

Factors Affecting the Uptake of Combination Therapy for the Treatment of COVID-19

ABSTRACT

Aims: To analyze factors affecting the use of a combination of herbs and medication or supplements for COVID-19 treatment among self-isolation patients.

Methodology: A cross-sectional study was conducted to 268 COVID-19 patients with home self-isolation in Indonesia. Data were collected by using a google form questionnaire, consisting of closed-formatted and open-ended questions, from October 9th to December 9th, 2021. A multivariate analysis was performed using a logistic regression test.

Results: The proportion of COVID-19 patients who used a combination of herbs and medication or supplements was 78.4%. Vitamin C, vitamin D, and paracetamol were the medication and supplements most frequently taken by patients. The most commonly consumed herbs were honey (70.7%), ginger (50.18%), and saffron (26.74%). The multivariate analysis results showed that the duration of infection, sunbathing activities, and marital status were factors significantly associated with the use of a combination of herbs and medication or supplements ($P < 0.05$). **Conclusion:** This study highlighted that most COVID-19 patients used herbs in combination with medication or supplements for their treatment. Therefore, there is a necessity for education, especially for patients and health professionals about the potential herb-drug interactions.

Keywords: COVID-19; medication; herbs; supplements; self-isolation.

1. INTRODUCTION

The coronavirus disease (COVID-19) is a disease carried by the SARS-Cov-2 and was firstly discovered in Wuhan, China, in December 2019. It has become a pandemic since March 2020 by The World Health Organization [1]. Consequently, lockdown measures were imposed to prevent the spread of the COVID-19 virus. The illness of COVID-19 progresses in a variety of ways including asymptomatic, mild symptoms, self-resolving flu-like illness, and moderate or severe disease with respiratory tract infection and shortness of breath or difficulty breathing [2]. According to the regulations from the Indonesian Ministry of Health, COVID-19 patients with asymptomatic or mild symptoms can self-isolate at home [3].

In the beginning of the COVID-19 pandemic, there were no specific, effective treatments or cures for COVID-19; however, concomitant treatments consisting of medicine, supplements, and herbs or natural products, have attracted much attention [4-9]. In addition, the prevalence of self-medication via the use of over-the-counter drugs and herbal medicine has increased during the COVID-19 pandemic [10,11]. Strengthening the immune system is the key to fighting the deadly coronavirus; thus, many believed that combining some medicines or medicine with herbs may be effective in COVID-19 treatment. Many medications have been prescribed to COVID-19 patients in order to prevent the progression of this disease.

Remdesivir, lopinavir/ ritonavir, umifenovir; corticosteroid, and chloroquine were used to treat COVID-19 [12]. A combination of azithromycin and antihistamine was also used to prevent the progression of the severity of COVID-19 [13]. Meanwhile, herbal medicine, such as honey, ginger, curcuma, saffron, and guava, has also been used to treat COVID-19. In Indonesia, traditional medicine including herbs and natural products has become an integral part of human culture. Herbal medicine is commonly used for the treatment and management of many diseases [14].

Drug interactions might be exacerbated by combining herbs and drugs. Drug-drug and drug-herbs interactions have been the subject of numerous investigations [15-17]. Despite the potential benefits, the incidence of adverse effects is likely to arise when a combination of treatments is used, particularly self-medicated. For example, propolis which is frequently used in pandemics decreased the AUC of fexofenadine, caffeine, and losartan. Meanwhile, omeprazole and midazolam increased in AUC [11]. Ginger is a common herb used during the COVID-19 pandemic. It has significantly inhibited CYP3A4 and CYP2C9 [18]. Therefore, the main aim of this study was to determine the factors associated with the uptake of the combination of herbs and medication or supplements for the treatment of COVID-19 with home self-isolation.

2. MATERIAL AND METHODS

2.1 Materials

A mixed questionnaire, consisting of close-formatted and open-ended questions, was used to gather information in reference to the study objectives [16,19,20]. The questionnaire was divided into four sections: the first section was close-formatted questions to collect data on the sociodemographic characteristics of the patients (age, gender, residence, marital status, education level, employment status) and sunbathing activities. The residence was categorized according to the metropolitan city (Jakarta, Bogor, Depok, Tangerang, Bekasi) and no metropolitan city (other cities except metropolitan city). Marital status was partitioned into marriage and non-marriage. The patient's education level was established by his or her most recent diploma. Employment status was divided into employed and unemployed. Sunbathing activities were sorted based on the frequency of the activity under the sun in a week. The second section was open-ended questions on the clinical characteristics of the patients, for instance, clinical manifestation, comorbidities, and duration of infection. The clinical manifestation referred to the symptoms during the infection. Comorbidities were defined as the presence of chronic illness in patients. The duration of infection was defined as the number of days that a patient spends from the time of infection until the infection healed. The third section was open-ended questions to collect information about medication and supplements used. The last part was open-ended questions to evaluate the information about the herbs used by patients for COVID-19 treatment. These data were collected based on the self-reported completed by patients.

2.2 Methods

Study design

This cross-sectional study was performed over 8 weeks, from October 9th to December 9th, 2021. An online questionnaire was created by the Google Form developer and informed consent to all people reached with the form was written at the top of the form.

Participant

The observation employed patients who had prior self-isolation experience for COVID-19 and were over the age of 12. A non-probability voluntary sampling technique was used to choose the patients. According to the calculation of the Lemeshow formula with an unknown population explained below [21], the minimum sample size needed was 96 patients, therefore the study collected a sample size more than required.

$$n = \frac{Z^2 p(1-p)}{d^2}$$
$$n = \frac{1.96^2 0.5(1-0.5)}{0.1^2}$$

n (minimum sample size)= 96

where,

Z = standard normal deviation set at 95% confidence level

P = percentage picking a choice or response

d= confidence interval

Data Collection

The data were collected by using Google Forms circulated through social media such as Facebook®, WhatsApp®, Instagram®, and emails in defining friend circles and asking them to forward the link to other potential patients as much as possible and inform us whether the form has been sent to others.

Analysis of data

Descriptive analysis of categorical socio-demographic and clinical characteristics variables was performed to show the frequency and percentage of each response. The Chi-Square test was performed to determine the association between socio-demographic and clinical characteristics of the use combination of herbs and medication or supplements used and then followed by an analysis of multiple logistic regression to analyze the factors that were significantly associated with using combinations of herbs and medication or supplements. A P-value of less than 0.05 was considered significant.

3. RESULTS AND DISCUSSION

The total of COVID-19 patients with home self-isolation obtained during the study period was 268 patients. The mean age of patients was 34.21 (SD=12.228) years. The majority of the study patients were female 68.5% (n=187), married 68.3% (n=183), general education level diploma and above 71.3% (n=87), employed 63.4% (n=170), and having sunbathing activities ≥ 4 times a week 67.9% (n=182). In detail, the characteristics of the socio-demographics of patients are presented in Table 1.

Regarding the clinical characteristics of patients, more than 70% of patients reported mild symptoms including cough, flu, fever, and anosmia. Dyspnea (26.5%) and diarrhea (25.7%) were also identified. However, the patients did not require hospitalization (Table 2). Mild fever and cough were the most prevalent signs in China [22]. Similar findings from other researchers were also reported [20,23]. The clinical symptom of COVID-19 varies between individuals from asymptomatic to severe symptoms [2]. Therefore, nonspecific gastrointestinal symptoms such as diarrhea and nausea also were documented [22-24]. Furthermore, The COVID-19 disease course also comprises a number of phases. First, the incubation phase of COVID-19 has varying duration with a median of 5.1 days but might last longer or shorter. Second, the mild acute phase is frequently associated with gastrointestinal problems, myalgia, fever, and cough (5-10 days). Third, a few individuals had hyperinflammatory acute respiratory distress syndrome, which is characterized by dyspnea, tachypnea, and hypoxemia [25]. Regarding comorbidities, 20.9% of patients reported having

comorbidities, whereas 79.10% (n=212) did not. Asthma, gastrointestinal disease, and hypertension were the majority of the comorbidities. Another study found that comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease may be related to the severity of COVID-19 [26]. Based on the duration of infection, less than 14 days of infection persisted in 79.5% of patients.

Table 1. Socio-demographic characteristics of self-isolation patients with COVID-19 (n=268).

Variable	N (%)
Gender	
Male	86 (31.50)
Female	187 (68.50)
Age (years)	
≤35	165 (61.60)
>35	103 (38.40)
Marital Status	
Non-Marriage	85 (31.70)
Marriage	183 (68.30)
Education level	
Secondary school or below	77 (28.70)
Higher diploma, degree, or above	191 (71.30)
Employment status	
Employee	170 (63.40)
Unemployed/Retired/Student/Housewives	98 (36.60)
Sunbathing Activities	
<4 times a week	86 (32.10)
≥4 times a week	182 (67.9)
Residence	
Jabodetabek*	146 (54.48)
Others	122 (45.52)

Jabodetabek : Jakarta, Bogor, Depok, Tangerang, Bekasi.

Table 2 Clinical characteristic among self-isolation patients with COVID-19 (n=268).

Variable	N (%)
Clinical Manifestation	
Cough and flu	202 (75.40)
Fever	199 (74.30)
Anosmia	195 (72.80)
Lose appetite	152 (56.70)
Sore throat	138 (51.50)
Dyspnea	71 (26.50)
Diarrhea	69 (25.70)
Comorbidities	
Yes	56 (20.90)
Hypertension	21 (7.69)
Asthma	15 (5.49)
Gastrointestinal disorder	15 (5.49)
Diabetes	4 (1.47)
Sinusitis	5 (1.83)
Hepatitis	2 (0.73)

Autoimmune	2 (0.73)
Vertigo	1 (0.37)
No	212 (79.10)
Duration of infection (days)	
<14	213 (79.50)
≥14	55 (20.50)

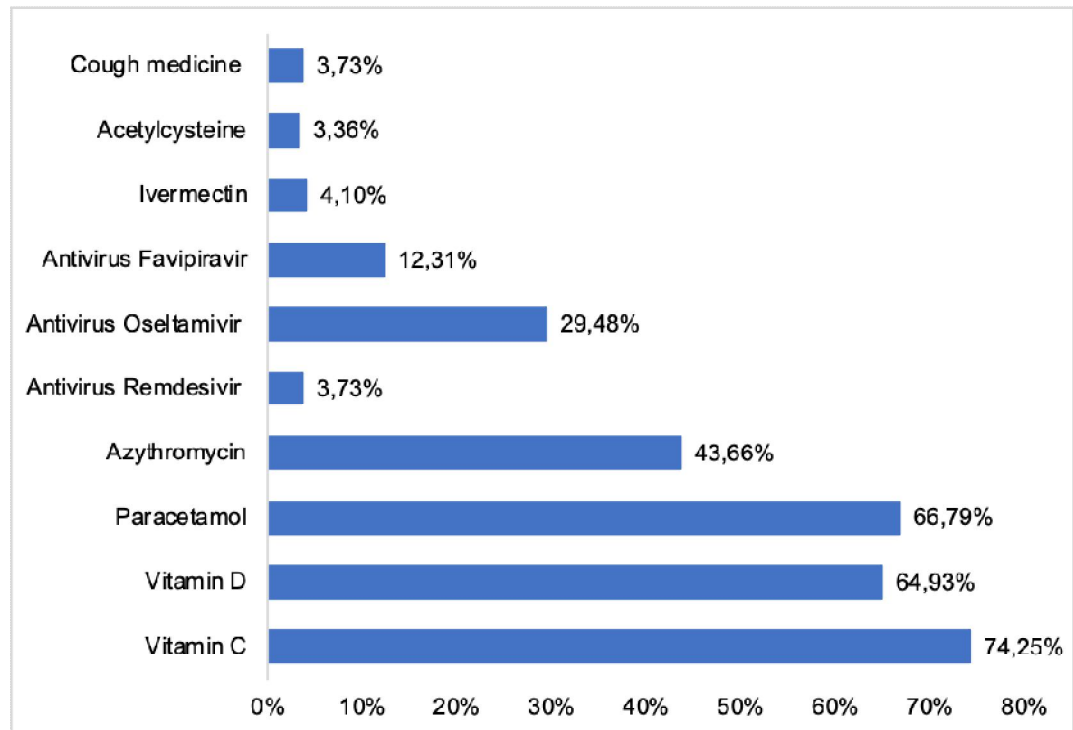


Figure 1. The pattern of medication/ supplement used among COVID-19 patients with home self-isolation (n=268).

As shown in Figure 1, more than 70% of COVID-19 patients with home self-isolation used vitamin C and then followed by paracetamol (66.79%), and vitamin D (64.93%). Among them, 43.66% of patients used antibiotics (Azithromycin) and 29.48 % of patients used Antivirus (Oseltamivir). Other surveys with similar findings were reported in Jordan [6], Peru [20], and Hongkong [27]. Vitamin D plays a role in reducing oxidative stress and clinical conditions due to viral infections such as COVID-19 [28,29]. Furthermore, Vitamin D could decrease the C-Reactive Protein level and the severity of the disease [30]. Even though the therapeutic evidence related to the efficiency of using vitamins in treating COVID-19 was still limited, vitamins were still used as a treatment due to clinical reports regarding their role in boosting the immune system, as an antioxidant, and antimicrobial effects [31].

The main herbs used by patients is showed in Table 3. The most frequent herbs used during isolation in this study was honey 72.01% (n=193), ginger 51.12% (n=137), Saffron 27.24% (n=73), propolis 23.13%, (n=62), and then followed by garlic 16.79% (n=45). (Table 3). However, the clinical evidence about its potential role to treat COVID-19 was still limited, the bioactive compounds from honey, such as methylglyoxal, chrysin, caffeic acid, galangin, and hesperidin have shown potential antiviral [32]. Other studies showed that honey or propolis

could improve clinical symptoms during viral infection [8,33,34]. Meanwhile, ginger was also used by the participants during the pandemic COVID-19. Similar results were found in Jordan [6], Peru [35], and Vietnam [36]. Ginger had strong anti-inflammatory, and antioxidant effects in animal experiments [8] and may act on viral [36]. In Nepal, ginger was the most popular herb cited during the pandemic [37]. Herbal medicines have a wide range of chemical activities and they can play a role in new drug development [38]. So, these herbs/natural products can be potentially developed as drugs for the treatment of COVID-19. Based on the virtual screening method to construct the 'Herb-Compound' and 'Compound-Protein' docking graph, there were 20 herbal combinations as a candidate for the treatment of specific infections, such as COVID-19 [39].

Table 3. Herbs and natural products used among self-isolation COVID-19 patients (n= 268).

Herb/natural product	N	Percentage (%)
Honey	193	72.01
Ginger	137	51.12
Saffron	73	27.24
Propolis	62	23.13
Garlic	45	16.79
Peronema leave	43	16.04
Aromatic ginger	30	11.19
Qustul Hindi	26	9.70
Sambiloto	22	8.21
Sapan	17	6.34
Curcuma	22	8.21
Galanga	15	5.60
Moringa	14	5.22
Black sead	11	4.10
Citus fruits	7	2.61
Lemongrass	6	2.24
Pegagan	4	1.49
Mahogani Seeds	3	1.12

Figure 2 shows the percentage use of the combination of herbs and medication or supplements during home self-isolation. Most of the patients (78.4%) used a combination even though 21.6% of patients did not use a combination. Some of them only used herbs for treatment (11.9% of patients), and the others solely used medication or supplements (9.7 % of patients).

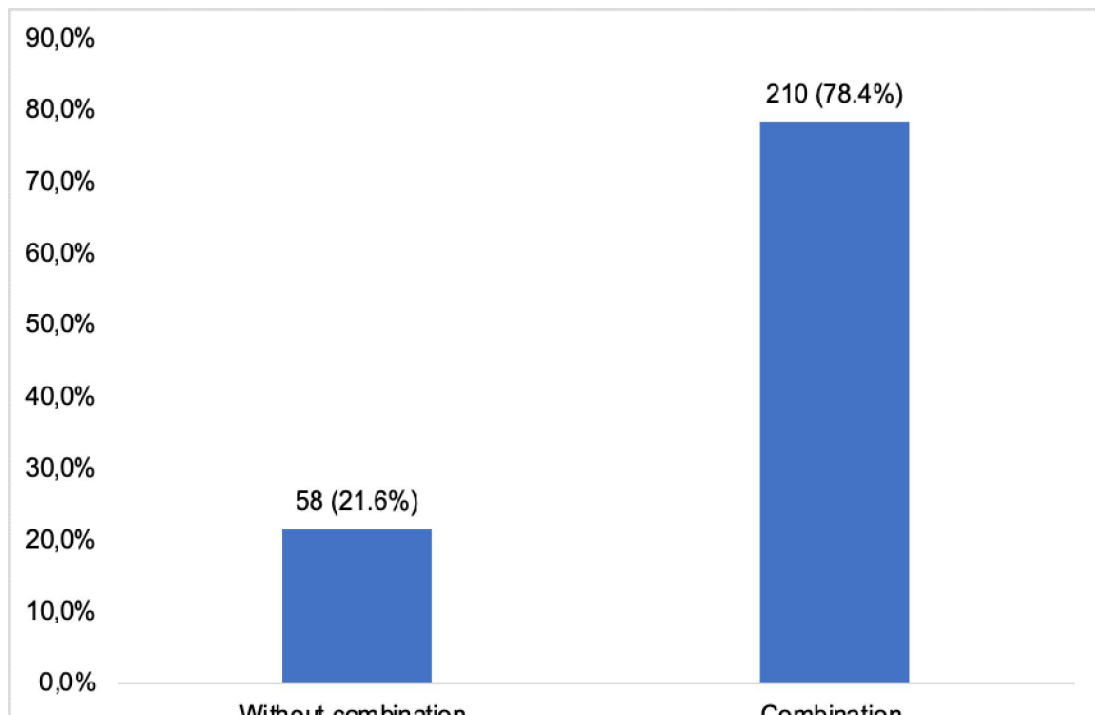


Figure 2. The percentage using a combination therapy of herbs and medication/supplements among COVID-19 patients with home self-isolation (n=268).

Among COVID-19 patients with home self-isolation, most of them used herbs and medication or supplements in combination for their treatment (78.4%). However, we also documented that 21.6% of patients did not use a combination (Figure 2). The high consumption of herbs was caused by Indonesian culture that uses herbs to treat all kinds of diseases. People believe herbs, used as an adjuvant with medicine prescribed, showed significantly more improvement than medicine alone [40]. In Bangladesh, people also used herbs and medicine to prevent COVID-19 [19]. This could be interpreted that there was a possible risk of drug interactions with herbs and medication during home self-isolation.

Medication and herbal interaction caused side effects [26], decreased response to drug therapy, and increased drug toxic effects [3,4]. A similar result found that one of the Chinese herbs used to treat COVID-19 had drug interaction through inhibiting CYP3 and prolonging $t_{1/2}$ lopinavir [41]. In addition, ginger, honey, and lemon were herbs frequently used in COVID-19 and several cases related to those herb-drug interactions were documented [18,42-44]. Therefore, patients need to provide information to healthcare professionals on the traditional medicines consumed when using medicine to avoid unintended interaction, and both patients and healthcare professionals should be aware of potential interaction between herbs and drugs prescribed [18,45,46].

The bivariate analysis is presented in Table 4. The analysis showed marital status ($P=0.006$), duration of infection ($P=0.011$), and sunbathing activities ($P=0.019$) had an important role in influencing patients to choose the use combination of herbs and medication or supplements during home self-isolation. Thus, the analysis was continued by multiple logistic regression analysis as shown in Table 5. The result of multiple logistic regression

analysis highlighted a similar finding. The duration of infection ($P=0.019$), sunbathing activities ($P=0.014$), and marital status ($P=0.020$) significantly affected the uptake of combination herbs and medication or supplements for the treatment of COVID-19. Unlike this study, the other factors associated with herbs and medication or supplements were age, education level, gender, and marital status [6].

Table 4. Bivariate analysis of the correlation between socio-demographic and clinical characteristics with the uptake of medication/supplements and herbs used.

Variable	Uptake of Combination Medication/Supplement and herbs		P Value*
	No	Yes	
Gender			0.900
<input type="checkbox"/> Male	18	67	
<input type="checkbox"/> Female	40	143	
Age (years)			0.107
<input type="checkbox"/> ≤35	41	124	
<input type="checkbox"/> >35	17	86	
Marital Status			0.006
<input type="checkbox"/> Non-Marriage	27	58	
<input type="checkbox"/> Marriage	31	152	
Education level			0.155
<input type="checkbox"/> Secondary school or below	9	56	
<input type="checkbox"/> Diploma or above	17	154	
Employment status			0.808
<input type="checkbox"/> Employee	17	134	
<input type="checkbox"/> Unemployed/Retired/Student/House wives	9	76	
Sunbathing Activities			0.019
<input type="checkbox"/> <4 times a week	26	60	
<input type="checkbox"/> ≥4 times a week	32	150	
Comorbidities			0.439
<input type="checkbox"/> Yes	10	46	
<input type="checkbox"/> No	48	164	
Duration of infection (days)			0.011
<input type="checkbox"/> <14	53	160	
<input type="checkbox"/> ≥14	5	50	

*Chi Square test. A P -value of less than 0.05 was considered significant.

Table 5. Factors associated with sociodemographic and clinical characteristics to the uptake of combination therapy among COVID-19 patients with home isolation.

Variable	Uptake of combination medication or supplements and herbs used n(%)		OR (95%CI)	P Value*
	No	Yes		
Age (years)				0.828
□ ≤35	41	124	1.091 (0.498-2.388)	
□ >35	17	86		
Marital Status				0.020
□ Non-Marriage	27	58	2.069(1.119-3.823)	
□ Marriage	31	152		
Education level				0.975
□ Secondary school or below	9	56	0.988 (0.461-2.117)	
□ Diploma or above	17	154		
Sunbathing Activities				0.014
□ <4 times a week	26	60	2.169(1.168-4.026)	
□ ≥4 times a week	32	150		
Duration of infection (days)				0.019
□ <14	53	160	3.260(1.211-8.772)	
□ ≥14	5	50		

* Using regression logistic multivariable model. These associations were expressed as adjusted odds ratios. Medication/supplements and traditional medicine used were coded as a binary variable (=1 if use combination of herbs and medication or supplements and = 0 if not).

The family had an important role in giving the advice to use a combination of herbs and medication [6]. In this study most of the patients who were married used combination medication and herbs for the treatment of COVID-19 during isolation. Furthermore, we documented that 79.5% (n=213) of the patients in our study had COVID-19 infections that lasted for fewer than 14 days, and the majority of them uptake combinations of herbs and medication for their treatment. People believe that the use of herbs as adjuvant therapy might hasten the healing process after infections [40]. In addition, the majority of patients who utilized a combination of herbs, medications, or supplements spent nearly every morning in the sun. Activities that involve exposure to the sun may help improve the condition during infection because they raise vitamin D levels. According to the study, the average COVID-19 patient had inadequate levels of vitamin D in their bodies. Therefore, taking vitamin D, magnesium, and vitamin B12 together may help COVID-19's clinical symptoms [47]. Other studies revealed that deficiency of vitamin D had a correlation with the severity of COVID-19 [48,49].

4. CONCLUSION

This study showed that the majority of COVID-19 patients who underwent home self-isolation employed herbs in addition to prescription drugs or dietary supplements. The length of the infection, sunbathing habits, and marital status were all major determinants of whether patients used combination herbal and pharmaceutical treatments or dietary supplements. The results of this study support the need for educational programs to educate patients and

healthcare providers about the possibility of herb-drug interactions. To prevent unwanted interactions, patients must inform healthcare professionals about the herbs they have taken.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The research carried out has passed the Research Ethics Committee of the Faculty of Health Sciences Syarif Hidayatullah State Islamic University Jakarta with the letter number. Un.01/F.10/KP.01.1/KE.SP/09.08.008/2021.1/F.10/KP.01.1/KE.SP/09.08.008/2021.

LIMITATION OF THE STUDY

The study had limitations. First, data were collected based on purposive sampling. Therefore, the results of this study may not be generalized to the entire population. Second, the research was an online survey and the data was based on self-reported data so there was a possibility of bias.

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