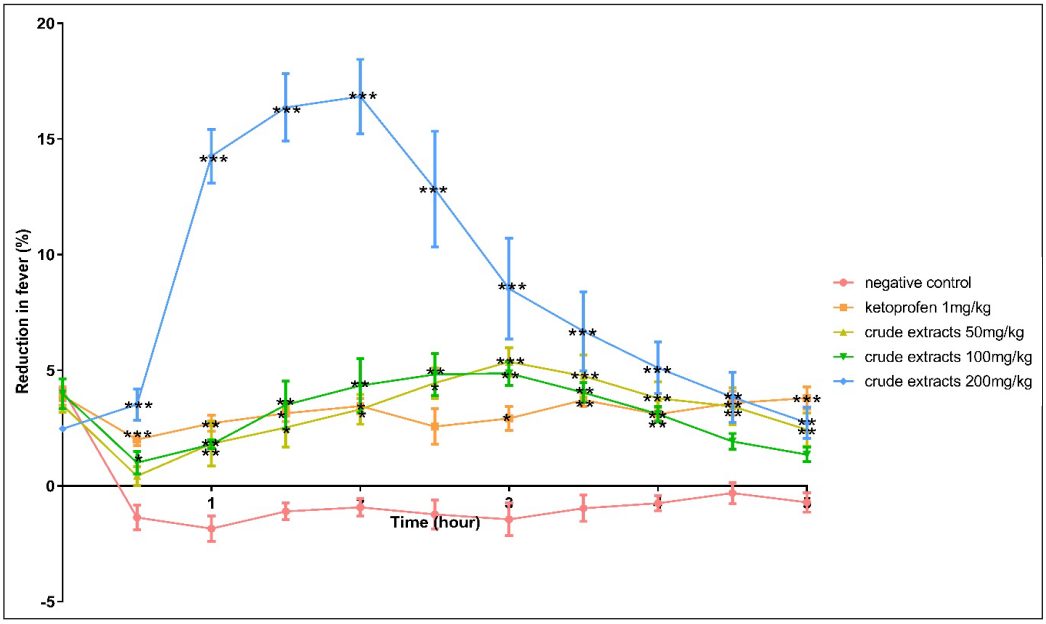

Figure 2. Percentage reduction of fever with methanolic extract of *Mitragyna speciosa* (MSM) administered intraperitoneally in Brewer's yeast-induced pyrexia in mice. (*P < 0.05, **P < 0.01, and ***P < 0.001 compared to the negative control)

Table 1

*Mean ± standard error of the mean (SEM) of rectal temperature with mitragynine administered intraperitoneally in Brewer's yeast-induced pyrexia in mice (*P < 0.05, **P < 0.01, and ***P < 0.001 compared to the negative control)*

Treatments	Before yeast	18 h after yeast	Time after treatment (hour)									
			0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Negative control	36.38 ± 0.145	37.97 ± 0.109	38.48 ± 0.164	38.67 ± 0.199	38.38 ± 0.168	38.32 ± 0.176	38.43 ± 0.276	38.52 ± 0.313	38.33 ± 0.235	38.25 ± 0.118	38.08 ± 0.199	38.23 ± 0.141
Ketoprofen 1 mg/kg	36.62 ± 0.048	38.10 ± 0.132	37.33 ± 0.092***	37.07 ± 0.067***	36.90 ± 0.115***	36.78 ± 0.111***	37.12 ± 0.189***	36.98 ± 0.091***	36.68 ± 0.079***	36.92 ± 0.060***	36.73 ± 0.112***	36.65 ± 0.163***
Mitragynine 5 mg/kg	36.83 ± 0.095	37.85 ± 0.067	37.90 ± 0.052	37.58 ± 0.154***	37.52 ± 0.158*	37.58 ± 0.154*	37.38 ± 0.114**	37.42 ± 0.149**	37.18 ± 0.119***	37.43 ± 0.126**	37.42 ± 0.149*	37.57 ± 0.228
Mitragynine 10 mg/kg	36.65 ± 0.165	37.73 ± 0.092	37.80 ± 0.113*	37.47 ± 0.225**	37.28 ± 0.221*	37.12 ± 0.199***	37.27 ± 0.117***	37.37 ± 0.099**	37.10 ± 0.121***	36.87 ± 0.220***	37.25 ± 0.188**	37.18 ± 0.149**
Mitragynine 20 mg/kg	36.92 ± 0.075	37.80 ± 0.026	37.12 ± 0.224***	36.82 ± 0.226***	36.92 ± 0.204***	36.75 ± 0.208***	36.80 ± 0.058***	36.62 ± 0.080***	36.50 ± 0.163***	36.50 ± 0.134***	36.87 ± 0.095***	37.05 ± 0.152***

Table 2

Mean ± standard error of the mean (SEM) of rectal temperature with methanolic extract of Mitragyna speciosa *(MSM) administered intraperitoneally in Brewer's yeast-induced pyrexia in mice. (*P < 0.05, **P < 0.01, and ***P < 0.001 compared to the negative control)*

Treatments	Before yeast	18 h after yeast	Time after treatment (hour)									
			0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Negative control	36.38 ± 0.145	37.97 ± 0.109	38.48 ± 0.164	38.67 ± 0.199	38.38 ± 0.168	38.32 ± 0.176	38.43 ± 0.276	38.52 ± 0.313	38.33 ± 0.235	38.25 ± 0.118	38.08 ± 0.199	38.23 ± 0.141
Ketoprofen 1 mg/kg	36.62 ± 0.048	38.10 ± 0.132	37.33 ± 0.092***	37.07 ± 0.067*	36.90 ± 0.115	36.78 ± 0.111	37.12 ± 0.189	36.98 ± 0.091	36.68 ± 0.079*	36.92 ± 0.060**	36.73 ± 0.112**	36.65 ± 0.163***
MSM 50 mg/kg	36.82 ± 0.054	38.15 ± 0.159	37.98 ± 0.105	37.45 ± 0.281	37.18 ± 0.280	36.88 ± 0.220	36.45 ± 0.219*	36.10 ± 0.207**	36.33 ± 0.304**	36.70 ± 0.256**	36.83 ± 0.260**	37.22 ± 0.180**
MSM 100 mg/kg	36.48 ± 0.172	38.00 ± 0.103	37.62 ± 0.135**	37.32 ± 0.070	36.67 ± 0.384	36.35 ± 0.447*	36.17 ± 0.340*	36.15 ± 0.198**	36.47 ± 0.169**	36.82 ± 0.095**	37.27 ± 0.056	37.48 ± 0.075*
MSM 200 mg/kg	37.06 ± 0.081	38.00 ± 0.055	36.66 ± 0.238***	32.58 ± 0.418***	31.78 ± 0.530***	31.60 ± 0.585***	33.12 ± 0.936***	34.76 ± 0.829***	35.46 ± 0.661***	36.06 ± 0.432***	36.54 ± 0.421**	36.96 ± 0.268**

administered in this experiment, the dose of 20 mg/kg in mice of Group 3 showed the highest percentage of temperature reduction, which occurred at 4.0 h (Table 1). As for the groups treated with MSM i.p., the greatest percentage of reduction of rectal temperature was observed in mice of Group 6 at 2.0 h. However, mice of this group showed hypothermia between 1.0 and 3.5 h. In general, both mitragynine and MSM administered intraperitoneally produced a dose-dependent antipyretic effect.

DISCUSSION

In this study, both mitragynine and MSM administered i.p. were observed to possess antipyretic properties in mice. The results suggested that administration of mitragynine at a dose of 20 mg/kg is marginally a more effective antipyretic compared to ketoprofen. On the other hand, administration of MSM at 200 mg/kg resulted in significantly more antipyretic effect compared to ketoprofen, to the point of adverse effect to the host. This is further discussed in a later paragraph.

Based on the pattern of rectal temperatures throughout the 5 h study, it was observed that the onset of action of both mitragynine and MSM was rapid, approximately 0.5 to 1.0 h after administration. However, in terms of duration of action, both mitragynine and MSM only provided a short duration of antipyretic activity, approximately 3.5 to 4.0 h. Ketoprofen provided a similarly rapid onset of action but with a longer duration of actions (Cossellu et al., 2019) compared to MSM and mitragynine.

Mitragynine and MSM were observed to possess dose-dependent antipyretic effects, where administration at high dose of either mitragynine or MSM resulted in a statistically significant degree of pyrexia inhibition over time. Based on the statistical analysis, and the fact that the temperature decreased from a pyretic state to normal, the effective antipyretic dose for mitragynine was found to be 20 mg/kg, and for MSM it was 100 mg/kg.

At the highest dose of 200 mg/kg tested in this study, MSM resulted in transient hypothermia of the mice, which lasted for 2.5 h. This dose-dependent effect may be explained by the fact that MSM has opioid-like effects at high doses (Babu et al., 2008). Hypothermia is a well-documented effect of opioids (Henderson-Redmond et al., 2016). This may be explained by a synergistic effect brought about by the presence of other compounds in MSM. This leads to a great reduction in body temperature, which subsequently leads to hypothermia. The synergistic effect could be more prominent compared to that of a single compound. A similar synergistic effect was previously postulated in assessment of analgesic properties of MSM (Reanmongkol et al., 2007). It is also possible that hypothermia was due to the presence of another important alkaloid that acts on the opioid receptor, such as 7-hydroxymitragynine or mitragynine pseudoindoxyl. The 7-hydroxymitragynine possesses higher affinity and is 1000 times more potent than morphine, particularly to the μ-opioid receptors, despite there being less of it compared to mitragynine

(McCurdy & Scully, 2005). On the other hand, mitragynine pseudoindoxyl was previously found to be 35-fold more potent than morphine in inhibiting electrically stimulated ileum contraction (Adkins et al., 2011). This potent alkaloid may act agonistically at the μ-opioid receptors, which are present abundantly especially in the hypothalamus, to affect the thermoregulation system of the body. This can produce antipyretic effects at the first 30 minutes post treatment, and then induce hypothermia.

Hypothermia after i.p. administration of 200 mg/kg MSM is an undesirable antipyretic effect related to MSM. Another undesirable effect that could be of concern is toxicity. Previously, a subchronic study concluded that mitragynine is relatively safe at doses of 1-10 mg/kg, but leads to a toxic effect at 100 mg/kg (Sabetghadam et al., 2013). In an acute toxicity study, rodents orally administered 1000 mg/kg of MSM exhibited a reversible effect, with hepato- and nephron-toxicity (Harizal et al., 2010). This is in agreement with the few reports pertaining to *M. speciosa* intoxication in humans (Domingo et al., 2017). In other reports, the role of mitragynine in human fatalities was not conclusive (Domingo et al., 2017; Holler et al., 2011). Although MSM and mitragynine have therapeutic potential, issues pertaining to toxicity and abuse of these substances require further clarification.

Yeast-induced hyperthermia is also known as "fever" or "pyrexia". Its pathogenesis includes the presence of exogenous pyrogens. These will eventually evoke the host-activated macrophages and mast cells to produce pyrogenic cytokines that act on the hypothalamus to induce a fever response (Werner et al., 2006). These cytokines will trigger another important mediator of fever, PGE_2 in the thermoregulatory center at the region of the preoptic nuclei of the anterior hypothalamus (Roth & Souza, 2001). PGE_2 activates the endocrine, autonomic, and behavioral responses that lead to fever (Saper & Breder, 1994). PGE_2 requires the action of cyclooxygenase (COX) and microsomal PGE synthase (mPGES). Ketoprofen is known to inhibit pyrexia partially by inhibition of the COX enzyme. Hence, it is possible that the modes of action of both mitragynine and MSM involve a mechanism similar to that of ketoprofen. However, more studies are needed to ascertain the antipyretic mechanism of action of mitragynine and MSM.

CONCLUSION

Both mitragynine and MSM possess a dose-dependent antipyretic effect, where i.p. administration of MSM results in an opioid-like effect. Effective doses to achieve a desirable antipyretic effect for mitragynine and MSM are 20 and 100 mg/kg, respectively. The onset of the antipyretic effect of mitragynine and MSM is rapid, but the duration of the antipyretic effect is short.

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AUTHORS' CONTRIBUTION

Annas Salleh planned and conducted the study, prepared the initial manuscript. Wan Mastura Shaik Mohamed Mossadeq provided the MSM and revised the manuscript. Arifah Kadir planned the study and revised the manuscript.

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