MEDICINES AS AN ALTERNATIVE THERAPY FOR COVID-19

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MEDICINES AS AN ALTERNATIVE THERAPY FOR COVID-19

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ABSTRACT

The coronavirus who that causes Covid-19 first appeared in Wuhan Distric, China, in December 2019, and has been a pandemic to date. In addition to the increasing prevalence of Covid-19 deaths, there are also several Covid-19 patients who have recovered. As we know that until now there is no single drug specifically for the treatment of Covid-19, so the reuse of available drugs is still carried out as an alternative. However, all these alternative medicines are still in the form of trial and error until now. The purpose of the research in this study is to find out what drugs have become alternatives for therapy in current Covid-19 patients. The method used in this research is literature study by collecting data from various scientific journals through various databases. From this research, after reviewing 12 journals. Drugs used as alternative treatments for Covid-19 patients that have been scientifically proven based on several literature studies include, Favipiravir, Remdesivir, Azithromycin, Levofloxacin, and several supporting nutrients namely Vitamin C, Vitamin E and Vitamin D.

Keywords: Covid-19, Literature study, Covid-19 alternative medicine, Covid-19 clinical trial treatment

ABSTRAK

Coronavirus yang menyebabkan Covid-19 pertama kali muncul di wilayah Wuhan, China, pada Desember 2019, dan telah menjadi pandemi hingga saat ini. Disamping pravalensi kematian kasus Covid-19 yang terus meningkat, terdapat pula beberapa pasien Covid-19 yang sembuh. Seperti yang kita ketahui bahwa hingga detik ini belum ada satupun obat yang dikhususkan untuk pengobatan Covid-19, sehingga penggunaan kembali obat-obat yang tersedia masih dilakukan sebagai alternatif. Namun, semua obat-obat alternatif tersebut masih berupa trial and error hingga saat ini. Tujuan penelitiam dalam pengkajian ini adalah untuk memperoleh data tentang obat-obat apa saja yang telah menjadi alternatif untuk terapi pada pasien Covid-19 saat ini. Metode yang digunakan pada penelitian ini yaitu studi literatur dengan mengumpulkan data dari berbagai jurnal ilmiah melalui berbagai database. Dari penelitian ini, setelah dilakukan pengkajian terhadap beberapa jurnal, obat-obat yang digunakan sebagai alternatif pengobatan pada pasien Covid-19 yang telah terbukti secara ilmiah berdasarkan beberapa studi literatur antara lain, Favipiravir, Remdesivir, Azitromisin, Levofloksasin, dan beberapa nutrisi penunjang yakni Vitamin C, Vitamin E dan Vitamin D.

Kata Kunci : Covid-19, Studi Literatur, Pengobatan alternatif Covid-19, Pengobatan uji klinis Covid-19

INTRODUCTION

At Desember 2019, in Wuhan Distric of China, the first death caused by a virus from a new strain of the Coronavirus family was reported as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and the disease caused by the virus is called Coronavirus Disease. The disease, also known as Coronavirus Infection Disease 2019 or Covid-19, is an infectious disease of the respiratory tract carried by the Novel Coronavirus (Pawar, 2020).

WHO declares that corona disease is a Public Health Emergency, it was reported that Covid-19 had penetrated as many as 219 countries with the number of confirmed cases as many as 49,242,837 and deaths reaching 1,242,187 with the number of patients increasing every time. Indonesia is ranked 15th in the highest number of deaths in the world, with 438,716 people who have been confirmed positive for Covid-19 (World Health Organization, 2020). As time goes by, the clinical spectrum of Covid-19 disease is getting wider, some cases are getting more complicated to be handled by medical personnel, especially by doctors, so they are also required to be really careful

and precise in diagnosing a disease and accompanied by giving treatment of patients as much as possible.

In Covid-19 patients with a fairly broad clinical spectrum, there are several clinical conditions suffered from asymptomatic form to presenting conditions accompanied by severe respiratory failure that require treatment in the Intensive Care Unit (ICU), mechanical ventilation assistance for multiorgan manifestations. Paucisymptomatic infections show several symptoms. The main symptoms reported were fever, cough, dyspnea, headache, sore throat and rhinorrhea to pneumonia. Pneumonia as manifestation of serious infection, characterized by high fever, cough, and bilateral infiltrates on chest radiograph. There are no specific clinical features that can be relied upon to differentiate Covid-19 from other respiratory viral infections due to the lack of specific symptoms. Respiratory droplet (splash) and airborne (airborne) transmission are the main routes of transmission of Covid-19, besides that it can also be transmitted through person-to-person contact by paucisymptomatic patients and also by asymptomatic patients (World Health Organization, 2020)

Until now, there has not been a single drug therapy specifically recommended and confirmed to be effective and safe for Covid-19, as we know that this disease is still quite new. Because it is known that the cause of Covid-19 is an infecting virus, so the curative therapy used for Covid-19, namely mostly broad-spectrum antiviral drugs as an alternative that has the potential to cure Covid-19. However, all these alternative medicines for Covid-19, both those used in Indonesia and in various other countries, are still in the form of trial and error until now.

Currently, the drugs used for patients infected with Covid-19 still refer to the use of drugs during the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) outbreaks several years ago. Several studies have shown that these drugs were quite effective at the time of the past epidemic to treat MERS and SARS. Until now, Indonesia itself has not received specific drug recommendations in dealing with Covid-19, which is relied on only drug preparations that are still available (Cai et al., 2020).

Reusing available drugs is one of the fastest ways to get Covid-19 treatment in an emergency (Aris et al., 2020). The prevalence or the overall number of Covid-19 cases is increasing from time to time, cases of death that sometimes decrease but suddenly increase often occur. However, in addition to cases of death, it turns out that many patients infected with Covid-19 can still be cured.

Based on the above background, the formulation of the problem in this literature study is the use of any drugs that have become alternatives for therapy in current Covid-19 patients.

MATERIAL AND METHOD

This research is a descriptive study with a literature study method through journal and document searches conducted from September 2020 to June 2021. The data used is in the form of literature based on inclusion and exclusion criteria. The inclusion criteria include journals published in the last 5 years (2016-2021), types of clinical trial journals, randomized clinical trials and original journals, types of research journals with single or combined alternative drugs that have been used by Covid-19 patients to date. and types of journals that have data on clinical trial results. The data obtained were collected and tabulated based on the literature review mapping. The tabulation contains the name of the author, year of publication, the method used and the results of the research which will then be analyzed and concluded.

RESULTS AND DISCUSSION

The results of the literature review on alternative medicines for Covid-19 can be seen in the table below:

Table 1. Alternative Medicines in the Treatment of Covid-19 Patients

No	Research Title	Researcher	Publication Type	Type of Study Research	Results
1.	Efficacy of Favipiravir in Covid-19 Treatment	Dabbous, et al.	PubMed, 25 January 2021	A multi-center randomized study.	This multicenter randomized controlled study stated that none of the patients in the Favipiravir arm required ventilation (p = 0.129). Based on these results, Favipiravir can be used as a Covid-19 drug
2.	Experimental Treatment with Favipiravir for Covid-19	Qingxian et al.	Elseiver, 6 2020	An Open-Label Control Study	A shorter mean viral clearance time was found in the Favipiravir group (4 days) versus the control group (11 days), P < 0.001). The Favipiravir group also showed significantly improved chest CT scans compared to the control group. Favipiravir showed better therapeutic activity in Covid-19 in terms of clinical improvement and viral clearance.
3.	Remdesivir for the Treatment of Covid-19.	Beigel, et al.	DOAJ, November 5, 2020.	Final Report	Open Label and Random Clinical Trial A total of 1,062 patients were randomized (541 patients to Remdesivir and 521 patients to placebo). Those who received remdesivir had an average recovery time of 10 days compared to those who received a placebo of 15 days. In an analysis using a proportional probability model with an eight-category ordinal scale, patients receiving remdesivir were found to be more likely to experience clinical improvement than those receiving placebo. The results data show that Remdesivir is superior to placebo in shortening recovery

					time in Covid-19 patients.
4.	Remdesivir for Severe Covid-19 Versus A Cohort Receiving Standard of Care	Olender et al.	Elseiver, July 2020.	Randomized, Open-Label Trial Comparing Two Clinical Trial	Randomized open-label trial comparing two groups namely standard treatment + Remdesivir group and standard care non-Remdesivir group, it was stated that on day 14 of treatment, 74.4% of patients in the Remdesivir group had recovered while only 59.0% in the non-Remdesivir group. So it was stated that standard treatment with additional therapy of Remdesivir had a faster healing activity compared to the group that was only treated with standard care without Remdesivir.
5.	Empirical Treatment with Azithromycin and Hydroxychloroquine for Suspected Cases of Covid-19.	Rodrigo et al.	ClinicalTrials, April 2020.	Therapeutic intervention studies	This clinical trial study was conducted with asymptomatic to mild-moderate telemedicine. Outcome Out of 636 symptomatic outpatients, 412 started treatment with Hydroxychloroquine and Azithromycin and 224 refused the drugs (control group). The need for hospitalization in the group with Azithromycin was 1.9% while it was 5.4% in the control group.
6.	Azithromycin for Covid-19	Bleyzac, et al	NCBI, 12 June 2020.	Clinical Trials	Patients admitted immediately after a Covid-19 diagnosis received HCQ + AZM or HCQ alone, or AZM alone. The mortality rate in patients with HCQ + AZM at 21 days was 22.5%, 18.9% in patients with HCQ alone and 10.9% in patients with AZM alone. However, these results need to be confirmed by further randomized studies. In conclusion, there are several arguments in favor of the potential effectiveness of AZM in

					SARS-CoV-2 infection, including its antiviral activity and immunomodulatory effects.
7.	The Clinical Value of Two Combination Regimens in the Management of Patients Suffering from Covid-19 Pneumonia	Vahedi et al.	NCBI, 19 Juni 2020.	A Single Centered, Retrospective	Observational Study Of 60 Covid-19 positive hospitalized patients 19 confirmed (≥18 years) in Hospital ward, Iran. The results of oxygen saturation (SpO2) and body temperature changed for the better in patients receiving regimen I compared to regimen II, changes in the two regimens were not clinically different. However, the findings showed a significant difference from the mean duration of hospital stay in regimen I indicating a shorter duration.
8.	The Use of IV Vitamin C for Patients with Covid-19	Raul et al.	NCBI, 1 Agustus 2020.	Clinical Trial Series	The inpatient mortality rate in this trial was 12% with an increase in intubation and mechanical ventilation of 17.6%. We noted a significant reduction in inflammation, including ferritin and D-dimer, and a trend toward a decrease in FiO2 requirement after vitamin C administration.
9.	Safety and Effectiveness of High-Dose Vitamin C in Patients with Covid-19.	Saeidreza et al	Pubmed, 11 February 2021.	Random clinical trial	The main results obtained were a decrease in mortality and the number of patients admitted to the ICU. The secondary outcome was an increase in SpO2 and an overall improvement in clinical symptoms in Covid-19 patients in the hospital.
10.	Role of Vitamin D in Preventing of Covid-19 and Infection Progression Severity	Nurshad Ali.	Elseiver, 7 May 2020.	Randomized trials and analyzes	This study shows that a significant negative correlation has been observed between average vitamin D levels and cases of Covid-19. Several studies have shown a role for vitamin D in reducing the risk of respiratory tract infections.

					However, evidence is still lacking. Therefore, further testing of cohort studies is still needed.
11.	The effect of Vitamin E and Vitamin C in Patients with Covid-19 Pneumonia	Hakamifar, et al.	DOAJ 20 December 2020.	A randomized controlled clinical trial	Covid-19 patients were divided into two groups: the intervention group (n=38) and the control group (n=34). Both groups were given oral vitamin C. The results obtained where 7.89% of the intervention group (3 people) and 14.71% of the control group (5 people) experienced treatment failure and the rest experienced clinical improvement (P=0.380). These results show that the administration of vitamins C and E cannot be an option in the treatment of COVID-19
12.	Immune-boosting Role of Vitamins D, C, E, Zinc, Selenium and Omega-3 fatty Acids?	Shakoor, et al.	Elseiver, 29 June 2020	Retrospektif Study.	The effects of Vitamins C, D, E, zinc, selenium, and omega-3 fatty acids are quite beneficial for people with Covid-19 on their immune systems. The results of trials from several studies are still urgently needed in the hope of clarifying the use of micronutrients during SARS-CoV-2 infection.

Based on the results of a review of reviewed journals, various kinds of drugs can be used for patients infected with Covid-19 at this time as an alternative treatment. Some of these studies generally aim to find out that these drugs are used for therapeutic reasons that are more beneficial than their bad effects. The following are drugs that have been and are still being used today as alternatives in the treatment of patients infected with Covid-19.

Favipiravir

Favipiravir is a class of antiviral drugs currently widely used by Covid-19 patients, one of the reasons is because Favipiravir targets RdRp on the Corona virus. RdRp is a protein that has an important role in the replication of Coronavirus in respiratory epithelial cells (Cao et al., 2020; Yavuz & Unal, 2020). In the research of Inoue et al. (2020) have also mentioned that Favipiravir works by selectively inhibiting viral RNA polymerase so that it can suppress replication, and has been shown to have antiviral effects on SARS-CoV-2. In addition, purine analogues have also been

considered for the treatment of Covid-19. Favipiravir acts as a purine analogue that can enter guanine or adenine sites and thereby inhibit viral replication.

Research conducted by Dabbous et al. (2020) at Ain-Shams University Hospital and Tanta University in the period April to August 2020, showed the results that antiviral therapy with Favipiravir was able to reduce virus eradication time. In addition, a non-randomized intervention study involving 80 Covid-19 patients stated that Favipiravir showed better treatment outcomes in Covid-19 patients in terms of reducing disease severity and viral clearance, this supports the possible use of Favipiravir in the treatment of Covid -19, Cai et al. (2020) also mentioned that Favipiravir showed significantly higher improvement rates on chest CT scans compared to the control group. In addition, fewer side effects were found in the Favipiravir group than in the control group.

Favipiravir was approved in Japan in 2014 as a treatment for viral infections ie its efficacy against the Ebola virus in the Ebola outbreak in West Africa from 2014 to 2015. Favipiravir has also shown efficacy in cases of infection by Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV). Based on this, Favipiravir is thought to have an inhibitory effect on viral replication on SARS-CoV-2, considering that Favipiravir's pharmacological action is considered effective in suppressing various viral replications (Inoue et al., 2020).

Remdesivir

Remdesivir is metabolized to an active form, namely an adenosine triphosphate analogue which has RdRp inhibiting activity which causes errors in proofreading by viral exonucleases so that it interferes and stops the viral RNA synthesis process (Cao et al., 2020; Sisay, 2020; Yavuz & Unal, 2020). Covid-19 patients confirmed by the Centers for Disease Control (CDC) in the United States, McCreary & Pogue (2020) stated that patients receiving Remdesivir showed clinical improvement, but patients complained of gastrointestinal disturbances and an increase in aminotransferases, so the efficacy and safety this drug is uncertain.

Testing of Remdesivir by Beigel et al. (2020) demonstrated infection control in adult patients infected with Covid-19 who were given Remdesivir at an initial dose of 200 mg on the first day. The outcome data suggest that the investigators recommend treatment with remdesivir to prevent the development of more severe respiratory disease.

Research by Neldi & Suharjono (2020) concluded that patients with Remdesivir experienced a faster clinical improvement. Based on the outcome data, the investigators also state that treatment with Remdesivir can prevent the development of more severe respiratory disease, lower side effects and lower incidence of oxygen use.

In light of the preliminary results regarding Remdesivir, the Food and Drug Administration (FDA) issued an Emergency Use Authorization on May 1, 2020, to authorize the use of Remdesivir for treatment in adults and children hospitalized with suspected or confirmed Covid-19 infection from laboratory. However, given the high mortality rate despite taking Remdesivir, it is clear that treatment with antiviral drugs alone may not be sufficient for all patients with different diagnoses.

Azithromycin

According to (Bleyzac et al., 2020) Azithromycin has been shown to have significant antiviral properties. Its activity against Respiratory Syncytial Virus (RSV) has been demonstrated in randomized studies in infants. Azithromycin has shown a synergistic effect when given with antivirals against SARS-CoV-2, or also when combined with hydroxychloroquine both in vitro and

in several clinical trials. Article from Andreani et al. (2020) also reported a significant antiviral effect of Azithromycin alone without any other drug combination on SARS-CoV-2. The antiviral effect of Azithromycin is a broad-spectrum antiviral. Azithromycin is also said to reduce the rate of entry of the virus into cells, by increasing the immune response to the virus. This mechanism is universally involved in the innate response to infectious agents, and has the potential to fight viruses including SARS-CoV-2.

Apart from the antiviral properties of Azithromycin, the immunomodulating properties of Azithromycin are also the reason for its use against inflammatory manifestations that cause lung disease. SARS-CoV-2 has been shown to exacerbate the inflammatory response of its host, causing serious damage to lung interstitial tissue. Patients with severe Covid-19-associated pneumonia may exhibit a systemic hyperinflammatory syndrome referred to as a cytokine storm. Cytokine storm in patients with severe Covid-19, showed a significant increase in several pro-inflammatory cytokines such as interleukins (ILY-1B, IL-2. IL-6. IL-8, IL-10, IL-17). Azithromycin has shown an immunomodulatory profile by inhibiting several cytokines involved in the COVID-19 severe respiratory syndrome (Bleyzac et al., 2020).

Levofloxacin

The antibiotic Levofloxacin exerts its bactericidal effect against gram-negative and gram-positive bacteria, anaerobes, mycobacteria and atypical pathogens. However, it has now become a consideration in the treatment of SARS-CoV-2, due to the immunomodulatory properties, pharmacokinetics, and good safety profile of levoflocin. (Karampela & Dalamaga (2020) proposed the use of Levofloxacin as an adjunct in treating patients with Covid-19.
Therapeutic efficacy of Levofloxacin compared with -lactams, in the treatment of mild to moderate community pneumonia, where clinical success rates of Levofloxacin were 96% and 90% for -lactams, respectively. In addition, research by Scroggs et al. (2021) that the efficacy and safety of Levofloxacin have also been evaluated in patients with mild to moderate and severe COVID-19.

Vitamin

Vitamin D is a fat-soluble precursor of steroid hormones arising from exposure to ultraviolet B (UVB) 7-dehydrocholesterol (7-DHC) radiation in the skin epidermis, where it is converted to cholecalciferol (25-OH-D) precursors in the systemic. Vitamin D has roles in various body systems, including in the innate and adaptive immune responses. Vitamin D also promotes the differentiation of monocytes into macrophages and also increases the production of superoxide, phagocytosis, and destruction of bacteria. Some results from studies are still unclear, therefore, vitamin D supplementation is only recommended to increase immunity against Covid-19 (Shakoor et al., 2021). Several clinical and epidemiological studies regarding Covid-19 and its relationship with vitamin D. In a randomized controlled trial with 5660 subjects, vitamin D supplementation was sufficiently shown to reduce the risk of respiratory disease (Ali, 2020).

In addition, vitamin E and selenium are also major components of antioxidant defense. It has been noted, that there is a correlation between selenium levels and Covid-19 cure rates in various provinces in China. Vitamin E and selenium both act through antioxidant pathways to increase T cell counts, enhance mitogenic lymphocyte responses, increase IL-2 cytokine secretion, increase NK cell activity, and, reduce the risk of infection. (Shakoor et al., 2021).

Vitamin C is highly recommended for Covid-19 patients especially those associated with the presence of a cytokine storm during Covid-19 infection, clinical studies have shown that intake of 1 g/day of vitamin C increases the secretion of IL-10 by peripheral blood mononuclear cells. IL-10 works by a negative feedback mechanism with IL-6 and controls critical inflammation in Covid-19. Vitamin C has also been shown to play a role in secondary sepsis and pneumonia in Covid-19 (Shakoor et al., 2021). According to a study by (Hiedra et al., 2020) that has identified 17 patients who were confirmed positive for SARS-CoV-2 through nasopharyngeal swab PCR. The patient was given intravenous vitamin C as part of the Covid-19 treatment. Analysis using a paired T test revealed significantly lower levels of D-dimer and ferritin after treatment with vitamin C and no side effects directly related to vitamin C administration were noted. This test also states that for the time being the use of intravenous vitamin C is quite safe and feasible in patients with Covid-19 with moderate to severe disease.

The use of available drugs as an alternative for Covid-19 patients is one of the efforts of the government and health workers in dealing with the emergency conditions of this pandemic. Antiviral drugs used such as Favipiravir and Remdesivir refer to the use of these drugs in the SARS and MERS epidemics of several years ago which proved effective in some patients. In addition to antivirals, antibiotics are also given to Covid-19 patients as a supporting treatment. Antibiotics are usually given in combination with several antivirals because of their synergistic effect on both. The use of antibiotics does not play a role in treating patients directly against Covid-19, but is used when a secondary bacterial infection occurs, because some patients infected with respiratory viruses are usually also infected with secondary bacteria. In addition, some antibiotics also have antiviral or immunodilator activity such as Azithromycin, for some of these reasons it is possible for some antibiotics to become an alternative in the current treatment of Covid-19 patients in combination with several other types of drugs. As for the treatment of Covid-19 by antivirals and antibiotics, patients are also given several vitamins and minerals such as vitamin C, vitamin D and vitamin E as well as zinc. As we know that the body's reaction when infected with a virus, especially Covid-19, is that the body will form resistance to prevent or eradicate viruses that will infect. If the immune system is strong, the virus can be prevented from entering the body. However, in people whose immune systems are weak, the virus can be difficult to fight, resulting in severe symptoms and fatal complications. Therefore, Covid-19 patients are given vitamins and minerals because one of the roles of vitamins and minerals is as an antioxidant that can strengthen the human immune system (immune system).

However, all of these alternative medicines in the treatment of Covid-19 are still in the form of trial and error, there has not been a single drug that has been specifically confirmed to be a safe and effective Covid-19 drug, so the use of these alternative medicines must be given by parties who authorities such as doctors accompanied by strict supervision assisted by other health workers, so as not to cause things that are not desirable.

CONCLUSION

Based on the review and amalgamation of several literatures, it can be concluded that the drugs used as an alternative treatment in patients infected with Covid-19 that have been scientifically proven based on several literature studies include, Favipiravir, Remdesivir, Azithromycin, Levofloxacin, and supporting nutrition namely vitamin C, vitamin D, vitamin E, and vitamin D.

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