In vivo test combination of green coffee seed extract *(Coffea canephora)* and yellow turmeric *(Curcuma domestica val.)* on IL-6 and CRP levels

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ABSTRAK

Latar Belakang: *Acute Respiratory Distress Syndrome* (*ARDS) merupakan suatu bentuk cedera jaringan paru sebagai respons inflamasi terhadap berbagai faktor penyebabnya, dan ditandai dengan adanya inflamasi, peningkatan permeabilitas vaskular, dan penurunan aerasi jaringan paru.*
Tujuan: *Penelitian ini bertujuan untuk mengetahui uji in vivo kombinasi ekstrak kopi hijau dan ekstrak kunyit kuning sebagai antiinflamasi terhadap kadar sitokin IL-6 dan CRP pada tikus jantan galur wistar.*
Metode: *Penelitian ini merupakan penelitian eksperimental dengan desain penelitian "Pre and Post Test With Control Group Design". Tikus wistar dalam kondisi peradangan dan inflamasi dengan pemberian LPS selama 14 hari. Tikus Wistar diberikan perlakuan pemberian dosis kombinasi ekstrak biji kopi hijau dan kunyit kuning secara bertingkat 200 mg/Kg BB, 400 mg/KgBB dan 600 mg/KgBB dan uji kadar IL-6 dan CRP setelah dilakukan perlakuan selama 28 hari. Analisis data menggunakan Uji One-way Anova dengan nilai p < 0,05.*
Hasil: *Hasil uji Paired T-test menunjukkan adanya perbedaan terhadap kadar IL-6 didapatkan hasil sig. yaitu 0,001 (p<0,005), sedangkan pada kadar CRP menunjukkan tidak adanya perbedaan dengan hasil sig. 0,517 (p>0,005). Hasil uji one way anova menunjukkan adanya perbedaan rata-rata terhadap kadar IL-6 dengan sig 0,010 sedangkan pada kadar CRP tidak terdapat perbedaan pada setiap kelompok perlakuan (p=0,215).*
Kesimpulan: *Terdapat perbedaan pemberian kombinasi ekstrak biji kopi hijau dan kunyit terhadap kadar IL-6, namun tidak terdapat perbedaan pemberian kombinasi ekstrak biji kopi hijau dan kunyit terhadap kadar CRP.*

Kata kunci*: ARDS; biji kopi hijau; CRP; IL-6; kunyit kuning*

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ABSTRACT

Background: *Acute Respiratory Distress Syndrome (ARDS) is a form of lung tissue injury as an inflammatory response to various causative factors, and is characterized by inflammation, increased vascular permeability, and decreased lung tissue aeration.*
Objective: *This study aims to determine the in vivo test of a combination of green coffee extract and yellow turmeric extract as an anti-inflammatory against the levels of cytokines IL-6 and CRP in male wistar strain rats.*
Methods: *This was an experimental study with a "Pre-Post Test with Control Group Design." Wistar rats were subjected to inflammation and LPS administration for 14 days. Wistar rats were given a combination of green coffee bean extract and yellow turmeric extract at graded doses of 200 mg/kg BW, 400 mg/kg BW, and 600 mg/kg BW. IL-6 and CRP levels were measured after 28 days of treatment. Data were analyzed using a one-way ANOVA with a p-value <0.05.*
Results: *The paired T-test showed a significant difference in IL-6 levels. The mean difference in IL-6 levels was 0.001 (p<0.005), while there was no difference in CRP levels with a significant difference of 0.517 (p>0.005). The results of the one-way ANOVA test showed a significant difference in IL-6 levels with a significant difference of 0.010, while there was no difference in CRP levels between the treatment groups (p=0.215).*
Conclusion: *There was a significant difference in the combination of green coffee bean and turmeric extract on IL-6 levels, but no difference in the combination of green coffee bean and turmeric extract on CRP levels.*

Keyword: *ARDS; CRP; green coffee bean; IL-6; yellow turmeric*

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INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a form of lung tissue injury as an inflammatory response to various causative factors, and is characterized by inflammation, increased vascular permeability, and decreased lung tissue aeration (1). In ARDS, capillary permeability increases due to damage to the vascular endothelium or alveolar epithelium which causes accumulation of protein-rich fluid in the alveoli, resulting in diffuse alveolar damage and release of pro-inflammatory cytokines such as Interleukin-1 (IL-1), IL-6 and Tumor Necrosis Factor (TNF). These cytokines attract neutrophils and activate them, resulting in the release of reactive oxygen species and proteases that cause oxidative damage to lung tissue. Various pathogenesis can contribute to the development of ARDS. This fluid accumulation phase is followed by a proliferation phase characterized by the easing of pulmonary edema, proliferation of type II alveolar cells, fibroblasts, and myofibroblasts and matrix deposition. ARDS can then progress to the fibroproliferative phase or resolution and the lungs return to normal (2). One of the main characteristics of ARDS in COVID-19 is the presence of a cytokine

storm. A cytokine storm is an abnormal systemic inflammatory response due to excessive production of pro-inflammatory cytokines and chemokines (3). Under normal conditions, the innate immune system response is the first line of defense against infection. However, an abnormal and excessive immune response can cause immune damage to the human body. The SARS-CoV-2 virus is mainly spread through infectious droplets that enter the body through the mucous membranes.

Treatment recommendations for COVID-19 therapy are developing very dynamically. Standard therapy currently adopted consists of antivirals, anticoagulants, symptomatic therapy and vitamin supplementation. There are also several other treatment options in the form of Host-modifier/Immune-Based therapy such as IL-6 inhibitors, convalescent plasma therapy, and other immunomodulators (4). Predictors of poor prognosis include shortness of breath, lymphopenia, neutrophilia, and low monocytes and platelets , There is suppression of cellular immunity along with a severe inflammatory reaction leading to death. Patients with old age, co-morbidities, especially diabetes and hypertension have the greatest mortality rate (5). ARDS is followed by complications of heart problems, then kidney and liver are common. In COVID-19 patients who died, an increase in *C reactive protein* (CRP) and serum amyloid A levels was found. Increased CRP, old age, presence of comorbidities, pneumonia are risk factors for abnormal cardiac function in COVID-19 patients. Cardiovascular protection needs to be considered in patients with COVID-19 (6). In the case of COVID-19, proinflammatory cytokines in the lungs trigger an increase in lung immune cells. COVID-19 patients show reduced levels of *suppressor of cytokine signaling* (SOCS), which is necessary to control IL-6 signaling. Cytokine storm release may also be observed if sepsis is present. This increase in cytokines is directly related to respiratory distress, and can even cause death. IL-6 is also known as a biomarker of sepsis (7). The development of anti-inflammatory drugs derived from plants was carried out based on the side effects of anti-inflammatory drugs. The medicinal ingredients used are fruit, leaves, bark, rhizomes and flowers (8). One of the natural ingredients that have active compounds that act as anti-inflammatory drugs are green coffee beans *(Coffea canephora)* and yellow turmeric *(Curcuma domestica Val.).*

Green coffee beans *(Coffea canephora)* are rich in active compounds, namely chlorogenic acid, caffeine, trigonellin, and diterpenes which, apart from playing an important role in producing the distinctive taste of coffee brew, also have pharmacological effects. Chlorogenic acid, which is a class of polyphenolic compounds, has antifungal, antiviral, antioxidant, anti-inflammatory, and antibacterial effects (11). In

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addition, caffeine also has effects as an antioxidant and immunomodulator (12). The antioxidant compounds contained in green coffee beans include cafestol, ‒, kahweol, acetyl methyl carbinol, quinic acid, 3,5-dicaffeolguinic acid, dimethylsulfide, quinic acid, 2-ethylphenol. These compounds have pharmacological effects, including protection from various diseases that occur due to the invasion of bacteria, viruses, and antigens (12). Chlorogenic acid is a phenolic compound that dissolves in water. The active compound chlorogenic acid is formed from the esterification of quinic acid and certain trans-cinnamic acids including caffeic acid, ferulic acid, and pcoumaric acid. Chlorogenic acid has an effect on the body's defense mechanism in increasing phagocytic activity by entering into infectious agents and damaging the wall structure of these infectious agents (12). Chlorogenic acid is known to act as an antioxidant by capturing hydroxyl free radicals (HO), so it does not oxidize fat, proteins and DNA in cells. Polyphenol content can also increase the production of IL-12 and IFN-γ which is associated with increased phagocytosis activity. Polyphenols have the ability to repair responses that activate neutrophils and monocytes or macrophages which function to phagocytize foreign agents. Polyphenolic compounds also affect signal transduction pathways that play a role in cell proliferation, antioxidant activity, modulate enzyme activity, and modulate cytokine production (14). Various studies on the immunomodulatory effects of coffee beans have been carried out and are proven to enhance human immune responses. Chlorogenic acid from coffee beans which functions as an antioxidant can increase phagocytosis activity and has an opsonin function to help phagocytic cells eat infectious agents (15).

Yellow turmeric *(Curcuma domestica Val.)* has a long history in traditional medicinal systems (16). Curcuminoids (3.0-5.0%) and essential oils (2.5-6.0%) are the main compounds found in rhizomes. turmeric. Other compounds contained in turmeric are calcium, phosphorus, iron, starch, fat, protein, camphor, gum, resin and resin. Various pharmacological effects of yellow turmeric have been reported as anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, antimalarial, anticarcinogenic and wound healing. Curcumin can inhibit a number of molecules involved in inflammation including phospholipase, lipoxygenase, COX2, leukotrienes, thromboxane prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12. Curcumin decreases the catalytic phospholipase A2 and phospholipase C g1, thereby reducing the release of arachidonic acid from cellular phospholipids. Curcumin has an inhibitory effect on phospholipase D activity. Curcumin can inhibit cyclooxygenase-2 (COX-2) expression

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(17). In addition, curcumin can also inhibit the synthesis of certain prostaglandins by inhibiting cyclooxygenase enzymes. Another mechanism of action of curcumin is by reducing leukotriene synthesis by inhibiting the lipooxygenase enzyme. Based on these several mechanisms, it can be seen that curcumin can reduce neutrophil infiltration in inflammatory conditions and inhibit platelet aggregation (18). The purpose of this study was to determine the potential of a combination of green coffee extract and yellow turmeric extract as an anti-inflammatory against the levels of cytokines IL-6 and CRP in Wistar male rats.

MATERIALS AND METHODS

This research is a true experimental research with a research design "Pre and Post Test With Control Group Design". This study will test the combination of green coffee bean extract and yellow turmeric on levels of IL-6 and CRP in Wistar rats given Lipopolysaccharide (LPS) with consentration 0.1 g/ Kg b.w via subcutaneous injection. The experimental animals used were 25 Wistar rats aged 2-3 months with an average weight of 160-200 grams. The treatment group consisted of 5 (five) groups with 5 (five) mice each for each group. Mice were placed in individual rat cages and labeled for each cage as a rat group marker. The individual rat cages are open rectangular plastic box cages with wire mesh lids for ventilation. The rat cages were placed on shelves in the same room and the room temperature was stable. The rat cages were cleaned every day. Maintenance is carried out every day by cleaning the cages and giving the same food to all groups of mice. The food given is AD II standard feed individually and drinking bottles using the ad libitum system. The time of feeding and giving the extract is done in the morning. The study used five groups, namely one healthy group, one control group and three treatment groups. Wistar rats that were previously in a state of inflammation and inflammation for 14 days characterized by increased levels of IL-6 and CRP. Wistar rats were treated with a combination dose of green coffee bean extract and yellow turmeric in P1 (50 mg: 10 mg/200gr b.w), P2 (100 mg: 20 mg/200gr b.w), and P3 (150 mg: 30 mg/200gr b.w) and tested for IL-6 and CRP levels after being treated for 21 days. Analysis using plasma collected using EDTA was then centrifuged for 30 minutes. Measurements were taken immediately and stored at -20^{0}C. Blood samples were taken on the 28th day and then the levels of cytokine IL-6 and CRP were measured using the ELISA kit of Rat Koma Biotech Inc.

The research was conducted at the IBL Faculty of Medicine, Sultan Agung Islamic University. The data obtained is in the form of primary data from direct

measurements. The data obtained, then processed using descriptive analysis presented in tabular form. The statistical test was carried out using the Shapiro Wilk test for normality, then the Paired T-test was carried out to test the differences between groups before and after being given treatment with graded doses. One-way Anova test to see in general the difference in mean levels of IL-6 and CRP levels with a p value <0.05 in the One-way Anova test and Post Hoc Tukey LSD. This research has received ethical approval from the Research Commission on Bioethics at Sultan Agung Islamic University with number No. 332/VIII/2022/Commission on Bioethics.

RESULTS AND DISCUSSIONS

The polyphenolic compounds contained in green coffea seeds affect signal transduction pathways that play a role in cell proliferation, antioxidant activity, modulate enzyme activity, and modulate cytokine production. In addition, the effect of the content of yellow turmeric is anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, antimalarial, anticarcinogenic and wound healing. Curcumin can inhibit a number of molecules involved in inflammation including phospholipase, lipoxygenase, COX2, leukotrienes, thromboxane prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12. Based on **Table 1**, it shows that there is a dispersion of data distribution with the highest average in the prek4 group of 5.11 and the lowest in the Post K1 group of 3.06 for the IL-6 level, while the data with the highest average in the prek1 group is 3.10 and the lowest was in the Pre K3 group of 2.16 for CRP levels.

Table 1. Comparison of the TNF-α level in groups before and after treatment with the combination of green coffee seed and yellow turmeric extracts.

Group	IL-6		CRP	
	Day 7 (mean±SD)	Day 21 (mean±SD)	Day 7 (mean±SD)	Day 21 (mean±SD)
Control	4.33±1.54	3.06±0.45	3.10±1.24	2.49±0.34
LPS	4.59±1.62	3.63±0.62	2.78±0.17	2.91±0.26
P1	7.01±3.51	3.11±0.60	2.16±0.50	2.71±0.69
P2	5.11±2.62	3.15±0.61	2.73±0.43	2.24±0.26
P3	4.19±0.76	3.15±0.61	2.49±0.34	2.59±0.31
Paired T-Test	0.001*		0.517	
One Way Anova	0.010*		0.215	

Post Hoc LSD after treatment P2+P3, *p value =0,041* (IL-6)

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Table 1 shows that there were differences before and after paired t-test the treatment of IL-6 levels, the results were sig. namely 0.001 ($p < 0.005$), while the CRP levels showed no difference before and after treatment with sig. 0.517 ($p > 0.005$). There is no difference in CRP levels, which can be caused by the lack of duration of inflammation which occurs slowly, the longer the disease lasts, the longer inflammation occurs in the body, resulting in an increase in lipid metabolism and levels of inflammatory cells such as monocytes in the blood. Lipopolysaccharide binds to specific proteins in plasma, namely lipopolysaccharide binding protein (LBP). Furthermore, this LPS-LBP complex will bind to CD14, which is a receptor on the macrophage membrane. CD14 will present LPS to toll-like receptor 4 (TLR4), which is a receptor for signal transduction resulting in macrophage activation. Macrophage activation will release inflammatory mediators which will activate the coagulation system and the complement system. In the coagulation system, an imbalance occurs between pro-inflammatory cytokines and anti-inflammatory cytokines (17). Widespread inflammatory conditions are associated with increased destruction due to changes in red blood cell membranes and interactions with white blood cells and cytokine activity. Inflammatory conditions are characterized by an increase in reactive oxygen species (ROS) production followed by a decrease in antioxidant defenses. ROS contains superoxide anion O_2-, hydroxyl radical OH- and hydrogen peroxide H_2O_2 (18). Giving LPS to rats experienced a systemic inflammatory condition. Extensive inflammatory conditions can cause hemolysis, causing hemoglobin to leak into the extracellular space as free hemoglobin which is toxic and reduces the ability to transport oxygen. Lipopolysaccharide (LPS) and other bacterial components can activate inflammatory cytokine cascades, which in turn may play a role in atherosclerotic heart disease either through direct action on the vessel wall or by inducing the liver to produce CRP (19). Acute Respiratory Distress Syndrome (ARDS) occurs primarily as a result of inflammatory injury to the alveoli resulting in diffuse alveolar damage. The lungs may be especially vulnerable to inflammatory injury because mediators are released into the bloodstream and the lungs receive all of the cardiac output. Proinflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL) 1, IL-6, and IL-8 are released into the interstitial and alveolar spaces by being active and the subsequent release of noxious proteases and reactive oxygen species (20). LPS is an endotoxin which induces the production of local factors, namely proinflammatory cytokines such as interleukin-1α (IL-1α), IL-1β, IL-6, tumor necrosis factor-α (TNF-α) and eicosanoids, namely prostaglandins (PGE2) (21).

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Table 1 shows that there is a difference in the one way anova test for treatment for IL-6 levels with sig. 0.010, while there is no average difference in CRP levels in each treatment group (sig. 0.215). There is no difference in CRP levels because the endotoxins in the blood present in the body are still not capable enough to affect lipid metabolism. The level of systemic toxicity and inflammation is likely to be influenced by the dose and interval of LPS administration, bone destruction, may also affect the inflammation that occurs, because there are differences in gene expression in regulating innate immunity (22). Green coffee is coffee beans from coffee beans that have not been roasted. Because the roasting process of coffee beans can reduce the amount of chlorogenic acid so that green coffee beans have a higher level of chlorogenic acid compared to regular coffee. Based on previous research, it was shown that CGA has a potential effect on suppressing the growth of cancer cells, especially through inhibiting the features of cancer metabolism (23).The benefits of chlorogenic acid for human health are as an antioxidant, antiviral, hepatoprotective, and play a role in antispasmodic activities. Chlorogenic acid is a compound that belongs to the phenolic component, which has water-soluble properties. Green coffee bean ethanol extract has high antioxidant activity. It was found that the ethanol extract from green coffee beans had the ability to scavenge the free radical DPPH (2,2-diphenyl-1-pikrylhidrakzyl) by 70.4% at 50 µM compared to ascorbic acid (86.1% inhibition at 50 µM) (24). Yellow turmeric is rich in antioxidants in that curcumin has the same antioxidant mechanism as anthocyanins because both of these compounds have phenolic groups which are important groups as antioxidants. The antioxidant mechanism has two functions. Its main function is in the provision of hydrogen atoms. The second function is a secondary function of antioxidants, namely slowing the rate of auto-oxidation with various mechanisms other than the mechanism of breaking the auto-oxidation chain by converting radicals to more stable forms (25). Antioxidants can help increase the response of the body's lymphocytes to respond to mitogens and increase the production of interleukin-2 which plays a role as an anti-inflammatory (26). ARDS conditions prevent oxygen from entering the lungs and can cause death. Oxidative stress increases so that cellular malfunction also increases and ends in organ failure. In ARDS there is the formation of free radicals and cytokine storms. Provision of anti-oxidants along with conventional supportive therapy is believed to have an important role. Antioxidants have been successful in showing good clinical outcomes in ARDS caused by influenza (27).

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CONCLUSIONS AND RECOMMENDATIONS

There was a difference in giving the combination of green coffee bean extract and turmeric to levels of IL-6, but there was no difference in giving the combination of green coffee bean and turmeric extract to CRP levels with the control group and the treatment group. Further research is needed regarding the role of other pro-inflammatory cytokines such as Il-1, in the administration of green coffee bean extract and yellow turmeric. There is a need for an examination of the antioxidant levels of each ingredient used and a histological examination to see an overview of the effects on organs.

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