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## **Effect of Mangosteen Peel Extract on Acute Inflammation in Men Following Short-Term Excessive Exercise**

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### **ABSTRACT**

**Potisaen J, Traiperm N, Pariwat P.** Effect of Mangosteen Peel Extract on Acute Inflammation in Men Following Short-Term Excessive Exercise. **JEPonline** 2019;22(7):72-87. The purpose of this study was to determine the anti-inflammatory action of mangosteen peel extract (MPE) following exercise. The subjects consisted of 16 males, 18 to 24 yrs of age who were placed either in the Placebo Group or in 1 of 3 Experimental Groups: Group 1 (MPE dose of 300 mg·kg<sup>-1</sup>), Group 2 (MPE does of 600 mg·kg<sup>-1</sup>), and Group 3 (MPE does of 900 mg·kg<sup>-1</sup>). Maximum oxygen consumption (VO<sub>2</sub> max) was determined at the beginning and at the end of the study. The subjects' blood samples were taken to the chemical and biological laboratories to determine creatine kinase (CK), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha). The findings indicate that there were no significant differences in IL-6 and CK 24 hrs after exercise in all groups. The MPE dose of 900 mg·kg<sup>-1</sup> resulted in decreased level of IL-6 and CK than did the other doses. Also, the effects of 900 mg·kg<sup>-1</sup> MPE on 15 km running immediately after treated with MPE at are greater than the placebo group. Thus, the anti-inflammatory action of MPE is beneficial in maintaining one's health by decreasing inflammation and muscle damage.

**Key Words:** Anti-inflammation, Exercise, Mangosteen, Muscle Damage

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## INTRODUCTION

Exercise is one of the essential elements of human life. Regular exercise results in strength of the vital organs of the body, and it decreases the risk of cardiovascular disease, some types of cancer, osteoporosis, and diabetes mellitus. However, when exercise is excessive and/or incorrect, it can result in negative effects on the body. During excessive exercise, the body responds by bringing oxygen into the cell by increasing expired ventilation and cardiac output (via an increase in heart rate and stroke volume). The problem with excessive exercise is that it results in an increase in free radical production, which is an important factor that may cause muscle damage.

The increase in muscle damage is linked to the increase in inflammation of which there is then an increase in creatine kinase into the blood stream (3,14,31). After exercise, the inflammatory process is also associated with an increase in lactate, and interleukin 6 (IL-6). In addition, numerous researchers (12,32,64) have reported that the decrease in the amount of antioxidants along with more free radicals that bring about the destruction of body structures such as proteins, fats, and the structure of genetic material.

When the muscles are injured from excessive and/or inappropriate exercise, it is a common practice for exercisers to buy a particular medication to relief the discomfort or pain. However, often times, the pain and/or discomfort results in an excessive consumption of medications with side effects due to gastrointestinal irritation, liver, and/or kidneys dysfunction. Currently, the alternative is the use of herbs to treat and/or lower side effects. Based on the research data, free radicals are an important factor that cause muscle cells to be damaged. But, fortunately, different herb extracts can help stop the acute inflammation (such as xanthones in mangosteen peels, vernoniacinerea, spilanthescacmella, and curcumin).

The scientific name for mangosteen is *Garciniamangostana Linn*. It is in the Guttiferae family, Guttiferales order, garcinia genus and mangostana type. Mangosteen is also known as the queen of fruits (28). It has been determined that mangosteen contains important substances, for example, xanthones (18) is a group of flavonoids, bioactive compounds of polyphenol compounds, which are mangosteen extracts that include  $\alpha$ -mangosteen and  $\beta$ -mangostin (59) with acceptable clinical and pharmacological properties (28). For example, there are numerous health-oriented benefits from the extraction from mangosteen peel that are anti-acne (2), anti-tumor (60), anti-dyslipidemic (24), hypoglycemic activity (51), neuroprotective (22,37), hepatoprotective (8,58), anti-asthmatic (21), and anti-Alzheimer (17,61) Moreover, xanthones have anti-inflammatory activity (9,50).

The purpose of this study was to determine the anti-inflammatory action of mangosteen peel extract (MPE) following excessive exercise. Moreover, it is anticipated that the findings from this study should help understand the anti-inflammatory action of mangosteen peel extract in exercise physiology. This latter point is rarely mentioned in the majority of the studies.

## METHODS

### Subjects and Experimental Protocol

Sixteen males, 18 to 24 yrs of age who were placed either in the Placebo Group or in 1 of 3 Experimental Groups: (a) Group 1 (MPE dose of  $300 \text{ mg} \cdot \text{kg}^{-1}$ ); (b) Group 2 (MPE does of 600

mg·kg<sup>-1</sup>); and (c) Group 3 (MPE does of 900 mg·kg<sup>-1</sup>). The experiment was divided into the primary and secondary phases. To calculate the dose for each group, the Human Equivalent Dose (HED in mg·kg<sup>-1</sup>) formula was used (44). The dose of mangosteen extract is 97.26 to 972.97 mg·kg<sup>-1</sup>. It does not cause toxicity when consumed. The Placebo Group was given a capsule that contained corn flour. It had the same characteristics as the capsule that contained the mangosteen peel extract).

### **Procedures and Data Collection**

All the subjects were invited to voluntarily participate in the research study. Each subject signed a consent form to participate in the research, which was required for all Human Research at KhonKaen University, Thailand no. 4.4.01: 01/2019. The study was approved by the Research Ethics Committee (HE612200). The purpose of the Primary Experimental Phase was to identify dose of mangosteen peel extract on the effect of inflammatory markers. Physical examinations and screening were performed by medical doctors. The day before experiment, the subjects underwent a VO<sub>2</sub> max test, using the Astrand-Ryhming Test (16) to place them into 1 of 4 groups using a stratified random sampling procedure.

**Day 1: Pre-Exercise.** All subjects stayed at the athlete camp at Rajabhat Mahasarakham University to control their dietary food intake, rest, and sleep. The subjects fasted at least 6 hrs at night. The 1<sup>st</sup> blood collection consisted of 10 mL of blood drawn from the median cubital vein by a nurse. The collected blood was kept in test tubes wrapped by foil to prevent light exposure. The tubes were kept in a cold container at 2 to 8°C. Then, the samples were taken to the chemical laboratory at KhonKaen University for analysis of total creatine kinase, interleukin-6, and tumor necrosis factor- $\alpha$ .

**Day 2: Experimental Exercise.** At 6:00 a.m., the subjects rode a bicycle ergometer at 70% of their VO<sub>2</sub> max while cycling 20 min at 60 rev·min<sup>-1</sup> to induce inflammation after exercise. After exercise immediately, the 2<sup>nd</sup> blood collection was performed using the same procedure as day 1. Then, the subjects in the Experimental Groups 1 to 3 received the mangosteen peel extract with breakfast-dinner diets at 300, 600, and 900 mg·kg<sup>-1</sup> while the subjects in Group 4 (the Placebo Group) was given a capsule that contained corn flour (as assigned by the researcher, respectively). The capsules of mangosteen peel extract and placebo were stored in a light-proof container where it was not hot or damp to prevent drug degradation and drug stability. A container of the extract was attached with a tag and clearly labeled for each group to avoid confusion and/or dispensing capsules to the wrong group.

**Day 3: Post-Exercise.** At 8:00 a.m., subjects went to the laboratory after fasting at least 6 hrs for the 3<sup>rd</sup> blood collection (24 hrs after exercise). Blood sample collection procedure was the same as day 1 and day 2. When knowing the results from the primary experiment phase, dose of mangosteen peel extract that resulted in the best effect on reduction of inflammatory markers was used in secondary experimental phase. After the primary phase, 2 wks wash-out period was applied to ensure that the results from the primary phase would have no effect to the secondary phase (57). All the subjects were divided into Experimental and Control groups. The Control Group received the placebo while the Experimental Groups received mangosteen peel extract, taking a dose of mangosteen peel extract that resulted in the best reduction of inflammatory markers (CK, IL-6, and TNF- $\alpha$ ). The subjects stayed at the athlete camp at Rajabhat Mahasarakham University to ensure that diets, drinks, sleep, and resting were controlled.

**Day 1: Pre-Exercise.** The 1<sup>st</sup> blood collection of 10 mL was carried out by a nurse using the median cubital vein. Blood sample collection procedure was the same as the primary phase. **Day 2: Experimental Exercise.** At 6:00 a.m., the subjects performed 15 km simulation of running (mini-marathon) to induce inflammation after strenuous exercise (53). After exercise immediately, the 2<sup>nd</sup> blood collection was performed using the same procedure as in day 1. Then, the subjects in the Experimental Group received mangosteen peel extract with breakfast-dinner diets at dose of the best inflammation reduction from the primary Experimental phase and the Control Group received the placebo as assigned by the researcher, respectively. **Day 3: Post-Exercise.** At 8:00 a.m., the subjects went to the Laboratory for the 3<sup>rd</sup> blood collection (24 hrs after exercise). The blood sample collection procedure was the same as day 1 and day 2.

### Statistical Analyses

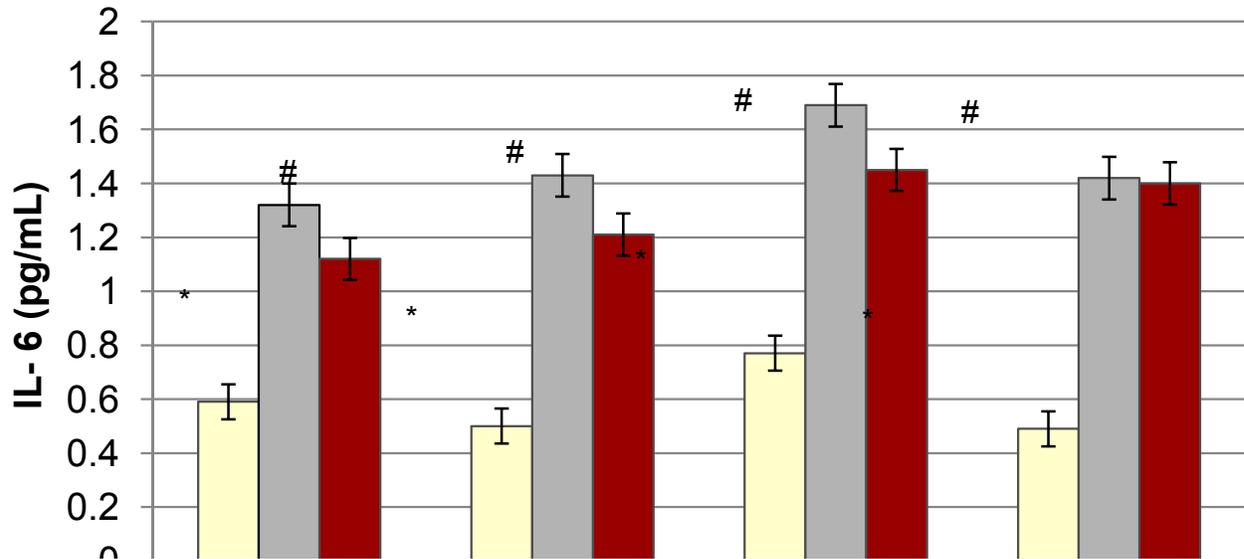
General information was presented as mean  $\pm$  standard deviation. ANOVA and Least Significant Difference (LSD) were applied to test CK, IL-6 and TNF-alpha in each time period: (a) Before; (b) Immediately; and (c) 24 hrs after exercise in all groups, respectively. A P value  $<0.05$  was considered statistically significant. Between the Control Group and the Experimental Group in the secondary experimental phase, a repeated measurement ANOVA was used. A comparison within groups was performed by paired *t* test. A P value  $<0.05$  was considered statistically significant.

### RESULTS

With regard to the baseline characteristics of the subjects in each of the 4 Groups, there were no significant differences (Table 1).

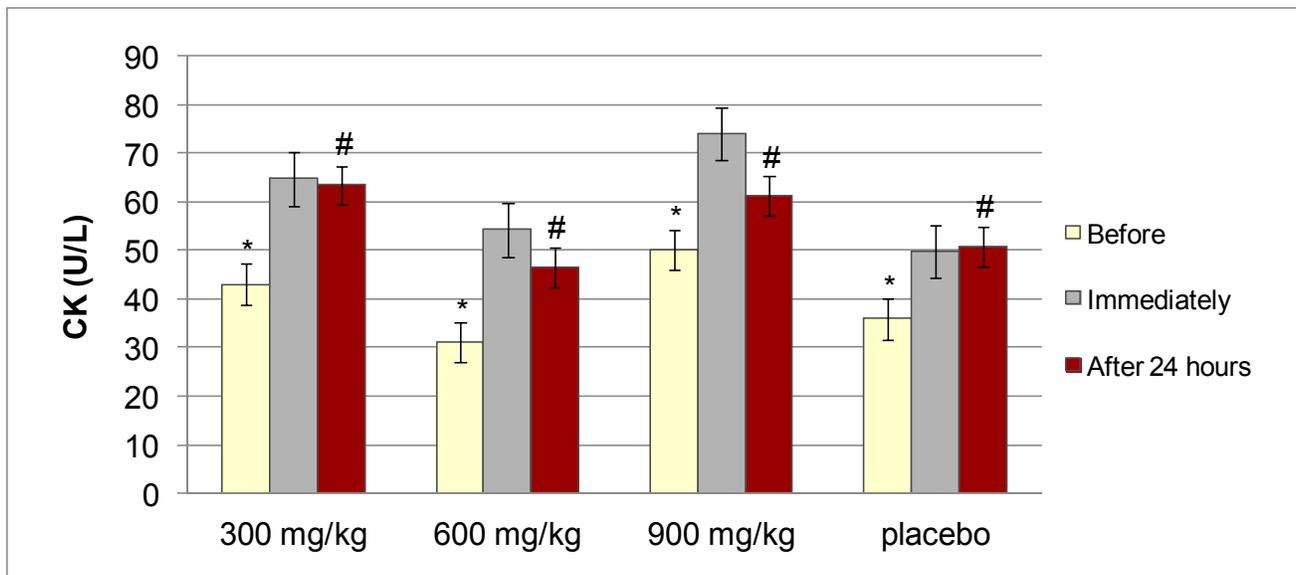
**Table 1. Personal Information for the Subjects in Each Group.**

Conditions	Group 1 (300 mg·kg <sup>-1</sup> )	Group 2 (600 mg·kg <sup>-1</sup> )	Group 3 (900 mg·kg <sup>-1</sup> )	Group 4 (Placebo)
<b>Age</b> (yrs)	20.5 $\pm$ 0.58	20.25 $\pm$ 0.50	20.00 $\pm$ 0.00	20.00 $\pm$ 0.00
<b>Weight</b> (kg)	50.89 $\pm$ 2.45	59.00 $\pm$ 6.38	62.50 $\pm$ 6.81	65.75 $\pm$ 8.10
<b>Height</b> (cm)	176.75 $\pm$ 3.95	168.00 $\pm$ 4.08	173.00 $\pm$ 8.60	173.75 $\pm$ 6.13
<b>BMI</b> (kg·m <sup>-2</sup> )	20.21 $\pm$ 1.52	20.87 $\pm$ 1.61	20.86 $\pm$ 1.30	21.76 $\pm$ 2.13
<b>VO<sub>2</sub> max</b> (mL·min <sup>-1</sup> ·kg <sup>-1</sup> )	47.58 $\pm$ 6.33	47.47 $\pm$ 6.31	47.47 $\pm$ 10.14	47.96 $\pm$ 4.90
<b>Heart Rate</b> (beats·min <sup>-1</sup> )	84.75 $\pm$ 5.85	84.75 $\pm$ 14.57	94.25 $\pm$ 19.96	81.00 $\pm$ 7.53
<b>SBP</b> (mmHg)	123.0 $\pm$ 15.36	118.50 $\pm$ 10.72	118.00 $\pm$ 11.34	116.00 $\pm$ 14.90
<b>DBP</b> (mmHg)	71.25 $\pm$ 11.47	71.00 $\pm$ 13.64	71.50 $\pm$ 7.72	70.75 $\pm$ 8.54



**Figure 1. The Effect of Mangosteen Peel Extract on Interleukin 6 (IL- 6) Concentrations Before, Immediately After Exercise, and 24 Hrs After Exercise.**

As shown in Figure 1, the concentration of interleukin 6 (IL-6) was significantly increased immediately after exercise in all groups (300 mg·kg<sup>-1</sup>; 0.59 ± 0.36, 1.32 ± 0.40 pg/mL 600 mg·kg<sup>-1</sup>; 0.50 ± 0.29, 1.43 ± 0.45 pg/mL 900 mg·kg<sup>-1</sup>; 0.77 ± 0.59, 1.69 ± 0.74 pg/mL placebo; 0.49 ± 0.35, 1.42 ± 0.52 pg/mL). On the other hand, IL-6 concentrations at 24 hrs after exercise were not changed, but still higher than before exercise in all groups. However, it seems likely that 900 mg·kg<sup>-1</sup> mangosteen extract may decrease the level of IL-6 more than the other doses. With regards to tumor necrosis factor-alpha (TNF-alpha), there was no detection of TNF-alpha within the detection limits.



**Figure 2. The Effect of Mangosteen Peel Extract on Total Creatine Kinase (CK) Concentration Before, Immediately After Exercise, and 24 Hrs After Exercise.**

Figure 2 shows that immediately after exercise creatine kinase was significantly increased in all groups when compared to before exercise (300 mg·kg<sup>-1</sup>; 67.94 ± 28.43, 72.25 ± 27.41 U/L 600 mg·kg<sup>-1</sup>; 101.09 ± 98.07, 80.72 ± 73.42 U/L 900 mg·kg<sup>-1</sup>; 96.68 ± 99.19, 102.49 ± 99.37 U/L placebo; 93.82 ± 16.09, 79.82 ± 30.83 U/L). After mangosteen peel extract supplementation (300-900 mg·kg<sup>-1</sup>) for 24 hrs, CK level did not change in all groups, when compared to immediately exercise (300 mg·kg<sup>-1</sup>; 72.25 ± 27.41, 43.05 ± 7.19 U/L 600 mg·kg<sup>-1</sup>; 80.72 ± 73.42, 43.61 ± 27.02 U/L 900 mg·kg<sup>-1</sup>; 102.49 ± 99.37, 62.48 ± 59.43 U/L placebo; 79.82 ± 30.83, 77.92 ± 36.83 U/L). However, the extract at the dose of 900 mg·kg<sup>-1</sup> was likely to show a mark decrease of CK after exercise more than the other doses.

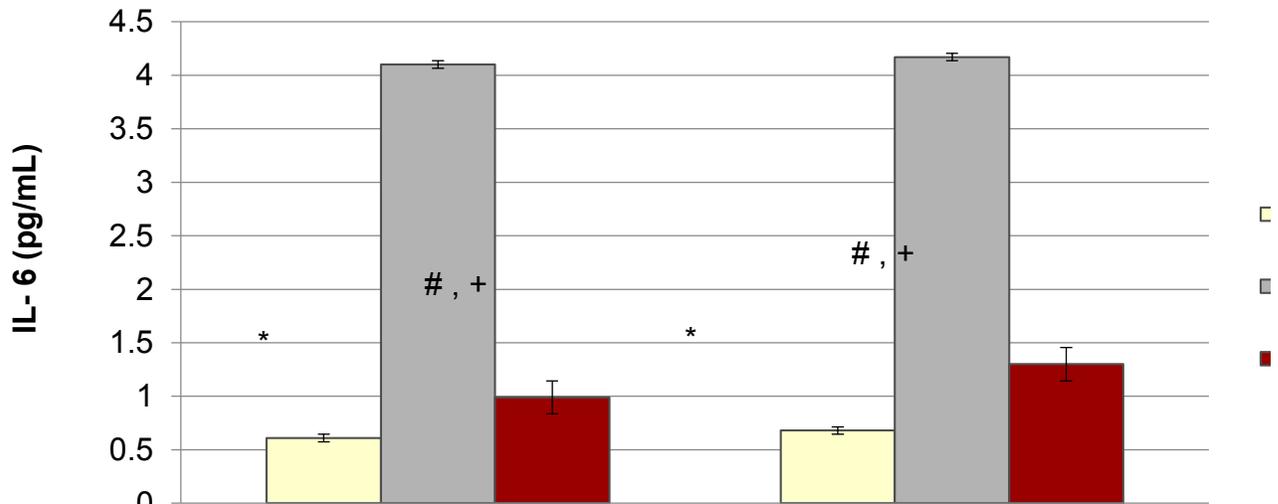
**Part 2: Aim: To evaluate mangosteen peel extract's activities on acute inflammatory response after short-term strenuous exercise by 15 km of running.**

**Table 2. Personal Information of the Participants in Both Groups.**

	<b>Experimental Group</b>	<b>Control Group</b>
<b>Conditions</b>	(900 mg·kg <sup>-1</sup> )	(Placebo)
<b>Age</b> (yrs)	20.38 ± 0.52	20.00 ± 0.00
<b>Weight</b> (kg)	63.13 ± 5.06	62.00 ± 7.41
<b>Height</b> (cm)	173.50 ± 5.93	172.25 ± 6.94
<b>BMI</b> (kg·m <sup>-2</sup> )	20.99 ± 1.60	20.86 ± 1.71
<b>VO<sub>2</sub> max</b> (mL·min <sup>-1</sup> ·kg <sup>-1</sup> )	47.92 ± 7.72	47.32 ± 5.37
<b>Heart Rate</b> (beats·min <sup>-1</sup> )	86.13 ± 16.59	86.25 ± 8.96
<b>SBP</b> (mmHg)	122.25 ± 12.73	115.50 ± 11.30
<b>DBP</b> (mmHg)	72.63 ± 8.57	69.63 ± 10.70

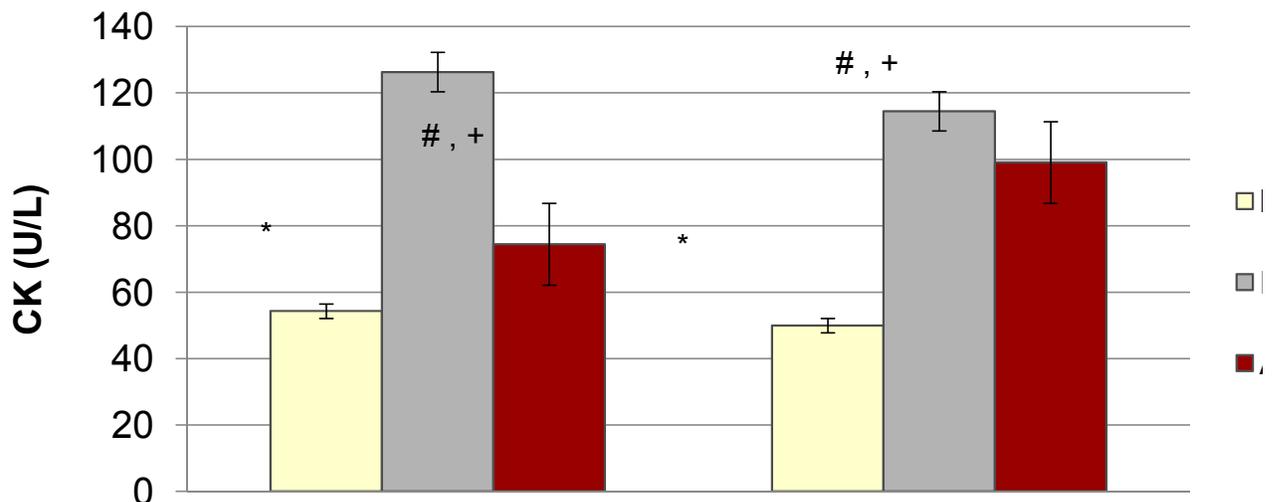
Data are expressed as mean ± SD; **BMI** = Body Mass Index; **SBP** = Systolic Blood Pressure; **DBP** = Diastolic Blood Pressure

The baseline parameters of all subjects between the Experimental Group (900 mg·kg<sup>-1</sup>) and the Control Group (placebo) were not significantly different (as shown in Table 2).



**Figure 3. Interleukin 6 Level, Before, Immediately, and 24 Hrs After 15 km Running.** Values are shown as means  $\pm$  SD. \*Significant differences between before and immediately,  $P < 0.05$ . #Significant differences between before and 24 hrs after the 15 km run,  $P < 0.05$ . +Significant differences between immediately and 24 hrs after 15 km running,  $P < 0.05$

Figure 3 shows that interleukin-6 concentration of the Experimental Group and the Control Group were significantly increased immediately after the 15 km run ( $0.61 \pm 0.35$  vs.  $4.10 \pm 1.64$  pg/mL,  $0.61 \pm 0.35$  vs.  $4.10 \pm 1.64$  pg/mL in the Experimental Group and the Control Group, respectively). After treated with mangosteen peel extract at the dose of  $900 \text{ mg} \cdot \text{kg}^{-1}$ , it was found that the IL-6 level was significantly decreased ( $4.10 \pm 1.64$  vs.  $0.99 \pm 0.55$  pg/mL). In addition, the IL-6 level in the Control Group was also significantly decreased ( $4.17 \pm 2.08$  vs.  $1.30 \pm 0.53$  pg/mL). However, when comparing the IL-6 levels between the Experimental and the Control Group, there was no statistically significant difference ( $P > 0.05$ ). Moreover, the concentration of tumor necrosis factor-alpha (TNF-alpha) from both Groups before exercise, immediately after exercise, and 24 hrs after exercise was also determined. However, tumor necrosis factor-alpha was not detected within the detection limits.

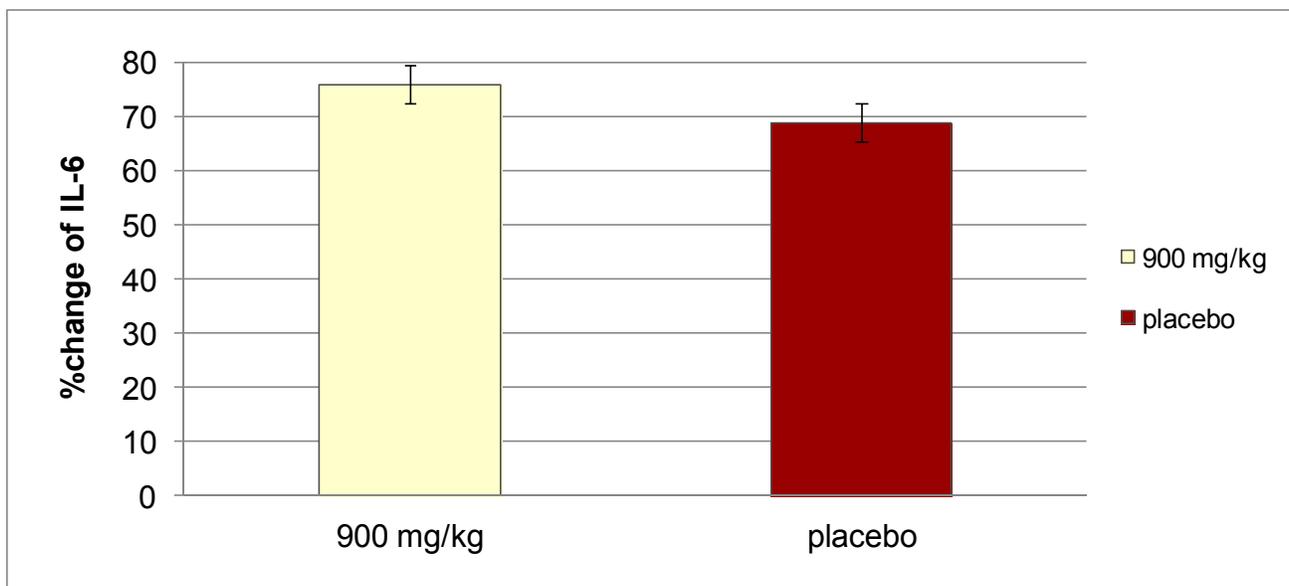


**Figure 4. Mean and Standard Deviation of Total Creatine Kinase Before, Immediately, and 24 Hrs After 15 km Running.** \*Significant differences between before and immediately,  $P < 0.05$ .

#Significant differences between before and 24 hrs after 15 km running,  $P < 0.05$ . +Significant differences between immediately and 24 hrs after the 15 km run,  $P < 0.05$

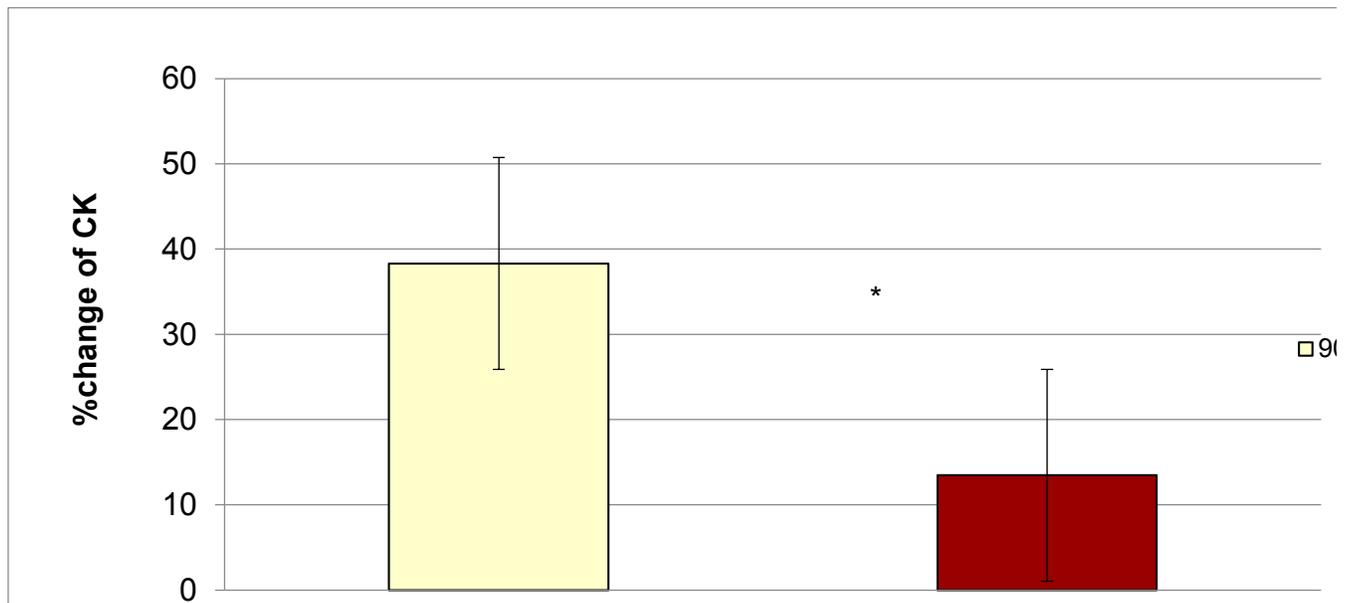
Figure 4 shows that total creatine kinase (CK) concentration in the Experimental Group and the Control Group was significantly increased immediately after the 15 km run ( $54.30 \pm 19.39$  vs.  $126.31 \pm 25.43$  U/L,  $49.93 \pm 21.42$  vs.  $114.52 \pm 25.97$  U/L, respectively). After treated with mangosteen peel extract at the dose of  $900 \text{ mg}\cdot\text{kg}^{-1}$  (Experimental Group), it was found that creatine kinase level was significantly decreased ( $126.31 \pm 25.43$  vs.  $74.46 \pm 19.65$  U/L). In addition, creatine kinase level in the Control Group was also significantly decreased ( $114.52 \pm 25.97$  vs.  $99.10 \pm 26.61$  U/L). However, when comparing creatine kinase levels between the Experimental Group and the Control Group, there was no statistically significant difference ( $P > 0.05$ ).

Figure 5 shows in the Experimental Group that after treatment with mangosteen peel extract supplementation at  $900 \text{ mg}\cdot\text{kg}^{-1}$ , the percentage change of interleukin-6 was greater than the Control Group (i.e., placebo) by 9.27%. However, when compare interleukin-6 levels between  $900 \text{ mg}\cdot\text{kg}^{-1}$  (Experimental Group) and placebo, there was no statistically significant difference.



**Figure 5. Comparison of Percentage Change of Interleukin 6 (IL- 6) from Both Groups at 24 Hrs After Running.**

As reported in Figure 6, after treated with mangosteen peel extract supplementation at the dose of  $900 \text{ mg}\cdot\text{kg}^{-1}$  (Experimental Group), the percentage of reduction in total creatine kinase was greater than the Control Group (placebo) by about 64.86%. When comparing total creatine kinase levels between the Experimental Group and the Control (placebo) Group, there was a statistically significant difference ( $P < 0.05$ ).



**Figure 6. Comparison of Percentage Change of Total Creatine Kinase from both Groups at 24 Hrs After Running.** \*Significant differences between 900 mg·kg<sup>-1</sup> and the placebo, P<0.05

## DISCUSSION

The unique aspect of the present study is its 2 parts: **Part I: Primary Experimental Phase:** The main finding was identifying the most effective dose of mangosteen peel extract on inflammatory markers and muscle damage. Also, this study measured the amount of TNF-alpha in the blood stream and found that the 4 sample groups' mean scores were not detected within the detection limits. Tumor necrosis factor-alpha is associated with infectious inflammatory situations (20,25). It is to different diseases, such as rheumatoid arthritis, Crohn's disease, and systemic lupus erythmatosus (34,36,41,46), physical frailty and/or muscle wasting (40), and early death (4). However, interestingly, the present study found no increase in TNF-alpha with the different exercise conditions.

This study found a statistically significant (P<0.05) increase in Interleukin-6 in the Control Group and the Experimental Group immediately after short-term strenuous exercise. The exercise induced increase in IL-6 is not linear over time. After exercise, there is a rapid increase in IL-6 that is exponential (48). Strenuous exercise such as downhill running on a treadmill shows a significant increase in the level of IL-6 (35). When an inflammation occurs, the density of protein will temporarily increase, especially during the training of the muscular system during sports and exercise. Then, after training, the density will gradually decrease for 4 to 24 hrs (26).

This study found that immediately after exercise the concentration of total creatine kinase was significantly increased in all groups when compared to before exercise. Namely, many free radical problems in human body are caused by different factors, such as over-exercising (42). According to the physical changes that occur during exercise, it is apparent that the muscular system needs more oxygen. Thus, more free radicals are produced inside the body in accordance with the breathing chain. The creatine kinase level was found to be increased more than normal after exercise (3,13,15,31).

Mangosteen peel extract at the dose  $900 \text{ mg}\cdot\text{kg}^{-1}$  was likely to show a mark decrease of interleukin-6 and creatine kinase after exercise more than others dose. Therefore, the  $900 \text{ mg}\cdot\text{kg}^{-1}$  was chosen with the anticipation that it would provide the best results in reducing inflammation and muscle damage. Moreover, the dose of  $900 \text{ mg}\cdot\text{kg}^{-1}$  per day does not endanger the subjects.

**Part II: Secondary Experimental Phase: Short-Term Strenuous Exercise (15 km Running).** This study found that TNF-alpha was not detected within the detection limits. Consistent with previous research, it was found that running marathon by experimenting before and after a competitive 42.195-km race, the cytokines TNF-alpha could not be detected (49). Therefore, the response of cytokines to exercise is not preceded by an increase in TNF-alpha (11,47,55). This study found that, interleukin-6 was significantly increased immediately after the 15 km run in the Experimental and Control Groups. Consistent with Kurhade et al. (27), who studied heavy training, they found that IL-6 was increased after 1 hr of exercise and remained in the body after 52 hrs of exercise. The strenuous exercise was associated with an increase in IL-6 in after exercise (13,55,56). This study found that creatine kinase was significantly increased ( $P<0.05$ ) in both the Control Group and the Experimental Group after strenuous exercise. Current studies support similar findings (38), immediately after the long-distance races (29,45), football (19), and eccentric exercises (29,45).

After given mangosteen peel extract, the Experimental Group's Interleukin-6 decreased the inflammation after the exercise. It was found that; the percentage change of Interleukin-6 was lower than the Control Group with a difference of 9.27%. Moreover, after treated with the mangosteen peel extract at a dose of  $900 \text{ mg}\cdot\text{kg}^{-1}$ , the percent change in creatine kinase was significantly decreased more than the percent change in Control Group (i.e., placebo). Therefore, the decrease in the release of IL-6 and creatine kinase (CK) caused by acute inflammation in response to the short-term strenuous exercise (15 km run) in this study will help explain the anti-inflammatory activity of  $\alpha$ -mangostin (the most abundant xanthone in mangosteen fruit), the PGE2 inhibition and nitric oxide (NO) production (7), and the inhibition of COX-2 mRNA transcription (54). Another action related to the anti-inflammatory effect of mangosteen is its antioxidant properties (39) in scavenging oxygen reactive species and other free radicals (30) and the inhibition of nuclear-kappaB (NF-kB) (5), which is consistent with many laboratory animal studies (1,10,23,33,63). In addition, studies in humans (52,62), that have been studied about mangosteen peel extracts, found that using a small dose will take at least a month to achieve the effect, 1 day in the experiment is too short. However, from this research, when compared to the percentage difference, it was found that the mangostin extract has an anti-inflammatory effect of 9.27% that can decrease muscle damage by 64.48%.

## CONCLUSIONS

A mangosteen peel extract dose of  $900 \text{ mg}\cdot\text{kg}^{-1}$  is beneficial in maintaining health after strenuous exercise by decreasing inflammation and muscle damage. However, this conclusion is basic information that needs to be further analyzed. In the future, there will probably be additional studies on taking the extract for a longer period of time after exercise (e.g., 48 hrs or 72 hrs to better understand its role in health and exercise).

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