

CURCUMIN AS ADJUVANT THERAPY IN MILD-MODERATE COVID 19

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Abstract

Background: Coronavirus (Covid-19) has spread rapidly to more than 200 countries, including Indonesia. Adjuvant therapy of Vitamin C, D, Zinc has become beneficial for Covid-19 treatment to improve the immune system, while Curcumin is still not standard therapy. Curcumin can stimulate specific immune cells and can reduce oxidative stress. There is currently no scientific evidence showing that the addition of Curcumin can protect COVID-19, especially as an anti-inflammation and anticoagulant effect. **Methods:** This cross-sectional study was conducted at Ukrida Hospital from January -June 2021. The inclusion criteria are Mild-Moderate Covid-19 use on Curcumin and Supplement therapy (Vitamin C, Vitamin D, and zinc). Data analyses with SPSS v.20 use Anova test and Kruskal Wallis test. This study had been approved by The Institutional Board of the Faculty of Medicine Universitas Krida Wacana, Indonesia (No. 1053/SLKE-IM/UKKW/FKIK/KE/II/2021). **Research Objectives:** To see the effect of Curcumin as an additional therapy from Covid-19 by clinical and laboratory inflammation indicators of the usefulness of Curcumin are such as ratio neutrophil/lymphocyte, ratio platelet/lymphocyte, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), and D Dimer. **Results:** There were 246 cases, with 62.6% male and 56.5% female taking Curcumin. Curcumin has a good effect in reducing inflammation and coagulation in mild-moderate Covid-19. Patient who got Curcumin or without Curcumin as additional supplement therapy shows patient that got Curcumin has decreased inflammatory markers N/L ratio ($p = 0.041$), P/L ratio ($p = 0.040$), ESR ($p = 0.013$), and CRP ($p = 0.045$). Curcumin also has an anticoagulant effect that shows a decrease of

D-Dimer ($p= 0.020$). **Conclusion:** Curcumin is beneficial in mild-moderate Covid-19 as an anti-inflammatory and anticoagulant.

Keywords: Covid-19, Adjuvant therapy, Curcumin, Anti-Inflammatory, Anticoagulant

Introduction

The immune system is a complex network consisting of cells, proteins, organs, and other substances whose job is to protect the body from various diseases caused by viruses, bacteria, fungi, and parasites. Intake supplements such as vitamin C, D, and zinc can increase immunity. In general, the benefits of vitamin C are increasing immunity by increasing natural killer cells' performance to find and kill infected cells or other cells that harm the body.¹ It also supports the work of neutrophils, the first cells of the immune system that respond by attacking bacteria or viruses, help improve the performance of lymphocytes in tracking viruses and bacteria, which can threaten the health of the body.² Among the many essential micronutrients that the body needs to boost immunity, zinc and vitamin C are arguably the "best pair" playing a central role.³ The reason is that zinc can help absorb vitamin C properly if consumed together. Zinc is a mineral that has an essential role in the body tissues' growth, development, and health. According to the European Journal of Immunology, zinc intake in the body helps activate T cells (T lymphocytes). These cells work in two ways: control the immune response and attack cells carrying disease-causing germs. That is why, if the body lacks zinc intake, the immune system will also be disturbed. Various studies have also revealed that zinc supplements can protect the body from respiratory infections. Vitamin D is currently also being considered for the treatment of COVID 19. Vitamin D is synthesized in the skin as vitamin D₃ (cholecalciferol) or obtained from food sources or supplements such as vitamin D₃ or vitamin D₂ (ergocalciferol). Some evidence found that vitamin D₃ seems to reduce mortality in COVID-19 patients with some comorbidities, such as in the elderly. Currently, the use of Curcumin for the treatment of COVID-19 is starting to develop.^{4,5}

Curcumin, a naturally occurring polyphenolic compound, could be a potential treatment option for patients with coronavirus disease. In this study, we review some of the potential effects of Curcumin, such as inhibiting viral entry into cells, inhibiting viral encapsulation and viral proteases, and modulating various cellular signaling pathways. This review provides the basis for further research and development of clinical applications of Curcumin for the treatment of the emerging SARS-CoV-2.⁶

Turmeric or Curcumin supplements are considered because turmeric is a local product in Indonesia. The benefits of Curcumin on the healing of Covid-19 still need to be proven through further research.^{6,7}

Turmeric (Curcumin longa L) contains metabolites of natural ingredients in the form of Curcumin. Curcumin is reported to have various therapeutic potentials such as antibiotics, antivirals, antioxidants, anticancer, and for the treatment of Alzheimer's disease. Curcumin or its derivatives, namely Curcuminoids, are also found in ginger, ginger,

and similar plants. In addition to Curcuminoid compounds, dozens of other chemical compounds are contained in these plants. People in general use these plants in their daily life and are safe in their use.⁸

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On the other hand, the results of the Bioinformatics research released in March 2020 using the bioinformatics modeling method (molecular docking), Curcumin can bind to the SARS-CoV 2 protein receptor, namely through binding to the protease domain (6Lu7) and spike glycoprotein. This bond has the potential to inhibit the activity of Covid-19. In addition, Curcumin is known to inhibit the release of body compounds that cause inflammation or pro-inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor- α .¹¹

Various studies show that Curcumin has various properties ranging from antibacterial, antioxidant, anti-inflammatory, anticancer, lowering blood sugar, and immunomodulator.^{10,11}

Hypothesis

Curcumin is safe and effective as mild to moderate COVID-19 anti-inflammatory and anticoagulation medication

General-purpose

To see the effectiveness of anti-inflammatory and anticoagulation effects of Curcumin in COVID-19 virus infection

Specific purpose

To see changes in Ratio N/L, P/L, ESR, CRP, and D-Dimer as an anti-inflammatory effect of Curcumin on Covid-19 therapy

Materials and Methods

Design This study used a cohort study using consecutive sampling from the medical records of Covid-19 patients treated at Ukrida Hospital in January June 2021. The population of this study was all Covid-19 patients treated at UKRIDA Hospital during a specific period with criteria inclusion of mild-moderate Covid-19, and sampling was carried out at least two times, when in the ER and when leaving the hospital. Exclusion criteria were patients with incomplete medical record data. Data analyses with SPSS v.20 use Anova test and Kruskal Wallis test.

Result

There were 246 cases, with 62.6% male and 56.5% female subjects. Based on symptoms of Covid-19, 47.2% of subjects were mild, and 52,8% had moderate symptoms (Table 1). Curcumin had a good effect in reducing inflammation and coagulation in mild-moderate Covid-19.

Table 1. Covid-19 patient in UKRIDA Hospital in January – June 2021 base on symptoms (Mild or Moderate Covid-19)

Covid-19 symptoms	n	Percentage (%)
Mild	116	47.2
Moderate	130	52.8
Total	246	100

Our result showed that adult patient has a similar risk of Covid-19 despite age. The Majority of Covid-19 patients in UKRIDA hospital were in the 51-60 years old group. Male subjects were more prevalent than women in mild-moderate Covid-19 patients (62.4% vs. 37.4%). The percentage of Covid-19 patients who got additional treatment Curcumin was higher than the non-Curcumin group (56.5% vs. 43.5%). (Table 2)

Table 2 Subject Characteristic Covid-19 patient in UKRIDA Hospital in January – June 2021

Mild-Moderate Covid-19	n	Percentage (%)
Age		
≤ 30 y.o	51	20.7
31-40 y.o	47	19.1
41-50 y.o	42	17.0
51-60 y.o	57	23.2
61-70 y.o	31	12.6
71-80 y.o	18	7.3
Gender		
Male	154	62.6
Female	92	37.4

Additional Treatment		
Curcumin	139	56.5
Non-Curcumin	107	43.5
Total	246	100

We identified markers to evaluate the anti-inflammation of Curcumin treatment, such as Δ ratio neutrophil/lymphocyte (Δ Ratio N/L), Δ ratio Platelet/ lymphocyte (Δ Ratio P/L), Δ Erythrocyte Sediment Rate (Δ ESR), and Δ C-Reactive Protein (Δ CRP). We also evaluate the effect of Curcumin as an anticoagulant based on Δ D Dimer. We compare the anti-inflammation and anticoagulant effects after adding Curcumin in supplement therapy in Covid-19 (Table 3).

Table 3. Effect use/not use Curcumin in Covid 19 patient base on anti-inflammation and anti coagulant by laboratory test

Inflammation Marker	Curcumin n=139	Non Curcumin n=107	P
Δ Ratio N/L	-0.94 (-6.85-4.66)	-0.52(-7.44-7.02)	p=0.041
Δ Ratio P/L	-0.99 (-5.61-4.76)	-0.50(-6.14-6.12)	p=0.049
Δ ESR	-13.0(-99.3-44.0)	-4.4(-78.9-60.9)	p=0.013
Δ CRP	-18.0 (-136.0-7.1)	-14.2(-152.9-84.3)	p=0.045
Δ D-Dimer	-3.0 (-32.3-43.11)	-0.3(-4.2-32.3)	p=0.020

* Median (min-max), Mann Whitney test

We also found that patients who received additional therapy with Curcumin had a shorter length of stay than patients who received supplements of vitamin C, vitamin D, zinc alone (Table 4).

Table 4. The relationship between therapy Covid-19 use/not use Curcumin and length hospital of stay

Therapy	Curcumin + Vitamin C, Vitamin D and Zinc	Vitamin C, Vitamin D and Zinc	p
Length of Hospitalized (day)	7.2 \pm 1.1	12.2 \pm 1.5	0.048

*Mean \pm SD, Anova test

Discussion

The ongoing Coronavirus Disease 2019 (COVID-19) pandemic, caused by the novel coronavirus SARS-CoV-2, has had devastating medical, social, and economic impacts worldwide. Patients with COVID-19 can present with acute symptoms of fever, dyspnea, and pneumonia. In the study of Covid-19 patients with mild to moderate criteria at the Covid-19 Hospital, the age distribution in young adults was almost evenly distributed even though most ages were in the range 51-60 years old. The findings are similar to WHO research, where the age susceptible to mild to moderate COVID-19 is young adults aged 51-60 years old.¹²

In our study, the male is the more common gender in UKRIDA hospitals. Men are more at risk for worse outcomes and death, independent of age, with COVID-19. While males and females have the exact prevalence of COVID-19, male patients have higher mortality. The previous study shows compared to females, males with COVID-19 had a higher rate of in-hospital mortality (13.8% vs. 10.2%, respectively, $p < 0.001$), the male also had a higher rate of respiratory intubation (21.4% vs. 14.6%, $p < 0.001$); and a longer length of hospital stay (9.5 ± 12.5 days vs. 7.8 ± 9.8 days, $p < 0.001$). It is related to the ACE-2 receptor in males greater than females.¹³

In this study, all mild COVID-19 patients received supplement therapy (Vitamin C, Vitamin D, and Zinc). However, some patients received additional Curcumin at a dose of 3 x 1 tablet and supplement therapy which is the standard for mild to moderate COVID-19 therapy.¹⁴

Curcumin, the active ingredient of the *Curcuma longa* plant, has received significant attention over the past two decades as an antioxidant, anti-inflammatory, and anticancer agent. This review summarizes Curcumin's medicinal chemistry and pharmacology and its derivatives concerning anticancer activity, their primary mechanisms of action, and cellular targets based on the literature data from the experimental and clinical evaluation of Curcumin in viral inflammation disease. In addition, the recent advances in the drug delivery systems for Curcumin delivery to cancer cells have been highlighted. Curcumin, the bioactive ingredient of Curcumin longa (turmeric) has various therapeutic effects that are chosen to be used as adjuvant therapy in the treatment of patients with COVID-19.¹⁵

Curcumin has potential antiviral effects, including a protein-binding affinity for the SARS-CoV-2 protein, antiviral, antifungal, anti-thrombotic, antiproliferative, hypoglycemic, anticarcinogenic, neuroprotective, cardioprotective properties and modulates several signaling molecules, including pro-inflammatory cytokines, apoptotic proteins. The anti-inflammatory properties of Curcumin are through inhibition of COX-1 and COX-2 to prevent the production of the eicosanoids prostaglandin E2 and 5-hydroxyeicosatetraenoic acid.¹⁶

Curcumin inhibits thrombin and reduces blood viscosity; therefore can alleviate COVID coagulopathy and thus increase survival rates. Preclinical studies have shown that Curcumin effectively inhibits viral infections, reduces the severity of lung injury by offsetting a cytokine storm, and inhibits subsequent fibrosis. Furthermore, Curcuminoids have been approved by the US Food and Drug Administration (FDA) and have good tolerability and safety profile, and few adverse side effects have been reported.¹⁷ Curcumin exhibits very poor bioavailability, with very low or undetectable concentrations in blood and extraintestinal tissues, possibly due to poor absorption, rapid metabolism, chemical instability, and rapid systemic elimination. We conducted a pilot study to determine the effect of Curcumin in patients with COVID-19 and observed a favorable trend. Therefore, we conducted this study to evaluate the efficacy of oral Curcumin as symptomatic adjuvant therapy for the treatment of COVID-19. Curcumin, a polyphenol responsible for the yellow color of the curry spice turmeric, possesses anti-inflammatory, antiproliferative, and antiangiogenic activities. However, anticoagulant activities of Curcumin have not been

studied. We suggest doing another research to see pathomechanism Curcumin as anticoagulant.¹⁸

Conclusion

In combination with other supplement agents (Vitamin C, Vitamin D, and zinc) in COVID-19, Curcumin reduces inflammatory markers. Curcumin also has an anticoagulant effect that shows the decrease of D-Dimer significantly.

Competing Interests

There is no competing interest in this study

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