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The Anti-Inflammatory Effects of Mango, Orange, and Dragon Fruit on C-reactive protein (CRP) Levels in a Hypercholesterolemic Rat Model

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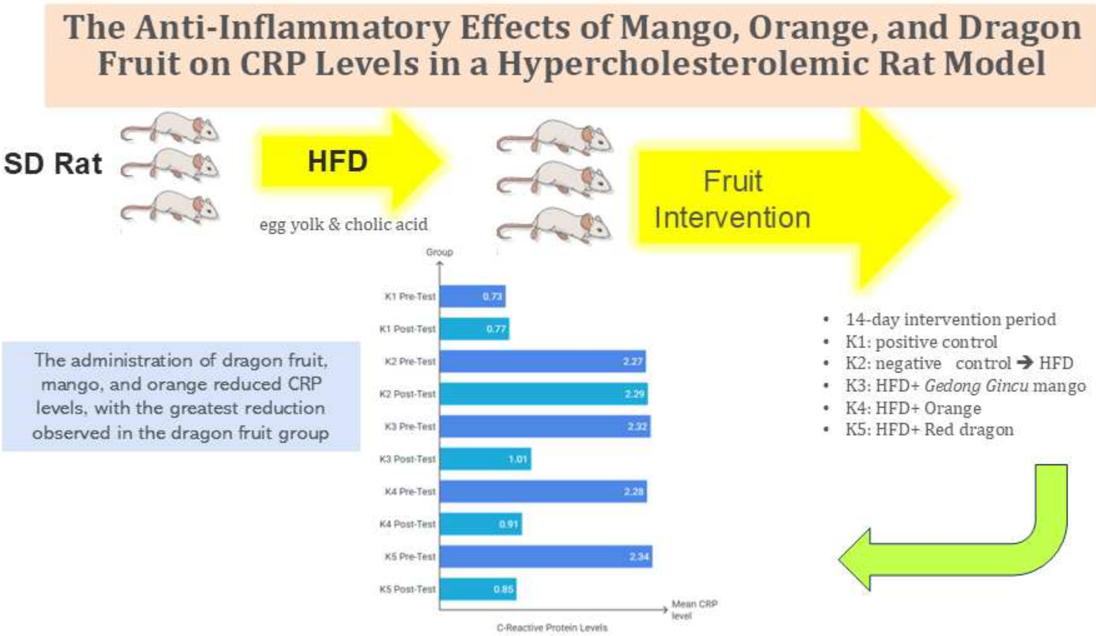
ABSTRACT

Inflammation is a response to tissue injury or infection. Fruits such as mango, oranges, and dragon fruit contain nutrients that can reduce levels of inflammation in the body. This study aimed to investigate the effect of mango, orange, and dragon fruit on C-reactive protein (CRP) levels in experimental animals. This study was conducted using a randomized controlled pre-posttest design with 30 Sprague Dawley rats were divided into five groups, group K1 without treatment, group K2 only received high fat diet (HFD), group K3 received HFD with intervention of gedong gincu mango at a dose of 3.6g/200g weight, group K4 received HFD with intervention of sweet orange at a dose of 9ml/200g weight, and K5 group receiving HFD with intervention of red dragon fruit at a dose of 3.6g/200g weight. Compared to Pre-test, Group K3, K4 and K5 had an average change of CRP levels at post-test: -1.30±0.08mg/L, -1.39±0.04 mg/L and -1.48±0.09 mg/L respectively. All samples resulted in reduction of CRP levels in Sprague-Dawley rats with Red dragon fruit showed greater effect compared to other fruits.

Key Messages:

- The findings of this study reveal the potential of incorporating antioxidant-rich fruits like Gedong Gincu mango, sweet orange, and red dragon fruit into the diets of individuals at risk of hypercholesterolemia and inflammation, providing a natural approach to managing chronic health conditions.
- This research contributes to the existing body of knowledge by specifically comparing the effects of local fruits—mango, orange, and dragon fruit—on C-Reactive Protein levels in a controlled experimental setting, highlighting the unique benefits of these fruits as effective anti-inflammatory agents.

GRAPHICAL ABSTRACT



INTRODUCTION

Inflammation is a biological response to tissue injury or infection. It is a natural process that helps maintain the body's homeostasis in response to foreign agents or compounds (1). The inflammatory process is initiated by stimuli that cause tissue damage or injury, which may include infection, trauma, or other forms of tissue damage. These stimuli trigger the migration of white blood cells, such as neutrophils and macrophages, to the site of injury, initiating the inflammatory response (2). These immune cells release cytokines and other inflammatory mediators that lead to clinical signs of inflammation, such as swelling, pain, heat, redness, and stiffness at the affected site (2). Although inflammation plays a key role in eliminating infections and harmful stimuli while initiating tissue repair, it can also be detrimental by causing damage to normal tissues, particularly in cases of severe infection, chronic inflammation, autoimmune disorders, or allergies (3).

Inflammation in the body can be assessed using biomarkers such as C-Reactive Protein (CRP), a well-established and sensitive indicator of inflammation. CRP is synthesized by the liver in response to infection, injury, or inflammatory stimuli. Elevated CRP levels are indicative of an ongoing inflammatory process and are associated with various health conditions, including cardiovascular disease, arthritis, and cancer. CRP is widely used as a clinical marker to assess the degree of inflammation and the risk of several diseases (4).

Hypercholesterolemia refers to elevated blood cholesterol levels, typically >240 mg/dL. Studies have shown that hypercholesterolemia is associated with increased inflammation, often reflected by elevated CRP levels (5). CRP is considered a strong inflammatory biomarker and predictor of cardiovascular disease (CVD). The aetiology of CVD is generally linked to both atherosclerosis and inflammation. Elevated CRP levels are correlated with increased cardiovascular risk. The relative risk categories for CVD based on CRP concentration are: low risk (<1.0 mg/L), moderate risk (1.0–3.0 mg/L), and high risk (>3.0 mg/L) (6,7).

One approach to lowering CRP levels is through the consumption of antioxidant-rich foods, particularly those high in omega-3 fatty acids, low in fat and carbohydrates, and rich in probiotics. Previous studies have reported that consuming antioxidant-rich foods, such as fruits and vegetables, can significantly reduce CRP levels (8). Vitamins such as vitamin C, vitamin E, and β-carotene function as antioxidants that neutralize free radicals. Several local fruits rich in these vitamins include mango, orange, and dragon fruit.

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Mango is a local fruit with high levels of vitamin C, vitamin E, and β-carotene. It also contains other essential vitamins such as vitamin A and various B-complex vitamins, with vitamin C being one of the most abundant. One notable local variety is *Gedong Gincu* mango. Zaki & Johan, 2015 found that administering 3.6 g/200 g BW/day of *Gedong Gincu* mango orally for 14 days to hypercholesterolemic rats significantly reduced LDL cholesterol levels and increased HDL cholesterol levels (9).

Orange is another Indonesian local fruit known for its high antioxidant content, including vitamin C, vitamin E, and β-carotene, which exhibit anti-inflammatory and antioxidant properties (10). Oranges also contain bioactive compounds such as hesperidin and quercetin, which act as anti-inflammatory agents. Research conducted by Pamungkas, 2019 showed that oral administration of 9 ml/200 g BW/day of sweet orange juice for 14 days led to a reduction in LDL cholesterol levels in rats. However, further studies are needed to investigate the relationship between orange consumption and CRP levels (11,12).

Dragon fruit is another antioxidant-rich fruit. Although originally native to the Americas, it has been widely cultivated and adopted as a local fruit in several regions of Indonesia. Red dragon fruit is particularly rich in antioxidants such as vitamin C, vitamin E, carotenoids (including β-carotene and lycopene), anthocyanins, and flavonoids (13). A study by Radinawati et al., 2022 demonstrated that oral administration of 2.86 g/kg BW/day of red dragon fruit to obese university students for 14 days before breakfast significantly reduced LDL cholesterol levels (14). Based on the potential antioxidant and anti-inflammatory properties of mango, orange, and dragon fruit, this study aimed to investigate the effect of mango, orange and dragon fruit on c-reactive protein (CRP) levels in experimental animals.

METHODS

This study employed a randomized controlled pre-posttest design. The experiment was conducted at the Experimental Animal Laboratory, Inter-University Centre (PAU), Gadjah Mada University (9). The subjects were healthy male Sprague Dawley rats, eight weeks old, weighing between 170–200 g. This study's use of animal models, particularly Sprague-Dawley rats, represents an essential preliminary step before conducting clinical trials in humans. Hypercholesterolemic rat models were selected due to their relevant physiological and metabolic similarities to humans, especially regarding lipid metabolism and inflammatory responses. These similarities make Sprague-Dawley rats a commonly used and scientifically valid animal model for evaluating the effects of interventions on inflammatory parameters and metabolic disorders (9,15,16).

The hypercholesterolemic rat model, induced by a high-cholesterol and saturated fat diet, triggers a systemic inflammatory response, marked by elevated C-Reactive Protein (CRP) levels as an acute-phase inflammation marker. CRP is a sensitive biomarker synthesised by hepatocytes in response to interleukin stimulation and reflects subclinical inflammation contributing to atherogenesis (17–19). Measuring CRP in this model allows quantitatively evaluating inflammatory responses to nutritional interventions. Investigating the effects of red dragon fruit, mango, and orange in hypercholesterolemia rats provides mechanistic insight into the potential of bioactive fruit compounds to reduce inflammation mediated by hypercholesterolemia. Moreover, animal models offer strict control over environmental, genetic, and dietary variables, enhancing internal validity before clinical trials in human subjects (16,20,21).

The animals were randomly allocated into five groups (n = 6 per group): Group K1 (positive control) received a standard diet; Group K2 (negative control) received a high-fat diet (HFD); Group K3 received HFD + *Gedong Gincu* mango (*Mangifera indica*); Group K4 received HFD + sweet orange (*Citrus sinensis*); and Group K5 received HFD + red dragon fruit (*Hylocereus polyrhizus*) (9,15,16).

The protocol began with a three-day acclimatization period during which all rats were fed a standard diet amounting to 10% of their body weight (9). After acclimatization, all groups received their respective diets ad libitum (22). Hypercholesterolemia was induced by administering a high-fat diet for seven consecutive days, followed by collecting baseline (pre-test) data on C-Reactive Protein (CRP) to confirm successful modelling. LDL and HDL levels were also measured as part of the observed parameters during this process. However, these data were analysed and discussed separately in the context of lipid profile modulation and are intended for publication in a separate article. This was followed by a 14-day intervention period, and post-test data were collected at the end of the intervention (9). Samples were

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prepared by washing the fruits thoroughly under running water to remove debris, followed by peeling, chopping, and homogenizing the edible portions. The mango variety used was *Gedong Gincu* (*Mangifera indica*), the orange variety was *sweet orange* (*Citrus sinensis L.*), and the dragon fruit variety was *red dragon fruit* (*Hylocereus polyrhizus*).

The high-fat diet (HFD) was prepared by mixing egg yolk with cholic acid until homogeneous. The cholic acid was added to accelerate the increase in serum cholesterol. The HFD mixture (2 ml/200 g body weight/day) containing 0.25 ml of cholic acid was administered orally to Groups K2, K3, K4, and K5 for seven days post-acclimatization (23,24). According to Asnilawati (2017), this dosage effectively induces hypercholesterolemia (23). Elevated cholesterol levels have been associated with increased CRP concentrations (5), hence the use of this model to elevate CRP levels.

The dosage of each fruit was based on previous studies and adjusted for rats using the human-to-rat dose conversion factor of 0.018 for a 70-kg human to a 200-g rat. The dosage of *Gedong Gincu* mango used was 3.6 g/200 g BW/day orally (9). The dose for sweet orange was 9 ml/200 g BW/day (25), while fresh red dragon fruit was administered at 2.86 g/kg BW/day, adjusted for rats using the same conversion factor (14).

Blood samples (~5 cc) were collected from the retro-orbital plexus using a capillary tube. Serum C-reactive protein (CRP) levels were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method, the measurement was taken at a wavelength of 450 nm (26).

Statistical analysis was performed using SPSS version 26.0 and Microsoft Excel 2016. Normality of the data was first tested, followed by paired sample t-tests to assess within-group changes. A one-way ANOVA was employed to compare the effectiveness of the different fruit interventions in reducing CRP levels.

CODE OF HEALTH ETHICS

The study protocol received ethical approval from the Health Research Ethics Committee, Faculty of Health Sciences, Universitas Jenderal Soedirman, with registration number 1156/EC/KEPK/VI/2023.

RESULTS

This study involved groups of six male Sprague-Dawley rats, each aged eight weeks, with initial body weights ranging from 170 to 200 grams. Based on Table 1, changes in CRP levels were observed between the pre-test and post-test across all treatment groups. Group K1, which did not receive a high-fat diet (HFD), maintained stable CRP levels within the normal range. In contrast, Group K2, which received only the HFD without any fruit intervention, exhibited a significant increase in CRP levels, with no reduction following the treatment period. Meanwhile, Groups K3, K4, and K5, which were administered HFD alongside fruit interventions, demonstrated significant reductions in CRP levels at post-test, indicating potential anti-inflammatory effects of the respective fruits.

Table 1. Pre-test and Post-test C-Reactive Protein (CRP) Levels in Each Experimental Group

Group	n	*Pre-Test* *Mean*±SD (ng/ml)	p*	*Post-Test* *Mean*±SD (ng/ml)	*p***
K1[a]	6	0.73±0.02		0.77±0.15	
K2[b]	6	2.27±0.19	*< 0,0001*	2.29±0.01	
K3[a]	6	2.32±0.08	*< 0,0001*	1.01±0.01	*< 0,0001*
K4[a]	6	2.28±0.04	*< 0,0001*	0.91±0.01	*< 0,0001*
K5[a]	6	2.34±0.07	*< 0,0001*	0.85±0.03	*< 0,0001*

[a]Comparators included groups not given a high-fat diet (HFD) and groups given an HFD.
[b]Comparators also included groups not receiving fruit intervention and groups receiving fruit intervention.
*P-value of One-Way ANOVA for differences in CRP levels between groups without HFD and those with HFD.
**P-value of One-Way ANOVA for differences in CRP levels between groups without fruit intervention and those with fruit intervention.

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A one-way ANOVA test was conducted to analyze the differences in CRP levels between the normal control group (K1), which did not receive a high-fat diet (HFD), and the groups that were administered HFD (K2, K3, K4, and K5). The results indicated a significant difference in CRP levels between the non-HFD group and the HFD-treated groups ($p < 0.05$). To evaluate the effect of fruit interventions on CRP levels, the K2 group (HFD without fruit intervention) was compared with the K3, K4, and K5 groups (HFD with fruit interventions). The analysis showed a significant difference in CRP levels between the non-intervention group and the fruit intervention groups ($p < 0.05$). These findings reinforce the hypothesis that fruit supplementation can significantly reduce CRP levels under inflammatory conditions induced by a high-fat diet.

Table 2 shows the results of the analysis of C-Reactive Protein (CRP) levels before and after intervention in the groups receiving fruit treatment. All three groups (K3, K4, and K5) showed a statistically significant reduction in CRP levels after intervention (p=0.000). In group K3, which received mango, the CRP level decreased from 2.32±0.08 ng/ml to 1.01±0.01 ng/ml, with a difference of -1.30±0.08 ng/ml. Group K4, which received orange intervention, showed a reduction from 2.28±0.04 ng/ml to 0.91±0.01 ng/ml, with a change of -1.39±0.04 ng/ml. Meanwhile, group K5, which received dragon fruit, experienced the greatest reduction, from 2.34±0.07 ng/ml to 0.85±0.03 ng/ml, with a change difference of -1.48±0.09 ng/ml.

Table 2. Analysis of CRP Levels Before and After Intervention

Group	***Pre-Test* *Mean*±SD (ng/ml)**	***Post-Test* *Mean*±SD (ng/ml)**	**Δ *Mean*±SD (ng/ml)**	**P**
K3	2,32±0,08	1,01±0,01	-1,30±0,08	*< 0,0001*
K4	2,28±0,04	0,91±0,01	-1,39±0,04	*< 0,0001*
K5	2,34±0,07	0,85±0,03	-1,48±0,09	*< 0,0001*

DISCUSSION

The reduction in CRP levels is influenced by the nutritional content of Gedong Gincu mango. Gedong Gincu mango contains Vitamin C and β-Carotene. A 100g serving of Gedong Gincu mango contains 30 mg of Vitamin C and 113 μg of β-Carotene. Vitamin C and β-Carotene act as antioxidants that neutralize free radicals. Vitamin C has anti-inflammatory effects and can help reduce oxidative stress, a risk factor for increased CRP. Research shows that Vitamin C administration inhibits and reduces oxidative stress in rats (27). Meanwhile, β-Carotene has antioxidant properties and helps protect cells from oxidative damage, which may also influence CRP levels (28). The results of this study also align with previous research indicating that β-Carotene administration can reduce total cholesterol levels in Sprague Dawley rats, which corresponds with the reduction in CRP levels (29).

Similar results were observed in the group administered sweet oranges. The administration of 9 ml/200g body weight of sweet oranges for 14 days reduced CRP levels by an average of 1.39 ng/ml. The findings of this study are consistent with previous research reporting that the administration of sweet orange juice reduces LDL cholesterol levels in rats, which is in line with the reduction in CRP levels (25). The Vitamin C content in oranges has anti-inflammatory effects and helps reduce oxidative stress, which is a risk factor for elevated CRP levels (30). Oranges contain hesperidin, a flavonoid specific to citrus fruits that can reduce cholesterol levels in the blood. Another flavonoid in oranges is quercetin. Quercetin is a strong antioxidant that is also used as a standard for determining cholesterol reduction in blood. Quercetin also has other biological activities, such as antiviral, antibacterial, anti-inflammatory, and anticancer properties (11). This is consistent with previous studies showing that hesperidin and quercetin administration can reduce oxidative stress in rats (31,32).

Adhering red dragon fruit extract (3.6 g/200 g body weight) for 14 days effectively reduced CRP levels by 1.48 ng/ml in hypercholesterolemic Sprague Dawley rats, with the most significant reduction observed in group K5. This effect indicates the potential of red dragon fruit to ameliorate inflammation associated with hypercholesterolemia, aligning with previous findings showing that anthocyanins in purple

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sweet potato also reduced CRP levels (33). The β-carotene (12 μg/100 g) and anthocyanin (88.7 mg/100 g) content in red dragon fruit act as antioxidants capable of neutralising free radicals, preventing oxidative damage, and providing anti-inflammatory and cardiovascular protective effects (34,35).

The presence of anthocyanins in red dragon fruit distinguishes it from the other two fruits, Gedong Gincu mango and sweet oranges. Anthocyanins have antioxidant properties and can prevent cardiovascular diseases due to atherosclerosis. Red dragon fruit also contains β-Carotene, which functions to prevent oxidative damage as an antioxidant, thus controlling CRP levels (35). Sweet oranges and Gedong Gincu mango contain Vitamin C, which has anti-inflammatory effects and can help reduce oxidative stress, a risk factor for increased CRP. The anthocyanin content in red dragon fruit is higher than the Vitamin C and Vitamin E content in sweet oranges and Gedong Gincu mango, making its antioxidant activity more pronounced. Research indicates that the administration of purple sweet potatoes, which are rich in anthocyanins, is more effective in reducing oxidative stress in rats compared to Vitamin C administration.

Sweet oranges have a higher Vitamin C content than Gedong Gincu mango, making sweet oranges more effective in reducing CRP levels compared to Gedong Gincu mango. However, sweet oranges also contain hesperidin, a citrus-specific flavonoid that can lower cholesterol levels in the blood. Another flavonoid present in oranges is quercetin. Quercetin is a potent antioxidant that is also used as a standard in determining blood cholesterol reduction. Quercetin also has other biological activities such as antiviral, antibacterial, anti-inflammatory, and anticancer properties (28).

CONCLUSION

The administration of Gedong Gincu mango, sweet orange, and red dragon fruit orally for 14 days was shown to be effective in reducing C-Reactive Protein (CRP) levels in Sprague Dawley rats induced with hypercholesterolemia with red dragon fruit showing the most optimal results. Future researchers could investigate the micronutrient and antioxidant content of the fruits used in the intervention. The intervention could also be applied to individuals with hypercholesterolemia to assess the effectiveness of fruit antioxidants in humans.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest concerning this article.

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