Original Research Article

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

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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: From October 9th to December 9th, 2021, a cross-sectional public survey was conducted in Indonesia. The survey distributed a mixed questionnaire, consisting of closed-formatted and open-ended questions, via Google Forms. In scrutinizing the data, logistic regression analysis was used to identify predictors of the use of a concoction of herbs and medication or supplements.
Results: This study observed 268 patients and revealed that 78.4% of patients used a combination between herbs and medication or supplements while 21.6% of patients did not use the combination. 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 statistical analysis showed that the duration of infection, sunbathing activities, and marital status were factors significantly associated with the use 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 need for educational campaigns to educate both patients and health care professionals about herb-drug interactions.

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

1. INTRODUCTION

The coronavirus disease (COVID-19) has become public health emergency of international concern and pandemic since it was declared in March 2020 by The World Health Organization [1]. Consequently, lockdown measures were imposed to limit the spread of the virus. The illness of COVID-19 progresses in a variety of ways: some people are asymptomatic, other people experience mild symptoms, self-resolving flu-like illness, and others can develop into moderate or severe disease [2]. Based on regulations from the Indonesian Ministry of Health, patients with asymptomatic or mild symptoms of COVID-19 can self-isolate at home [3].
In the early stages of pandemic COVID-19, the absence of treatment regimens and vaccines was performed. However, concomitant medicine, supplements with herbs, and natural products have attracted much attention [4-9]. During the pandemic of COVID-19, there was an increase in the tendency of self-medication with over-the-counters used and herbal medicine used [10,11]. To fight against this illness, combining some medicines or medicine with herbs is used 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 was 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 has also been used to treat COVID 19, especially in Indonesia. In Indonesia, traditional medicine such as herbs and natural products has become an integral part of human culture. People almost use herbal medicine for every kind of disease [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 during their combination use needs to be concerned, mainly when self-medicating. 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 pandemic COVID-19. It has significantly inhibited CYP3A4 and CYP2C9 [18]. Therefore, the main aim of this study was to determine the factors that impacted the uptake of the combination of herbs and medication or supplements to treat COVID-19.

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 monthly income) and sunbathing activities; the second section was open-ended questions on clinical characteristics of the patients; 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.

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 observed to have clinical manifestations, 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 duration of infection, less than 14 days of infection persisted in 79.5% of patients. Additionally,

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)

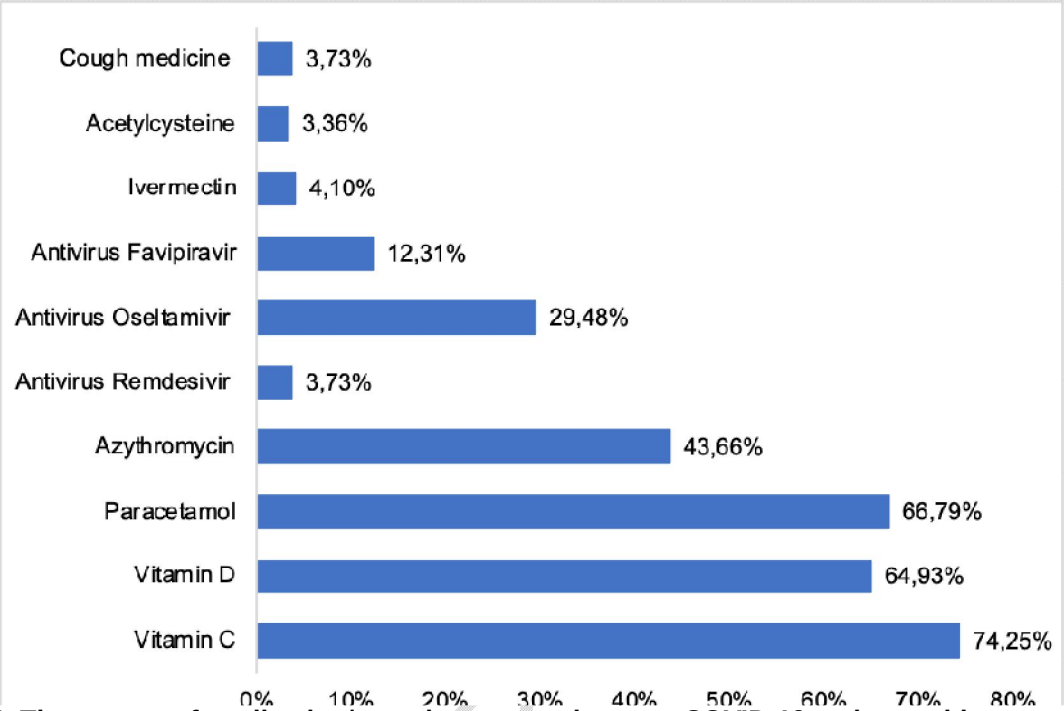

Figure 1. The pattern of medication/ supplement used among COVID-19 patients with home self-isolation (n=268).

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 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 anti-oxidant 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.

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).

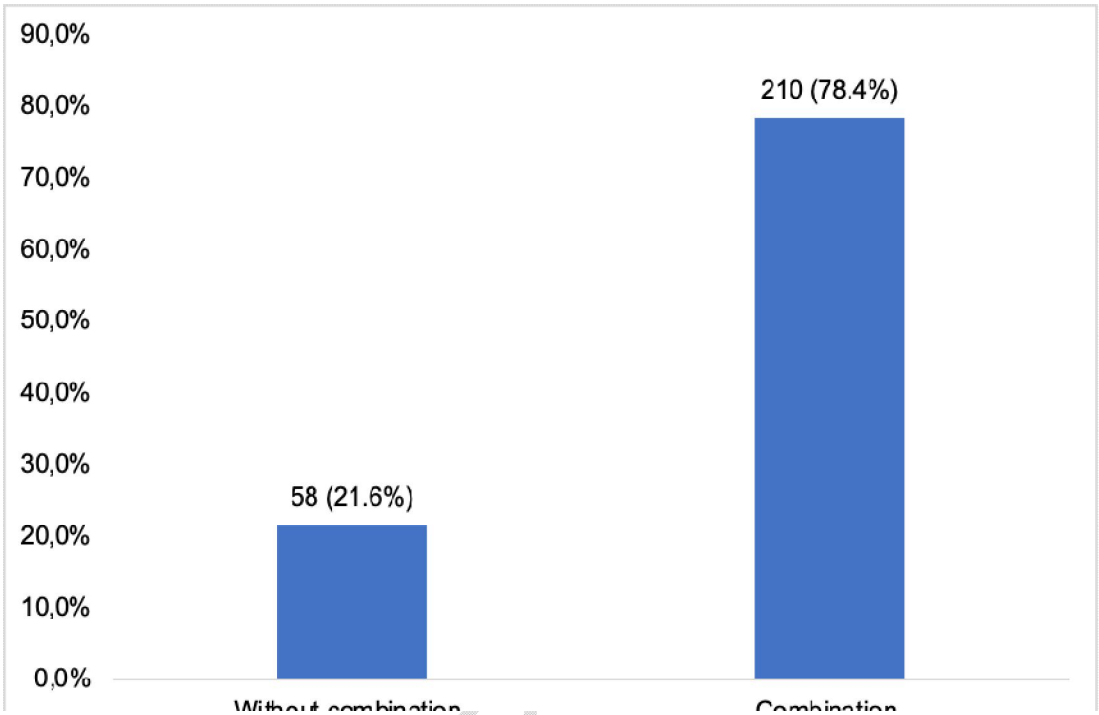

Figure 2. The percentage using a combination therapy of herbs and medication/supplements among COVID-19 patients with home self-isolation (n=268).

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 [39]. 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 t1/2 lopinavir [40]. In addition, ginger, honey, and lemon were herbs frequently used in COVID-19 and several cases related to those herb-drug interactions were documented [18,41-43]. 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 [18,44,45].

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
Male	18	67	
Female	40	143	
Age (years)			0.107
≤35	41	124	
>35	17	86	
Marital Status			**0.006**
Non-Marriage	27	58	
Marriage	31	152	
Education level			0.155
Secondary school or below	9	56	
Diploma or above	17	154	
Employment status			0.808
Employee	17	134	
Unemployed/Retired/Student/House wives	9	76	
Sunbathing Activities			**0.019**
<4 times a week	26	60	
≥4 times a week	32	150	
Comorbidities			
Yes	10	46	0.439
No	48	164	
Duration of infection (days)			**0.011**
<14	53	160	
≥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		
>35	17	86	1.091 (0.498-2.388)	
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		
Diploma or above	17	154	0.988 (0.461-2.117)	
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 [39]. 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 [46]. Other studies revealed that deficiency of vitamin D had a correlation with the severity of COVID-19 [47,48].

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

It was approved by every patient in this study.

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.

REFERENCES

1. World Health Organization. 2020. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. Available from: https://www.who.int/director- general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on- covid-19---11-march-2020.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054–62.
3. Decree of The Minister of Health of The Republic of Indonesia Number HK.01.07/MENKES/413/2020 about prevention and control guidelines coronavirus disease 2019 (COVID-19).
4. Szulińska M, Kręgielska-Narożna M, Świątek J, Styś P, Kuźnar-Kamińska B, Jakubowski H, et al. Garlic extract favorably modifies markers of endothelial function in obese patients –randomized double blind placebo-controlled nutritional intervention. Biomed Pharmacother. 2018;102:792–7.
5. Niv N, Shatkin JP, Hamilton AB, Unützer J, Klap R, Young AS. The use of herbal medications and dietary supplements by people with mental illness. Community Ment Health J. 2010;46(6):563–9.
6. Thiab SH, Nassar RI, Thiab S, Basheti IA. Medications and natural products used in jordan for prevention or treatment of covid-19 during the second wave of the pandemic: a cross-sectional online survey. Saudi Pharm J. 2022; 1-7.
7. Bossi P, Cortinovis D, Fatigoni S, Cossu Rocca M, Fabi A, Seminara P, et al. A randomized, double-blind, placebo-controlled, multicenter study of a ginger extract in the management of chemotherapy-induced nausea and vomiting (CINV) in patients receiving high-dose cisplatin. Ann Oncol. 2017;28(10):2547–51.
8. Silveira MAD, De Jong D, Berretta AA, Galvão EB dos S, Ribeiro JC, Cerqueira-Silva T, et al. Efficacy of Brazilian green propolis (EPP-AF®) as an adjunct treatment for

hospitalized COVID-19 patients: A randomized, controlled clinical trial. Biomed Pharmacother. 2021;138.

9. Rokhmah D, Ali K, Putri SMD, Khoiron K. Increase in public interest concerning alternative medicine during the COVID-19 pandemic in Indonesia: a Google Trends study [version 2; peer review: 2 approved, 1 approved with reservations]. F1000Research. 2021;9:1–19.

10. Karlsson P, Nakitanda AO, Löfling L, Cesta CE. Patterns of prescription dispensation and over-the-counter medication sales in Sweden during the COVID-19 pandemic. PLoS One. 2021;16(8 August):1-13.

11. Cusinato DAC, Martinez EZ, Cintra MTC, Filgueira GCO, Berretta AA, Lanchote VL, et al. Evaluation of potential herbal-drug interactions of a standardized propolis extract (EPP-AF®) using an in vivo cocktail approach. J Ethnopharmacol. 2019;245:112174.

12. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agent. 2020;56(2):106080.

13. Morán Blanco JI, Alvarenga Bonilla JA, Homma S, Suzuki K, Fremont-Smith P, Villar Gómez de las Heras K. Antihistamines and azithromycin as a treatment for COVID-19 on primary health care – A retrospective observational study in elderly patients. Pulm Pharmacol Ther. 2021;67(January).

14. Elfahmi, Woerdenbag HJ, Kayser O. Jamu: Indonesian traditional herbal medicine towards rational phytopharmacological use. J Herb Med. 2014;4(2):51–73.

15. Rezaee H, Pourkarim F, Pourtaghi-Anvarian S, Entezari-Maleki T, Asvadi-Kermani T, Nouri-Vaskeh M. Drug-drug interactions with candidate medications used for COVID-19 treatment: An overview. Pharmacology Research and Perspectives. 2021;9.

16. DiPietro MA, Mondie C. Toxicity of herbal medications suggested as treatment for COVID-19: A narrative review. J Am Coll Emerg Physicians Open. 2021;2(2).

17. Cho HJ, Yoon IS. Pharmacokinetic interactions of herbs with cytochrome p450 and p-glycoprotein. Evidence-based Complement Altern Med. 2015;2015:1-10.

18. Revol B, Gautier-Veyret E, Arrivé C, Fouilhé Sam-Laï N, McLeer-Florin A, Pluchart H, et al. Pharmacokinetic herb-drug interaction between ginger and crizotinib. Br J Clin Pharmacol. 2020;86(9):1892–3.

19. Ahmed I, Hasan M, Akter R, Sarkar BK, Rahman M, Sarker MS, et al. Behavioral preventive measures and the use of medicines and traditional medicines among the public in response to Covid-19 in Bangladesh: A cross-sectional study. PLoS One. 2020;15(12 December):1–13.

20. Quispe-Cañari JF, Fidel-Rosales E, Manrique D, Mascaró-Zan J, Huamán-Castillón KM, Chamorro–Espinoza SE, et al. Self-medication practices during the COVID-19 pandemic among the adult population in Peru: A cross-sectional survey. Saudi Pharm J. 2021;29(1):1–11.

21. Chadha VK. Sample size determination in health studies. 2006;55–62.

22. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.

24. Ye L, Yang Z, Liu J, Liao L, Wang F. Digestive system manifestations and clinical significance of coronavirus disease 2019: A systematic literature review. J Gastroenterol Hepatol. 2021;36(6):1414–22.

25. Meyerowitz EA, Vannier AGL, Friesen MGN, Schoenfeld S, Gelfand JA, Callahan M V., et al. Rethinking the role of hydroxychloroquine in the treatment of COVID-19. FASEB J. 2020;34(5):6027–37.

26. Bassendine MF, Bridge SH, McCaughan GW, Gorrell MD. COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity? J Diabetes. 2020;12(9):649–58.

27. Lam CS, Koon HK, Chung VCH, Cheung YT. A public survey of traditional, complementary and integrative medicine use during the COVID-19 outbreak in Hong Kong. PLoS One. 2021;16(7 July).

28. Abdrabbo M, Cole |, Birch M, Brandt M, Cicigoi KA, Coffey SJ, et al. Vitamin D and COVID-19: A review on the role of vitamin D in preventing and reducing the severity of COVID-19 infection. Protein Science.2021;30:2206-20.

29. Khemka A, Suri A, Naveen •, Singh K, Sanjiv •, Bansal K. Role of Vitamin D Supplementation in Prevention and Treatment of COVID-19. Indian J Clin Biochem. 2020; 35(4):502-3.

30. Demir M, Demir F, Aygun H. Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease. J Med Virol. 2021;93(5):2992–9.

31. Jovic TH, Ali SR, Ibrahim N, Jessop ZM, Tarassoli SP, Dobbs TD, et al. Could vitamins help in the fight against covid-19? Nutrients. 2020;12(9):1–30.

32. Al-Hatamleh MAI, Hatmal MM, Sattar K, Ahmad S, Mustafa MZ, Bittencourt MDC, et al. Antiviral and immunomodulatory effects of phytochemicals from honey against COVID-19: potential mechanisms of action and future directions. Molecules. 2020;25(21).

33. Dilokthornsakul W, Kosiyaporn R, Wuttipongwaragon R, Dilokthornsakul P. Systematic Review Potential effects of propolis and honey in COVID-19 prevention and treatment: A systematic review of in silico and clinical studies. J Integr Med. 2022;20(2):114–25.

34. Kosari M, Noureddini M, Seyed |, Khamechi P, Najafi A, Amir Ghaderi |, et al. The effect of propolis plus Hyoscyamus niger L. methanolic extract on clinical symptoms in patients with acute respiratory syndrome suspected to COVID-19: A clinical trial. 2021;35:4000-6.

35. Villena-Tejada M, Vera-Ferchau I, Cardona-Rivero A, Zamalloa-Cornejo R, Quispe-Florez M, Frisancho-Triveño Z, et al. Use of medicinal plants for COVID-19 prevention and respiratory symptom treatment during the pandemic in Cusco, Peru: A cross-sectional survey. PLoS One. 2021;16(9 September):1–18.

36. Hung P, Tran V De, Toan D, Nhat T, Dao P, Susan R. European Journal of Integrative Medicine Use of and attitudes towards herbal medicine during the COVID-19 pandemic : A cross-sectional study in Vietnam. 2021;44(February):101328.

37. Mu C, Sheng Y, Wang Q, Amin A, Li X, Xie Y. Potential compound from herbal food of Rhizoma Polygonati for treatment of COVID-19 analyzed by network pharmacology: Viral and cancer signaling mechanisms. J Funct Foods. 2021;77:104149.

38. Khadka D, Dhamala MK, Li F, Aryal PC, Magar PR, Bhatta S, et al. The use of medicinal plants to prevent COVID-19 in Nepal. J Ethnobiol Ethnomed. 2021 Dec 1;17(1).

39. Zohra T, Ovais M, Khalil AT, Qasim M, Ayaz M, Shinwari ZK, et al. Bio-guided profiling and HPLC-DAD finger printing of Atriplex lasiantha Boiss. BMC Complement Altern Med. 2019;19(1):1–15.

40. Kumar A, Rai A, Khan MS, Kumar A, Haque ZU, Fazil M, et al. Role of herbal medicines in the management of patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. J Tradit Complement Med. 2022 Jan 1;12(1):100–13.

41. Awortwe C, Makiwane M, Reuter H, Muller C, Louw J, Rosenkranz B. Critical evaluation of causality assessment of herb–drug interactions in patients. Br J Clin Pharmacol. 2018;84(4):679–93.

42. Alonso-Castro AJ, Ruiz-Padilla AJ, Ortiz-Cortes M, Carranza E, Ramírez-Morales MA, Escutia-Gutiérrez R, et al. Self-treatment and adverse reactions with traditional medicines for treating symptoms associated with anxiety and depression in adults from the central-western region of Mexico during the Covid-19 pandemic. J Ethnopharmacol. 2021;272:113952.

43. Zhang F, Huang J, Liu W, Wang CR, Liu YF, Tu DZ, et al. Inhibition of drug-metabolizing enzymes by Qingfei Paidu decoction: Implication of herb-drug interactions in COVID-19 pharmacotherapy. Food Chem Toxicol. 2021;149:111998.

44. Singh D, Gupta R, Saraf SA. Herbs-Are they Safe Enough? An Overview. Crit Rev Food Sci Nutr. 2012;52(10):876–98.

45. Awortwe C, Bruckmueller H, Cascorbi I. Interaction of traditional medicines with prescribed medications: A systematic review and meta-analysis. Pharmacol Res. 2019;141(December 2018):397–408.

46. Spanakis M, Sfakianakis S, Sakkalis V, Spanakis EG. medicines PharmActa: Empowering Patients to Avoid Clinical Significant Drug-Herb Interactions. 2019.6(26):1-18.

47. Tan CW, Ho LP, Kalimuddin S, Cherng BPZ, Teh YE, Thien SY, et al. Cohort study to evaluate effect of vitamin D, magnesium, and vitamin B12 in combination on severe outcome progression in older patients with coronavirus (COVID-19). Nutrition. 2020;79–80:111017.

48. Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity – plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. J Intern Med. 2021 Jan 1;289(1):97–115.