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The Effect of Green Coffee Seed *(Coffea Canephora)* and Yellow Turmeric *(Curcuma Domestica Val.)* Extract on TNF-α Level in Acute Respiratory Distress Syndrome

Catur Retno Lestari[1*], Restu Ayu Eka Pustika Dewi[1], Siti Nurjanah[2], Lusiana Cici Sabarani[2], Fibra Resputri[2]

1. Department of Biomedical Science, Faculty of Health, Ivet University, Central Java , Indonesia
2. Student Program of Biomedical Science, Faculty of Health, Ivet University, Central Java, Indonesia

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**Corresponding author:*
Catur Retno Lestari, MSc;
Department of Biomedical Science, Faculty of Health, Ivet University, Central Java , Indonesia.
Tel: +62-858-39161260
Email: caturretno.lestari@gmail.com
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ABSTRACT

Background: Green coffee seed (*Coffea canephora*) are rich in polyphenolic compounds and yellow turmeric (*Curcuma domestica val.*) is rich in curcuminoids and essential oils. This study determined the combination effect of green coffee seed and yellow turmeric extracts on TNF-α in acute respiratory distress syndrome (ARDS) in rat model.

Methods: Thirty rats were randomly grouped into five equal groups of 5 rats. Control group received normal diet and distilled water, positive control was administered with 0.8 mg/kg of LPS to induce ARDS in absence of any treatment, Treatment group 1 received 200 mg/kg/day of the combination of green coffe seed and yellow tumeric extract intraperitoneally (IP) for 14 days, Treatment group 2 was given 400 mg/kg/day of the combination similarly, and treatment group 3 was injected with 600 mg/kg/day of the combination identically. TNF-α level was compared between groups.

Results: The combination of green coffee seed and yellow turmeric extract (400 mg/kg/day) given for 14 days could significantly decrease TNF-*α* level in rats after induction of ARDS ($p<0.05$).

Conclusion: A combination of green coffee seed and yellow turmeric extract could decrease TNF-α. Therefore it can be considered as a therapeutic choice in ARDS.

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Introduction

Severe Acute Respiratory Coronavirus 2 virus (SARSCoV-2) is a new coronavirus that has appeared since late December 2019 and was first detected in Wuhan, China. This virus caused COVID-19 disease in humans; while has also been found in camels, bats, civet cats, rats, dogs and cats. It is suspected that the first cause of COVID-19 was a virus in the body of bats which was transmitted to humans through lying animals. After infecting humans, this virus is then transmitted from human to human (1, 2).

The clinical manifestations of COVID-19 patients vary widely, ranging from asymptomatic, mild symptoms, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis and even septic shock (3-5). Some of the symptoms that can be found in COVID-19 patients are fever, fatigue, cough, anorexia, sore throat, nasal congestion, and headache. The most common complication in COVID-19 patients is ARDS (6, 7). In addition, kidney disorders, septic shock, liver and heart dysfunction have been reported (8, 9). Injury to the myocardium is a major complication and can occur in patients without preexisting cardiovascular disorders (10, 11).

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 therapeutic options in the form of host-modifier/immune, while an *in vitro* cell experiment showed that in the early stages of SARS-CoV infection there is a delayed release of cytokines and chemokines by respiratory epithelial cells, dendritic cells and macrophages. Then, cells secrete antiviral factor interferons (IFNs) and pro-inflammatory cytokines (interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF) and chemokines (C-C chemokine ligand motif (CCL)-2, CCL- 3, and CCL-5) in large quantities (12, 13).

The development of anti-inflammatory drugs derived from plants is based on the side effects of anti-inflammatory drugs. The medicinal ingredients used are fruit, leaves, bark, rhizomes and flowers (14). One of the natural ingredients that have active compounds that act as anti-inflammatory drugs are green coffee seed (*Coffea canephora*) and yellow turmeric (*Curcuma domestica Val.*) extracts (15). The pathogenesis of COVID-19 occurs through an inflammatory process, while the disease progression of COVID-19 is caused by cytokine storm syndrome and changes in immune cell expression. Cytokine storm is a phenomenon of massive inflammatory reactions mediated by the rapid production of large amounts of cytokines in response to infection. One of the natural ingredients with minimal side effects that has a fairly high immune response is green coffee seed (16).

Green coffee seed 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 (17). In addition, caffeine also has an effect as an antioxidant and immunomodulator (18). Antioxidant compounds in green coffee seed are cafestol, kahweol, acetyl methyl carbinol, quinic acid, 3,5 dicaffeolguinic acid, dimethylsulfide, quinic acid, and 2-ethylphenol. These compounds have pharmacological effects, including protection from various diseases that occur due to the invasion of bacteria, viruses, and antigens (19).

Chlorogenic acid is a phenolic compound that is soluble in water. 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 can affect the body's defense mechanism by increasing phagocytic activity, by entering into infectious agents and by damaging the wall of infectious agents. Chlorogenic acid is known to act as an antioxidant by capturing hydroxyl free radicals (HO), so it does not oxidize fat, protein 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 influence signal transduction pathways that play a role in cell proliferation, antioxidant activity, modulate enzyme activity, and modulate cytokine production (20).

Yellow Turmeric (*Curcuma domestica Val.*) has a long history in traditional medicine (21). Curcuminoids (3.0-5.0%) and essential oils (2.5-6.0%) are the main compounds found in turmeric rhizome. Other compounds in turmeric are calcium, phosphorus, iron, starch, fat, protein, camphor, gum, 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, lipooxigenase, COX2, leukotrienes, thromboxane prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, TNF-α, and IL-12. Curcumin decreases the catalytic phospholipase A2 and phospholipase C g1, thereby reducing the release of arachadonic acid from cellular phospholipids. Curcumin has an inhibitory effect on phospholipase D activity and can inhibit cyclooxygenase-2 (COX-2) expression (22, 23).

Materials and Methods

The experimental animal research protocol with the research design "Pre Test and Post Test with Control Group Design"has been approved by the Research Ethics Committee, Faculty of Medicine,

Sultan Agung Islamic University, Central Java, Indonesia (Certificate Ethical Clearance no: 332/VIII/2022/Komisi Bioetik, 31 August 2022). The independent variables were green coffee seed and yellow turmeric extracts, while the dependent variable was TNF-α. This research was conducted at the IBL (Integrated Biomedical Laboratory) Building Center Laboratory, Faculty of Medicine, Sultan Agung Islamic University Semarang, Central Java Province, Indonesia. The population in this study were 30 male Wistar rats weighing 180-200 grams which were conditioned to experience ARDS utilizing lipopolysaccharides (LPS). A blood sample was provided from animals to assess the TNF-α level in serum after administration of green coffee seed and yellow turmeric extracts. The rats were randomly grouped into five equal groups of 5 rats in each group (Table 1), including the control group received normal diet and distilled water, positive control was administered with 0.8 mg/kg of LPS to induce ARDS in absence of any treatment, Treatment group 1 received 200 mg/kg/day of the combination of green coffe seed and yellow tumeric extract intraperitoneally (IP) for 14 days, Treatment group 2 was given 400 mg/kg/day of the combination similarly, Treatment group 3 was injected with 600 mg/kg/day of the combination identically. The tools that have been prepared were first sterilized by cleaning, wrapped in heat-resistant paper and plastic and then put into the autoclave for 20 minutes (1.5 atm, 121 °C). The animals received 15-20 grams standard animal food per day and drinking was *ad libitum*. Mice were placed in cages individually according to the group with an ambient temperature of 28-30 °C.

The ELISA test was carried out by first preparing the reagents to be used in each kit (Sigma-Aldrich, USA). In the ELISA test, a series of working solutions with a concentration of 1000, 500, 250, 125, 62.5, and 31.25 µg/mL were prepared. The solution is prepared by performing serial dilutions of the standard solution. The standard solution (centrifuged: 10,000 ×g) to which 1 mL of referenced standard sample diluent has been added was put into a vial containing 500 µL of referenced standard sample diluent, then homogenized (concentration of 2000 µg/mL) and 500 µL was taken to be put into the next vial in a concentration of 1000 µg/mL.

This step was continued for all concentrations. Thereafter, 750 mL of wash buffer was prepared by dissolving 30 mL of concentrated wash buffer with 720 mL of deionized water. Biotinylated detection Ab working solution was made by dissolving 100× Concentrated Biotinylated Detection Ab which was centrifuged with biotinylated detection Ab diluent according to the total requirement with 100 µL of each well. Concentrated horseradish peroxidase (HRP) conjugate working solution was prepared in the same way as biotinylated detection Ab working solution.

The microplate that was available in the kit was coated with specific antibodies for rat TNF-α. The standard solution and samples were added to the microplate according to the mapping including 100 µL for each, then covered with a sealer and incubated for 90 minutes at 37 °C. The solution was then discarded and 100 µL of biotinylated detection Ab working solution was added to each well. The microplate was covered again and incubated for one hour at 37 °C. The microplate was aspirated by putting the plate on a tissue until the plate was dried. Wash buffer was added as much as 350 µL and then allowed to stand for 1-2 minutes and continued with further aspiration. This step was repeated three times. A total of 100 µL of HRP conjugate working solution was then added and incubated for 30 minutes at 37 °C. Later, the microplate was aspirated and washed with wash buffer five times. Substrate reagent was added as much as 90 µL without being exposed to light and was incubated for 15 minutes at 37 °C. Stop solution was finally added to the microplate as much as 50 µL and the optical density (OD) was measured at 450 nm using a microplate reader.

Absorbance data for correction of standard concentration of each cytokine was graphed designing a standard curve. Standard curves or calibration curves were used to determine concentrations based on a method that provided a type of regression,

Table 1: Groups before and after treatment with the combination of green coffee seed and yellow turmeric extract.

Group	Day 7	Days 8-21
Control	Normal diet and distilled water	Normal diet and distilled water
LPS	Induced LPS	No treatment
Treatment 1	Induced LPS	200 mg/kg/day of combination extract
Treatment 2	Induced LPS	400 mg/kg/day of combination extract
Treatment 3	Induced LPS	600 mg/kg/day of combination extract

Control: Normal diet and distilled water, Positive control: 0.8 mg/kg of LPS (lipopolysaccharides), Treatment 1: 200 mg/kg of the combination of green coffee seed and yellow turmeric extracts, Treatment 2: 400 mg/kg of the combination of green coffee seed and yellow turmeric extracts, Treatment 3: 600 mg/kg of the combination of green coffee seed and yellow turmeric extracts.

Table 2: Comparison of the TNF-α level in groups before and after treatment with the combination of green coffee seed and yellow turmeric extracts.

Group	Duration		TNF-α	P value[a]
	Day 7 (mean±SD)	Day 21 (mean±SD)		
Control	84.82±39.63	83.83±16.50	-52.54±54.52	0.962
LPS	117.01±14.63	84.13±21.84	-3.27±69.07	0.65
Treatment 1	91.39±12.82	74.90±15.55	-0.76±33.74	0.57
Treatment 2	136.76±22.16	63.19±36.05	21.94±125.19	0.017*
Treatment 3	84.32±56.81	56.81±33.30	-23.12±78.14	0.206
Treatment[b]	0.020*	0.381	0.020*	

*A significant difference, [a](p<0,05), [b](p<0,05), TNF-α: Tumor Necrosis Factor-alpha, Control: Normal diet and distilled water, Positive control: 0.8 mg/kg of lipopolysaccharides (LPS), Treatment 1: 200 mg/kg/day of the combination of green coffee seed and yellow turmeric extract for 14 days, Treatment 2: 400 mg/kg/day of the combination of green coffee seed and yellow turmeric extract for 14 days, Treatment 3: 600 mg/kg/day of the combination of green coffee seed and yellow turmeric extract for 14 days.

so that it could be measured in proportion to a known amount of a standard. A known standard group would estimate the needed concentration by interpolating from the standard curve. The corrected absorbance value for each cytokine was then entered into the equation contained in each curve to obtain the cytokine concentration value. Statistical tests were carried out using SPSS software (Verssion 20, Chicago, IL, USA). To compare groups before and after administration of the combination treatment of green coffee seed and yellow turmeric extracts, a normality test utilizing Shapiro Wilk, paired T-test and one way-ANOVA were carried out. A p value<0.05 was considered statistically significant.

Results

Table 2 shows the differences between the groups receiving the combinations of green coffee seed and yellow turmeric extracts in different doses. Before the intervention, no significant difference in TNF-*α level* was noted between groups. When received the combinations of green coffee seed and yellow turmeric extracts, the differences between groups were statistically significant (p<0.05). A combination of green coffee seed and yellow turmeric extracts can affect TNF-*α level* induced in ARDS (p=0.020). The dose of 400 mg/kg of the combination given for 14 days had significant effect on TNF-*α level* (p=0.017).

Discussion

ARDS is a form of lung tissue injury and an inflammatory response to various causative factors, and is characterized by inflammation, increased vascular permeability, and decreased lung tissue aeration (24). In ARDS, there is an increase in capillary permeability 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 the release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-*α*. These cytokines attract neutrophils and activate them, resulting in the release of reactive oxygen species and proteases which cause oxidative damage to lung tissue. Various pathologies can contribute to the development of ARDS. This fluid accumulation phase is followed by a proliferative phase characterized by easing of pulmonary edema, proliferation of type II alveolar cells, fibroblasts, and myifobroblasts, as well as matrix deposition. Furthermore, ARDS can progress to the fibroproliferative phase or resolution occurs and the lungs return to normal (12).

One of the main features of ARDS in COVID-19 is the presence of a cytokine storm. Cytokine storm is an abnormal systemic inflammatory response due to excessive production of pro-inflammatory cytokines and chemokines (25, 26). 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. An *in vitro* cell experiment showed that in the early stages of SARS-CoV infection, there is a delayed release of cytokines and chemokines by respiratory epithelial cells, dendritic cells and macrophages. Then, cells secrete antiviral factor interferons (IFNs) and pro-inflammatory cytokines (IL)-1*β, IL-6, and tumor necrosis factor (TNF)* and chemokines [CC chemokine ligand motif (CCL-2, CCL-3, and CCL-5)] in large quantities (12).

An acute inflammatory response occurs to heal damaged tissues when the body is injured, irritated, or infected. However, when that acute response is ineffective, the body resumes a chronic inflammatory response. Oxidative stress is a major contributor to the inflammatory response and functional decline that are characteristic of aging and the diseases

of aging. Immune cells use free radicals such as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) to eliminate viruses and bacteria that cause disease. Overproduction of free radicals results in a state of oxidative stress, which destroys the polyunsaturated fats in lipoproteins and cell membranes and alters proteins such as DNA and RNA. This damage leads to impaired cell function and an inflammatory response that contributes to cell damage, aging, and disease (27).

Chronic inflammation and oxidative stress result in increased serum levels of the NF-KB transcription factor. NF-KB controls DNA transcription and can be activated by factors that trigger an inflammatory response, such as a viral infection. The NF-KB signaling pathway prompts macrophages and neutrophils to respond and is part of the immune response. NF-KB increases the expression of many cytokines and enzymes active in this chronic inflammatory disease. Cytokines are hormone-like proteins that act as signaling molecules to regulate immune responses and responses to infection, inflammation, and trauma. Some cytokines are anti-inflammatory and heal after an injury, infection, or foreign body has been destroyed. Other cytokines are proinflammatory, such as TNF-*α*. The release of proinflammatory cytokines into the bloodstream signals the liver to produce proteins such as acute phase reactants and cell adhesion molecules that respond to trauma or infection and serve as additional biomarkers of inflammation. Cyclooxygenase-2 (COX-2), Nitric Oxide Synthase (iNOS), and lipoxygenase (LOX) are important enzymes that mediate the inflammatory process. COX and LOX enzyme-dependent pathways synthesize lipid mediators involved in inflammation (28).

Other studies have described the mechanism by which persistent oxidative stress occurs. Oxidative stress is defined as a disturbance of the balance between ROS production and antioxidant defense as a protective mechanism. This imbalance causes damage to biomolecules and cells, as well as potential impacts on organisms. ROS play a central role both upstream and downstream of the NF-κB and TNF-α pathways, which are located at the center of the inflammatory response. Curcumin is thought to be able to reduce oxidative stress, inflammation of chronic diseases through the NRF2-keap1 pathway. Curcumin can suppress proinflammatory pathways associated with most chronic diseases and inhibit TNF production and TNF-mediated cell signaling in various cell types. Curcumin can also be a TNF inhibitor from *in vitro* and *in vivo* studies by directly binding to TNF (29, 30).

The role of chlorogenic acid as the main phenolic component of the polyphenolic extract of robusta coffee seed is effective in reducing the degree of inflammation which is characterized by a decrease in TNF-α expression (31). 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 (19). Chlorogenic acid is known to act as an antioxidant by capturing hydroxyl free radicals (HO), so it does not oxidize fat, protein 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 influence signal transduction pathways that play a role in cell proliferation, antioxidant activity, modulate enzyme activity, and modulate cytokine production (20). Various researchers studied the immunomodulatory effects of coffee see and have been proven it to increase the human immune response. Chlorogenic acid from coffee seed which functions as an antioxidant can increase phagocytic activity and has an opsonin function to help phagocytic cells devour infectious agents (32).

Conclusion

A combination of green coffee seed (*C. canephora*) and yellow turmeric (*C. domestica Val.*) extract (400 mg/kg/day) given for 14 days could significantly lower the TNF-α level in ARDS. This combination can be considered a therapeutic choice in ARDS.

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Conflict of Interest

None declared.

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