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The Effects of *Zingiber Officinale* and Propolis Supplementation on Hospitalized Covid-19 Patients' Oxygen Saturation and Hematology Profiles

Ratih Dewi Yudhani[1,5*], Yuliana Heri Suselo[2,5], Dwi Rahayu[3,5], Jatu Aphridasari[4] and Hartono[2,6]

1. Department of Pharmacology, Faculty of Medicine, Universitas Sebelas Maret, Jl. Ir. Sutami No.36 A, Jebres, Surakarta, Central Java, Indonesia, 57126
2. Department of Physiology, Faculty of Medicine, Universitas Sebelas Maret, Jl. Ir. Sutami No.36 A, Jebres, Surakarta, Central Java, Indonesia, 57126
3. Department of Nutrition, Faculty of Medicine, Universitas Sebelas Maret, Jl. Ir. Sutami No.36 A, Jebres, Surakarta, Central Java, Indonesia, 57126
4. Department of Pulmonology, Dr. Moewardi Hospital / Faculty of Medicine, Universitas Sebelas Maret, Jl. Kolonel Sutarto No.132, Jebres, Surakarta, Central Java, Indonesia, 57126
5. Biomedical Laboratory, Faculty of Medicine, Universitas Sebelas Maret, Jl. Ir. Sutami No.36 A, Jebres, Surakarta, Central Java, Indonesia, 57126
6. UNS Hospital, Jl. Ahmad Yani No.200, Kartasura, Sukoharjo, Central Java, Indonesia, 57161

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*Corresponding author
Ratih Dewi Yudhani

Email:
ratihyudhani@staff.uns.ac.id

ABSTRACT

Antiviral, anti-inflammatory, and supportive therapy are required in the Covid-19 management, whilst there is no available specific antiviral for Covid-19 patients**.** *Zingiber officinale* and Propolis were reported to suppress the pro-inflammatory cytokines and their safety profiles were considered in several toxicity studies. However, their efficacy in hospitalized Covid-19 patients has not been clarified yet. This study explored the activity of *Z. officinale* and Propolis in modulating the clinical signs and hematology parameters in hospitalized Covid-19 patients. This study is a pre and post-test-controlled group design. A total of 22 subjects were divided into a control group (standard therapy), and a treatment group (standard therapy and supplemented with the combination of *Z. officinale* 500 mg/day and Propolis 1000 mg/day). We analyzed the differences in demographic characteristics, clinical signs, and hematology parameters in pre- and post-treatment in both groups. The increased oxygen saturation in control and treatment groups were 0.45 ± 0.45 and 3.45 ± 1.16, respectively (p = 0.01). Moreover, the high-fluorescent lymphocyte count (HFLC) and mean platelet volume (MPV) in the treatment group tend to be lower compared to the control. The supplementation of *Z. officinale* and Propolis has beneficial effects in alleviating clinical signs of Covid-19 disease, especially in the enhancement of oxygen saturation, and tends to restore the hematological parameters.

Key words: Covid-19 Hospitalized patients, Oxygen saturation, Propolis, *Zingiber officinale*, Supplementation

INTRODUCTION

A severe acute respiratory syndrome known as Coronavirus Disease 2019 (Covid-19) was first discovered in Wuhan, Hubei, China in December 2019 and was later identified as being caused by a new type of coronavirus (SARS-CoV-2) (Ganesh *et al*., 2020). Covid-19 is spreading rapidly, reaching almost all countries and causing tremendous mortality and morbidity worldwide, and on March 11, 2020, the World Health Organization declared this disease as a global pandemic (Muniyappa & Gubbi, 2020). On July 25, 2021, the total confirmed cases reached 194 million with more than 4 million deaths (World Health Organization, 2021). The data analysis in Indonesia, until August 8, 2021, showed that there were more than 3.6 million confirmed cases with case fatality rate (CFR) 2.92%, higher than the CFR worldwide (2,12%) (Satuan Tugas Penangan Covid-19, 2021).

The SARS-CoV-2 infection affects circulating immune components and triggers the apoptosis of lymphocytes cells such as helper and suppressor T-cells that determine the disease severity. In severe cases, there was also a reduction in the degree of memory Th cells and regulatory T-cells (Muniyappa & Gubbi, 2020; Qin *et al*., 2020). The decrease in the T-cells functions suppresses the innate immune system as well as triggers the excessive secretion of inflammatory cytokines such as interleukin 2 (IL-2), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and various chemokines. Furthermore, the hyper inflammation condition known as cytokine release syndrome caused by cytokines storm increases the risk for the development of acute respiratory distress syndrome and multiple organ failure (Hojyo *et al*., 2020; Muniyappa & Gubbi, 2020).

Anti-viral and supportive therapy are important components for the management of Covid-19 patients, and anti-inflammatory agents are also needed to prevent further disease progression caused by cytokines storm (Zhang *et al*., 2020). This is because there is no available specific antiviral treatment for Covid-19 patients (Nile *et al*., 2020). Conversely, the development of new drugs will be impractical to be pursued considering the fast spread of the pandemic and it is already a global emergency (Hu *et al*., 2020). Currently, herbal medicines are utilized as an alternative for the treatment and maintenance of health care. The affordable reason and its availability promote the popularity of herbal medicine, especially in developing countries (Mesri *et al*., 2021). The use of herbs with potent anti-inflammatory effects potential to minimize the negative symptoms related to excessive cytokines release in Covid-19 patients.

Ginger (*Zingiber officinale*) is rich in phenolic compounds such as gingerol and shogaol, which have been shown *in vitro* to suppress pro-inflammatory cytokines (interleukin 1, interleukin 8, and TNFα). The *in vivo* evidence also supported that ginger possesses anti-inflammatory activity in mice through the inhibition of nuclear factor kappa beta (NFκβ) and TNFα expression (Grzanna *et al*., 2005; Habib *et al*., 2008). Furthermore, scientific evidence related to the activity for suppressing inflammation in diabetic patients has also been reported. The supplementation of dry powder ginger capsule suppresses the inflammation in type 2 DM (T2DM) patients through the reduction of TNFα, IL6, and hs-CRP (Mahluji *et al*., 2013). The extract formula of *Z. officinale* has been proven safe based on acute, subacute, and chronic toxicity tests in rats. There were no signs of toxicity or death in tested animals with maximum dose tolerance in acute and subacute toxicity tests for 5000 mg/kg and 2000 mg/kg of body weight respectively. Moreover, chronic toxicity tests indicated no observed adverse effect level (NOAEL) at the maximum dose of 1000 mg/kg of body weight (Plengsuriyakarn & Na-Bangchang, 2020).

Propolis contains a large number of flavonoids and quercetin which, according to *in vitro* studies, suppress mRNA expression and the production of nitric oxide (NO), IL1β and IL6 (K. Wang *et al*., 2013). This is also supported by in vivo evidence in C57BL/6 mice which showed that the 14 days administration of Propolis 200 mg/kg BW inhibited several pro-inflammatory cytokines including IL1β, IL6, and IFN-γ (Missima *et al*., 2010). A randomized double-blind clinical trial in T2DM patients showed that Propolis capsules at doses 2 x 500 mg/kg BW decreased pro-inflammatory cytokines (IL1, IL6, and TNFα) and suppressed hs-CRP in the treatment group compared to placebo (Zakerkish *et al*., 2019). Interestingly, acute toxicity test based on OECD guidelines showed that Propolis at doses 500-5000 mg/kg BW was safe, and the sub-chronic toxicity test during 60 days administration of 25-100 mg/kg BW Propolis showed no signs of toxicity (Khacha-Ananda *et al*., 2018).

The collecting evidence above showed that the *Zingiber officinale* and Propolis activities in suppressing pro-inflammatory cytokines through *in vitro*, *in vivo,* and RCT studies are underlying its use as a dietary supplement in humans. The safety profiles of the two compounds have also been supported by several toxicity studies. Regarding the anti-inflammatory effects and safety profile, the supplementation of the two compounds potential to suppres the clinical symptoms of Covid-19 patients. Therefore, this study aims to explore the activity of *Zingiber officinale* and Propolis in modulating the clinical signs and hematology parameters in Covid-19 patients. It was conducted as an effort to assess the efficacy of both compound combinations as supplementation in hospitalized patients.

MATERIAL AND METHODS

This is an experimental study with a pre-post-only controlled group design conducted at UNS Hospital from November 2020 – January 2021.

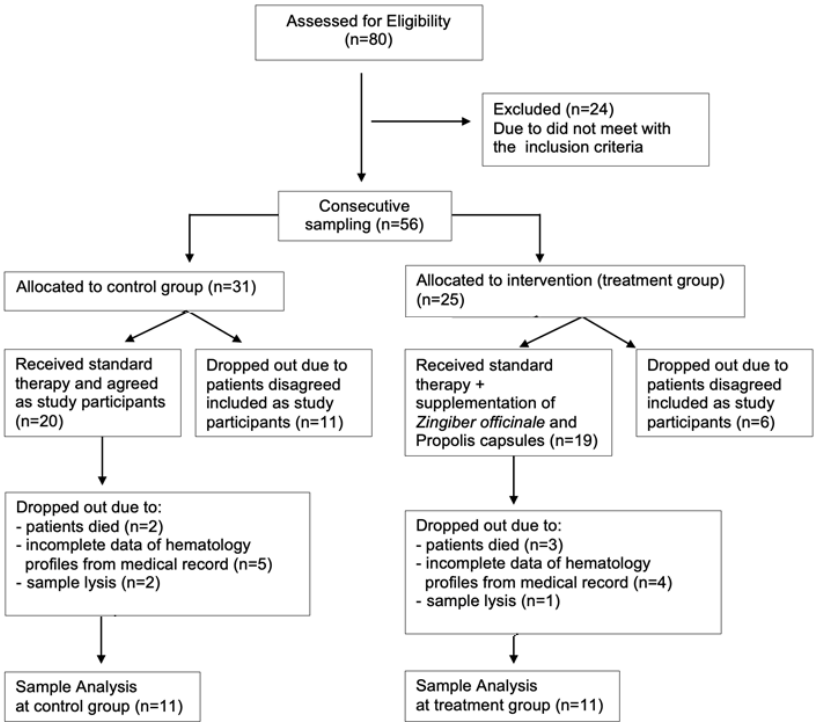

Figure 1. The flowchart of recruitment and sample distribution

The inclusions criteria for subject recruitment are Covid-19 confirmed patients based on PCR swab examination, which was performed on Covid-19-suspected patients with mild and moderate clinical symptoms who arrived in the emergency room. Meanwhile, patients with severe and critical symptoms were excluded from this study, and the classification of disease severity was based on the Covid-19 Clinical Management Living Guidelines from the World Health Organization. Patients with fever, cough, sore throat, nasal congestion, and myalgia/arthralgia without signs of severe pneumonia ($SpO_2 \geq 90\%$) were classified as mild. Severe Covid-19 was defined by clinical findings including pneumonia, RR > 30 breaths/min, and oxygen saturation < 90% on room air. In addition, severe pneumonia (computed tomography or chest radiography showed more than 50% of bilateral lung involvement), respiratory distress (RR ≥ 30 breaths/min), oxygen saturation ≤ 90%, systolic blood pressure < 65 mmHg, HR > 100 beats/min or required intensive care unit was categorized as critical Covid-19 patients (WHO, 2021).

This study was approved by the Health Research Ethics Committee of Universitas Sebelas Maret (No.103/UN27.06.6.1/KEPK/EC/2020), and informed consent was obtained from each participant. The total 22 subjects were distributed by the pulmonologist into 2 groups using consecutive sampling based on the inclusion and exclusion criteria which were already mentioned before. The minimal sample size in each group was calculated by sample size formula of paired numerical analytic study (Dahlan, 2019). The flowchart of recruitment and sample distribution between the two groups was depicted in Figure 1.

$$n1 = n2 = 2\left[\frac{(z\alpha + z\beta)S}{x1 - x2}\right]^2$$

n= sample in each group; Zα = type 1 error = 1.64; Zβ = type 2 error = 0.84; x1-x2 = the minimum mean difference that is considered significant = 1.42; S = standard deviation = 1.35; n1 = n2 = 11.12 (it rounded into 11 sample in each group).

The control group was received standard therapy for hospitalized Covid-19 patients (Favipiravir 2 x 1600 mg at day one followed by Favipiravir 2 x 600 mg at day 2-5, vitamin C 1 x 1000 mg, vitamin D 1 x 500 IU). A treatment group was received standard therapy and supplementing with the combination of *Zingiber officinale* capsules (Herbana, Deltomed®) at dose 1x500 mg and 1x1000 mg of Propolis capsules (Blackmore®) during the hospitalization periods.

The drugs administration was performed by nurses in the covid-19 isolation ward according to the protocol developed by the research team. *Zingiber officinale* capsules and Propolis capsule are each administered in the morning and evening, respectively along with the standard therapy.

The blood samples in both groups were taken from the median cubital vein (5 cc/subject) before and after the treatment (day 0 and the last day of hospitalization) by the laboratory staff who have been recruited in the research team. The pre-test parameters as a baseline are measured on day 0 since the initial treatment has not yet begun, whereas the post-test parameters are assessed on the last day of the patient's hospitalization.

The parameters used for measuring primary outcome of this study are clinical signs including vital signs and oxygen saturation, whereas the hematological parameters are used for assessing secondary outcomes. The differences (delta value) between the pre and post-test parameters in both group regarding the demographic characteristics, clinical signs, and hematology parameters were analyzed using an independent sample t-test or its alternative test (Mann Whitney), and the significant value was obtained at p-value < 0.05.

RESULT AND DISCUSSION

Characteristics Demographic of Participants

At a baseline, the demographic characteristics of hospitalized Covid-19 patients as participants of this study were similar and distributed equally in both groups (Table I). Most of the Covid-19 patients were over 45 years old with the mean age in the control and treatment groups as 46.82 ± 3.97 and 54.64 ± 4.82, respectively. Tabernero *et al*. reported that the largest number of infected patients were young and middle-aged adults, and it was estimated that more than 75% of individuals infected worldwide are in the 18-65 years of age range. This age range is a working age with a higher level of both mobility and interaction between individuals (Tabernero *et al*., 2021). A systematic review and meta-analyses reported Covid-19 patients ≥ 50 years old are at higher increased risk for mortality (15.4-folds) compared to those at age < 50 years (Biswas *et al*., 2021).

In this present study, the male and female gender was also distributed equally in the control and treatment groups (54.55% and 45.45% respectively). Supporting this finding, Gebhard *et al*. reported that until 2 April 2020, there were no significant gender differences in the absolute number of confirmed Covid-19 cases in some European countries (France, Spain, and Switzerland) (Gebhard *et al*., 2020). The prevalence of Covid-19 cases between males and females is similar and comparable. Meanwhile, the male is at higher risk for the worse outcome and mortality rate when infected by Covid-19. Therefore, gender acts as a crucial risk for the higher disease severity in Covid-19 which is independent of age (Jin *et al*., 2020).

The duration of treatment in both groups is 8 days on average (Table I), and there were no reported specific side effects or adverse events such as diarrhea or the signs of allergy during the supplementation. This supported the safety profile of Zingiber officinale and Propolis capsules as supplementation in hospitalized Covid-19 patients. Furthermore, Mesri *et al.* reported that the combination of *Zingiber officinale* and *Echinacea* did not cause any specific side effects during the randomized clinical trial in the health center of the urban community, Seventh, Iran (Mesri *et al*., 2021).

The Effects of Supplementation *Zingiber officinale* and Propolis on The Clinical Signs and Hematological Parameters of Hospitalized Covid-19 Patients

Several clinical signs including respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP), and body temperature as well as laboratory findings (lymphocyte, neutrophils, and platelet counts) were suggested to predict disease severity in patients (Az *et al*., 2021). Therefore, we accessed the clinical signs including vital signs and oxygen saturation (Table II) and hematological parameters (Table III) to obtain the efficacy of *Zingiber officinale* and Propolis capsules.

The most interesting finding is the combination of *Zingiber officinale* and Propolis significantly enhance the oxygen saturation of hospitalized Covid-19 patients (Table II). The oxygen saturation especially < 90% at the admission stage is a strong predictor for a higher mortality rate (Mejía *et al*., 2020). Similarly, a retrospective cohort study by Xie *et al*. showed that hypoxemia with the oxygen saturation < 90% is an independent risk factor for mortality rate in hospitalized Covid-19 patients at Union Hospital, Wuhan (Xie *et al*., 2020). Hypoxemia is one of the common symptoms related to interstitial pneumonia caused by a respiratory viral infection, and it initiates a decrease in lung capacity.

Table I. The Characteristic of Hospitalized Covid-19 Patients

Characteristic of Hospitalized Covid-19 Patients		Control Group (n=11)	Treatment Group (n=11)	Significance value (p<0.05)
Age (yrs)		46.82 ± 3.97	54.64 ± 4.82	0.23
Gender	Male	6 (54.55 %)	6 (54.55 %)	1.00
	Female	5 (45.45 %)	5 (45.45 %)	
Duration of treatment (days)		8.36 ± 0.51	8.45 ± 0.51	0.84

Data of age and treatment duration were presented as mean ± SE; Data of gender was presented in percentage (%)

Table II. The Clinical Signs of Hospitalized Covid-19 Patients

Clinical Signs	Control Group (n=11)	Treatment Group (n=11)	Significance value (p<0.05)	Mean Difference (CI 95%)
Sistole (mmHg)				
Sistole pre-treatment	140.27±8.04	128.09±5.57	0.23	12.18±2.47
Sistole post-treatment	127.55±6.49	130.18±3.37	0.72	2.63±3.12
Delta Sistole	-12.73 ±9.63	2.09±7.32	0.24	4.82±16.95
Diastole (mmHg)				
Diastole pre-treatment	78.64±4.35	81.36±3.72	0.64	2.72±0.63
Diastole post-treatment	77.45±2.80	74.91±3.02	0.43	2.54±0.22
Delta Diastole	-1.18±4.79	-6.45±5.57	0.24	5.27±0.78
Heart Rate (beat/minutes)				
Heart Rate pre-treatment	98.36±3.64	92.55±4.67	0.34	5.81±1.03
Heart Rate post-treatment	84.00±2.53	82.91±4.34	0.83	1.09±1.81
Delta Heart Rate	-14.36±4.98	-9.64±6.76	0.58	4.72±1.78
Respiration Rate (RR) (breath/minutes)				
RR pre-treatment	21.09±0.49	23.27±1.58	0.39	2.18±1.09
RR post-treatment	20.55±0.39	20.55±0.39	1.00	0.00±0.00
Delta RR	-0.55±0.47	-2.73±1.44	0.24	2.18±0.97
Temperature (^{0}C)				
Temperature pre-treatment	36.93±0.23	36.70±0.25	0.51	0.23±0.02
Temperature post-treatment	36.48±0.91	36.50±0.11	1.00	0.02±0.80
Delta Temperature	-0.45±0.27	-0.20±0.23	0.74	0.25±0.04
Oxygen Saturation (%)				
Oxygen Saturation pre-treatment	97.27±0.60	95.09±1.16	0.07	2.18±0.56
Oxygen Saturation post-treatment	97.73±0.30	98.55±0.25	0.03*	0.82±0.05
Delta Oxygen Saturation	0.45±0.45	3.45±1.16	0.01*	3.00±0.71

Data were presented as mean ± SE; The independent sample t-test and its alternative (Mann Whitney test) were used to determine the p-value; * Significant (p<0.05)

Moreover, microembolism associated with coagulopathy that often occurs in Covid-19 patients decreases lung perfusion (Allado *et al*., 2021).

TNFα cytokine can be considered as the key factor in causing lung symptoms in Covid-19 patients. This is because it induces the destruction and rearrangement of microtubule filaments. This will destabilize the microtubule in endothelial cells of the human pulmonary artery which leads to the increase of intracellular permeability. Furthermore, it inhibits the drainage process of alveolar and interstitials fluid concerning its downregulation effect on the mRNA expression of the epithelial sodium channel. It also emerged as a major regulator of the inflammatory process since it stimulates the release of various inflammatory mediators (IL6, IL1, and GMCSF) that often increase in Covid-19 lung disease (Eisenhut & Shin, 2020).

Table III. The Laboratory Findings of Hospitalized Covid-19 Patients

Laboratory findings	Control Group (n=11)	Treatment Group (n=11)	Significance value (p<0.05)	Mean Difference (CI 95%)
Hemoglobin (g/dL)				
Hb pre-treatment	13.51±1.55	11.86±2.72	0.10	1.65±1.17
Hb post-treatment	12.95±1.31	12.13±1.84	0.25	0.82±0.53
Delta Hb	-0.56±0.28	-0.84±1.62	0.86	0.28±1.34
Erythrocyte (10^3/uL)				
Erythrocyte pre-treatment	4.94±0.46	4.34±1.03	0.09	0.60±0.57
Erythrocyte post-treatment	4.74±0.46	4.46±0.78	0.33	0.28±0.32
Delta Erythrocyte	-0.21±0.10	0.51±0.35	0.06	0.72±0.45
Leucocyte (10^3/uL)				
Leucocyte pre-treatment	7.81±4.59	7.81±4.07	1.00	0.00±0.52
Leucocyte post-treatment	10.76±4.82	11.84±5.20	0.62	1.08±0.38
Delta Leucocyte	2.95±1.50	4.03±1.74	0.65	1.08±0.24
Thrombocyte (10^3/uL)				
Trombocyte pre-treatment	216.91±73.12	260.00±98.72	0.28	43.09±25.60
Trombocyte post-treatment	355.27±125.56	418.00±135.24	0.28	62.73±9.68
Delta Trombocyte	138.36±33.31	121.25±49.61	0.77	17.11±16.30
Neutrophil (10^3/uL)				
Neutrophil pre-treatment	67.20±9.77	72.89±15.15	0.31	5.69±5.38
Neutrophil post-treatment	75.00±4.03	78.62±4.47	0.55	3.62±0.44
Delta Neutrophil	7.80±4.00	5.73±3.59	0.70	2.07±0.41
Monocyte (%)				
Monocyte pre-treatment	8.61±2.88	7.96±3.12	0.62	0.65±0.24
Monocyte post-treatment	7.14±0.84	6.63±1.10	0.72	0.51±0.26
Delta Monocyte	-1.47±0.94	-1.33±0.99	0.92	0.14±0.05
Lymphocyte (%)				
Lymphocyte pre-treatment	23.58±8.52	19.44±13.33	0.40	4.14±4.81
Lymphocyte post-treatment	16.69±3.09	13.66±3.47	0.52	3.03±0.38
Delta Lymphocyte	-6.89±3.38	-5.77±2.24	0.73	1.12±1.14
Eosinophil (%)				
Eosinophil pre-treatment	0.42±0.33	0.79±0.57	0.58	0.37±0.24
Eosinophil post-treatment	0.90±0.37	0.93±0.68	0.97	0.03±0.31
Delta Eosinophil	0.48±0.29	0.05±0.10	0.20	0.43±0.19
Basophil (%)				
Basophil pre-treatment	0.19±0.03	0.18±0.04	0.88	0.01±0.01
Basophil post-treatment	0.27±0.06	0.24±0.06	0.76	0.03±0.00
Delta Basophil	0.08±0.07	0.06±0.05	0.84	0.02±0.02
MPV (fL)				
MPV pre-treatment	9.38±0.54	10.25±1.12	0.30	0.87±0.58
MPV post-treatment	9.39±0.17	8.83±0.91	0.55	0.56±0.74
Delta MPV	0.01±0.13	-1.47±1.05	0.19	1.48±1.18
HFLC (%)				
HFLC pre-treatment	0.75±0.17	1.35±0.25	0.06	0.60±0.08
HFLC post-treatment	0.35±0.09	0.65±0.12	0.07	0.30±0.03
Delta HFLC	-0.39±0.18	-0.70±0.28	0.36	0.31±0.10

Data were presented as mean±SD, *Significant (p<0.05)
The independent sample t-test and its alternative (Mann Whitney test) were used to determine the p-value. MPV: Mean platelet Volume. HFLC: High-fluorescent lymphocyte count.

The effect of *Zingiber officinale* (Ginger) and Propolis supplementation in improving oxygen saturation is probably mediated by their abilities in suppressing the pro-inflammatory cytokines, particularly TNFα. The meta-analysis of published-RCT stated the beneficial effects of the Ginger supplementation on the modulation of inflammatory markers, since it significantly reduces the circulation level of TNFα, CRP and hs-CRP (Morvaridzadeh *et al*., 2020). *Zingiber officinale* (Ginger) powder supplementation at dose 1 g/day for 3 months effectively reduce the TNFα and IL1β level compared to the placebo in elder osteoarthritis patients (Mozaffari-Khosravi *et al*., 2016). In terms of Propolis, it was proven effective in attenuating acute lung inflammation in mouse models. This anti-inflammatory property exert through Propolis ability to decrease alveolar macrophage, neutrophils, and TNFα expression to restore lung histological structure (Lopes *et al*., 2013).

This study also evaluated the effect of *Zingiber officinale* and Propolis supplementation on the hematological parameters. The high-fluorescent lymphocyte count (HFLC or HFLs) and mean platelet volume (MPV) in the treatment group tend to be lower compared to the control group, although it is not statistically significant (Table III). The HFLs in the blood are cells related to activated B or plasma cells (Van Mirre *et al*., 2011), and the level is correlated with disease severity in patients with COVID-19 (Z. Wang *et al*., 2020). It can be easily counted by an automated hematology analyzer as one of the parameters of a full blood count (Van Mirre *et al*., 2011). Furthermore, platelet activation plays a crucial role in the inflammatory mechanism with MPV acting as a marker. Platelet activation has a strong association with lung injury in viral pneumonia (Zhong & Peng, 2021). Therefore, the supplementation suppressed the clinical severity of Covid-19 possibly through their role in lowering HFLs and MPV. This study documented the benefits of *Zingiber officinale* and Propolis combination in improving clinical signs, especially oxygen saturation. The results support the combination of both compounds as an adjuvant modality in Covid-19 patients, and the antiviral effectiveness of both compounds have been proven in several previous studies.

The Molecular docking study suggested that some of the phytoconstituents from *Zingiber officinale* (Ginger) have a significant affinity to bind with S protein and ACE-2 receptor. This result indicated the potential properties of *Zingiber officinale* since S protein and ACE-2 receptor are determinant factors for cellular entry and the replication of SARS-CoV-2 (Haridas *et al*., 2021). Other in silico findings showed that 8-Gingerol and 10-Gingerol from Ginger have potential activities against Covid-19 considering they effectively bind to the main protease receptor of SARS-CoV-2 cocrystallized with 6-(ethylamino) pyridine-3-carbonitrile (PDB ID: 5R82) (Rajagopal *et al*., 2020). Subsequently, *in vitro* studies in both human upper (HEp-2) and low (A549) respiratory tract cell lines showed fresh Ginger significantly inhibits the plaque formation induced by the Human respiratory syncytial virus (HRSV) (Chang *et al*., 2013).

Propolis is proposed as one of the possible complementary treatments that will be beneficial in Covid-19 patients regarding the collection of evidence from experimental and clinical studies. It was elucidated that Propolis from temperate climate serves potential antiviral properties against many types of viruses such as Influenza virus type A and B, Parainfluenza virus, avian reovirus, HSV type 1 and 2, adenovirus, etc (Bachevski *et al*., 2020; Scorza *et al*., 2020). Moreover, propolis exhibits promise in reducing SARS-CoV-2 infection (Covid-19 disease), owing to its ability to hinder viral replication and serve as a potent anti-inflammatory agent by modulating the immune system (Berretta *et al*., 2020). This antiviral activity is mediated by several phytochemicals. Chrysin and kaempferol from Propolis actively inhibit viral replication. In addition, the flavonoid quercetin combined with vitamin C inhibits the main proteases of the SARS and MERS viruses through their aminopeptidase inhibitor activity (Bachevski *et al*., 2020; Scorza *et al*., 2020).

This study provides evidence of the beneficial effects of *Zingiber officinale* and Propolis capsule supplementation in enhancing the clinical condition of hospitalized Covid-19 patients, particularly in increasing oxygen saturation, without any observed side effects. This supports the efficacy of those supplements for Covid-19 infection and is the study's most important strength. However, there were also limitations to this study, such as the limited baseline characteristics and the fact that it did not assess any comorbidities, which also had an impact on the Covid-19 clinical symptoms. A subgroup analysis to reduce bias was not yet provided. In addition, its findings were constrained by sample size and a single-center study design.

The findings of this pilot study are intriguing and promising. However, to be broadly generalizable, further investigations with a multicenter study design, a large number of participants, and extended follow-up periods are required. In addition, it was necessary to support the implementation of *Zingiber officinale* and Propolis supplementation in clinical practice in order to improve the clinical outcome of Covid-19 hospitalized patients.

CONCLUSION

It is reasonable to conclude that the supplementation of *Zingiber officinale* 500 mg/day and Propolis 1000 mg/day can alleviate clinical signs of Covid-19 disease, especially in the enhancement of oxygen saturation. Moreover, the combination of both compounds tend to restore the hematological parameters (MPV and HFLC) in Covid-19 hospitalized patients. The results support the potential of the *Zingiber officinale* and Propolis supplementation as adjuvant therapy for Covid-19 patients. However, further studies should be conducted on its use in clinical settings.

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