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Masters Program in Public Health, Universitas Sebelas Maret

Meta-analysis

Meta-Analysis the Effectiveness of Ivermectin Use on the Length of Stay in Inpatients of COVID-19

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ABSTRACT

Background: COVID-19 is a common problem in global health. COVID-19 is a disease that infects the respiratory tract caused by the Coronavirus virus. Symptoms range from mild to severe and life-threatening pneumonia can occur. At the beginning of the PSBB, information circulated that Ivemectin could treat COVID-19 infections. Ivermectin is an antiparasitic drug that can be used as prophylaxis and therapy for coronavirus disease 2019. Ivermectin is an alternative therapy for COVID-19 because there is a previous drug, chloroquine, which can be used to treat COVID-19. This study aims to estimate the effectiveness of Ivermectin on the duration of hospitalization of patients with COVID-19 based on the results of previous similar studies.
Subjects and Method: This study is a meta-analysis with the following PICO, population: COVID-19 patients. Intervention: ivermectin. Comparison: standard therapy. Outcome: shorter duration of hospital stay. Meta-analyses and systematic studies using the PubMed, Scopus, Scholar, Springlink, Cochrane, Clinical Key, and Science Direct databases. Keywords using Ivermectin AND RCT AND COVID-19 AND "Coronavirus Disease" AND "NCOV disease" AND "COVID-19 treatment". The article under study is a full-text article with a randomized controlled clinical trial (RCT) study design. Articles were collected using PRISMA diagrams and analyzed using Review Manager 5.3.
Results A total of 9 Randomized Control Trial (RCT) studies from Europe, America, Asia and Africa were selected for systematic review and meta-analysis. COVID-19 patients receiving Ivermectin therapy decreased the duration of hospital stay by 1.52 units compared to standard therapy and this result was statistically significant (SMD= -1.52; 95% CI= -2.34 to -0.70; p= 0.003).
Conclusion: Ivermectin can reduce the duration of hospital stay for COVID-19 patients.

Keywords: COVID-19, ivermectin, duration hospital stay

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BACKGROUND

At the beginning of 2020, the world was shocked by the outbreak of a new virus, namely the new type of coronavirus (SARS-CoV-2), and the disease is called coronavirus disease 2019 (COVID-19). It is known, the origin of this virus came from Wuhan. The coronavirus disease (COVID-19) has been identified as the cause of the respiratory disease outbreak in Wuhan, Hubei Province, China starting December 2019 (Yuliana, 2020).

As of January 31, 2020, the epidemic has spread to 19 countries with 11,791

confirmed cases, including 213 deaths. Coronaviruses are a group of enveloped, single-stranded, positive-stranded RNA viruses belonging to the order Nidovirales (Weiss and Navas-martin, 2005). Previous coronavirus outbreaks included severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV which were previously characterized as causative agents of great threat to public health (Rothan and Byrareddy, 2020).

To reduce the very fast spread, the government did various things, one of which was by setting a *PSBB* policy (Large-Scale Social Restrictions), including school and work holidays, restrictions on religious activities, restrictions on activities in public places or facilities, restrictions on transportation, restrictions on transportation, and restrictions on transportation. social and cultural activities, as well as restrictions on other activities specifically related to defense and security aspects. In other words, *PSBB* can be carried out by staying at home, self-isolation (quarantine) and reducing activities outside the home unless there is an urgent need.

At the beginning of the *PSBB*, information circulated that Ivemectin could treat COVID-19 infections. Ivermectin is an anti-parasitic drug that can be used as prophylaxis and therapy for coronavirus disease 2019 (Caly et al., 2020). Ivermectin is an alternative therapy for COVID-19 because there is a previous drug, namely chloroquine, which can be used to treat COVID-19. The antiviral effect of chloroquine tested on primate cell cultures (Vero E6) infected with the SARS-Cov virus showed that chloroquine was effective in reducing the number of infected cells (Perdafki, 2020). Chloroquine has been reported to inhibit the multiplication of the SARS-CoV-2 virus at concentrations that can be achieved with standard doses used in humans. This study aims to estimate the effectiveness of Ivermectin on the duration of hospitalization of COVID-19 patients based on the results of previous similar studies.

SUBJECTS AND METHOD

1. Study Design

Online literature searches are sourced from Pubmed, Scopus, Scholar, Springlink, Cochrane, Clinical Key, and Science Direct. Keywords using Ivermectin AND RCT AND COVID-19 AND "Coronavirus Disease" AND "NCOV disease" AND "COVID-19 treatment". The selected articles are in the period 2020 to 2022.

2. Inclusion criteria

The selected articles are in English and Indonesian. The sample of this study is people infected with COVID-19.

3. Exclusion criteria

Article is not full text. The study was conducted with a cohort, case control, quasi experience, protocol study and pilot study.

4. Study Variables

The independent variable is ivermectin and the dependent duration of hospitalization for COVID-19 patients.

5. Operational Definition of Variables

Ivermectin is an anti-parasitic drug used to treat infections caused by parasites such as roundworms or mites. This drug belongs to the anthelmintic group that is able to paralyze or kill worms so that they can be removed with feces. Ivermectin at least 12 mg/day is recommended especially in patients infected with COVID-19. The standard drug is a combination of lopinavir and ritonavir associated with clinical benefit. Currently, the use of lopinavir and ritonavir is still being studied regarding their effectiveness and safety in COVID-19 infection.

Length of Stay for COVID-19 Patients is a parameter that is assessed from the shorter duration of hospitalization, namely the

length of stay in the hospital, which is less than 14 days.

6. Study Instruments

The study was guided by the PRISMA flow chart and quality assessment using the Randomized Control Trial (RCT) Study Checklist published by the Center for Evidence Based Medicine (CEBM, 2018).

7. Data analysis

The data in the study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots were used to determine the size of the relationship and heterogeneity of the data. The fixed effects model was used for homogeneous data, while the random effects model was used for heterogeneous data across studies.

RESULTS

The article search process was carried out through several journal databases, including Pubmed, Scopus, Scholar, Springlink, Clinical Key, Cochrane and Science Direct. The review process for related articles can be seen in the PRISMA flowchart in figure 1. Research related to the effectiveness of ivermectin for the duration of hospitallization for COVID-19 patients consists of 9 articles from the initial search process yielding 72 articles, after the deletion process was published articles with 16 requirements for full-text review. Furthermore. A total of 9 articles that met the quality assessment were included in the quantitative synthesis using a meta-analysis.

It can be seen in Figure 2 that the research articles come from four continents, namely Asia (Iran, Bangladesh, Iraq and Malaysia), North America (Mexico), Africa (Nigeria), and Europe (Greece). Table 1, the researchers conducted an assessment of the quality of the study. After assessing the quality of the study, 9 articles were synthesized by quantitative meta-analysis using RevMan 5.3.

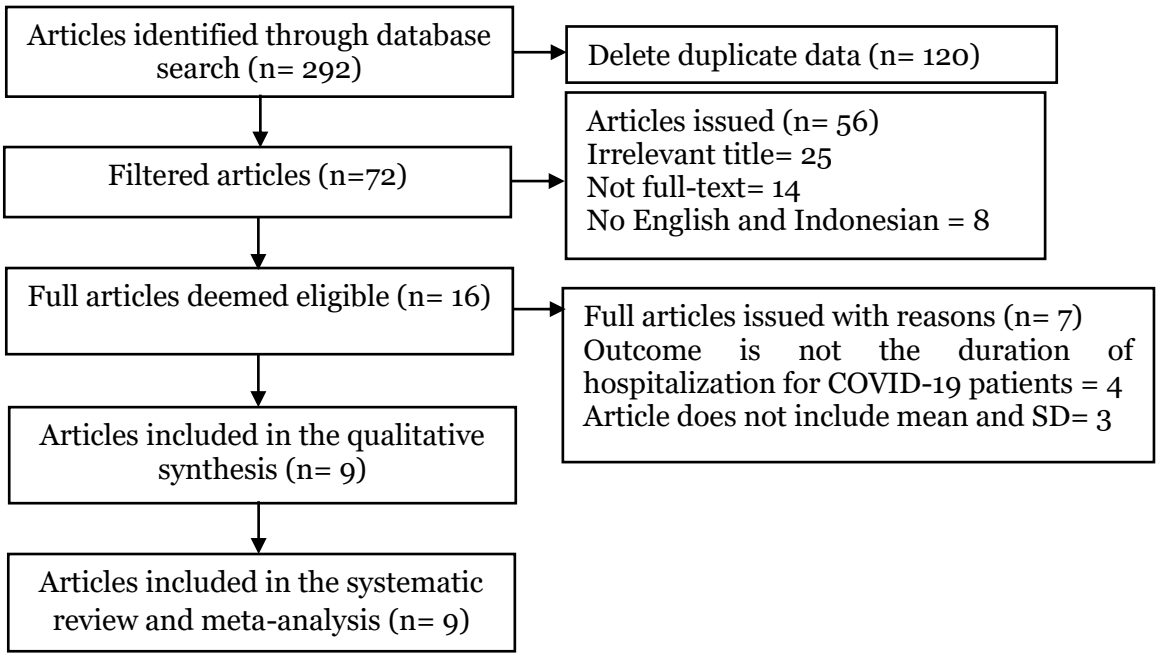

Figure 1. PRISMA flow diagram

Table 1. Description of the primary studies included in the meta-analysis of the effectiveness of Ivermectin use for the duration of hospitalization of COVID-19 patients

Author (year)	Country	Study design	Sampel	Population	Intervention	Comparison	Outcome	Ivermectin		Standard therapy	
								Mean	SD	Mean	SD
Niaee et al. (2020)	Iran	RCT	208	Mild to moderate COVID-19 patients	Ivermectin	Standard therapy	Recovery	5.25	0.73	30	0.75
Gorial et al. (2021)	Iraq	RCT	87	Mild to moderate COVID-19 patients	Ivermectin	Standard therapy	Recovery	7.62	2.75	13.22	5.90
Podder et al. (2020)	Bangladesh	RCT	62	Mild to moderate COVID-19 patients	Ivermectin	Standard therapy	Recovery	10.09	3.24	11.5	5.32
Shahbaznejad et al. (2021)	Iran	RCT	69	COVID-19 patient	Ivermectin	Standard therapy	Recovery	7.10	0.50	8.4	0.60
Beltran et al. (2021)	Mexico	RCT	141	COVID-19 patient	Ivermectin	Standard therapy	Recovery	6.75	5.19	5.25	2.20
Ahmed et al. (2021)	Bangladesh	RCT	72	COVID-19 patient	Ivermectin	Standard therapy	Recovery	9.60	4.75	9.7	4
Lim et al. (2021)	Malaysia	RCT	490	COVID-19 patient	Ivermectin	Standard therapy	Recovery	7.30	4.40	7.3	4.30
Babalola et al. (2021)	Nigeria	RCT	62	COVID-19 patient	Ivermectin	Standard therapy	Recovery	5.33	3.12	9.15	7.42
Abd-Elsalam et al. (2021)	Greece	RCT	164	COVID-19 patient	Ivermectin	Standard therapy	Recovery	8.82	4.94	10.97	5.28

Table 2. Results of Quality Assessment of RCT Studies on the Effectiveness of Ivermectin Use for Duration of Hospitalization for COVID-19 Patients

No	Questions	Publication (Authors and Year)								
		Lim et al. (2021)	Ahmed et al. (2021)	Beltran et al. (2021)	Gorial et al. (2021)	Niaee et al. (2020)	Podder et al. (2021)	Babalola et al. (2021)	Shahbazn ejad et al. (2021)	Abd El-Salam et al. (2021)
1	Does this study address a clear research focus?	2	2	2	2	2	2	2	2	2
2	Is the Randomized Controlled Trial research method appropriate to answer the research question?	2	2	2	2	2	2	2	2	2
3	Are there enough subjects in the study to establish that the findings were not coincidental?	2	1	2	1	2	1	1	1	2
4	Were the subjects randomly divided into the experimental and control groups? If not, could this be biased?	2	2	2	2	2	2	2	2	2
5	Does the study use inclusion/exclusion criteria?	2	2	2	2	2	2	2	2	2
6	Were the two groups comparable at the start of the study?	2	2	2	2	2	2	2	2	2
7	Are objective and unbiased outcome criteria used?	2	2	2	2	2	2	2	2	2
8	Is the measurement method used objective and valid to measure the results? If not, was there any blinding in the study?	2	2	2	2	2	2	2	2	2
9	Is effect size practically relevant?	2	2	2	2	2	2	2	2	2
10	Is the estimated effect correct? Is there a confidence level interval?	2	2	2	2	2	2	2	2	2
11	Are there any confounding factors that have not been taken into account?	0	0	0	0	0	0	0	0	0
12	Can the results be applied to your research?	2	2	2	2	2	2	2	2	2
	Total of Score	22	21	22	21	22	22	21	21	22

Answer 2=Yes; 1=Hesitant; 0=Can't tell

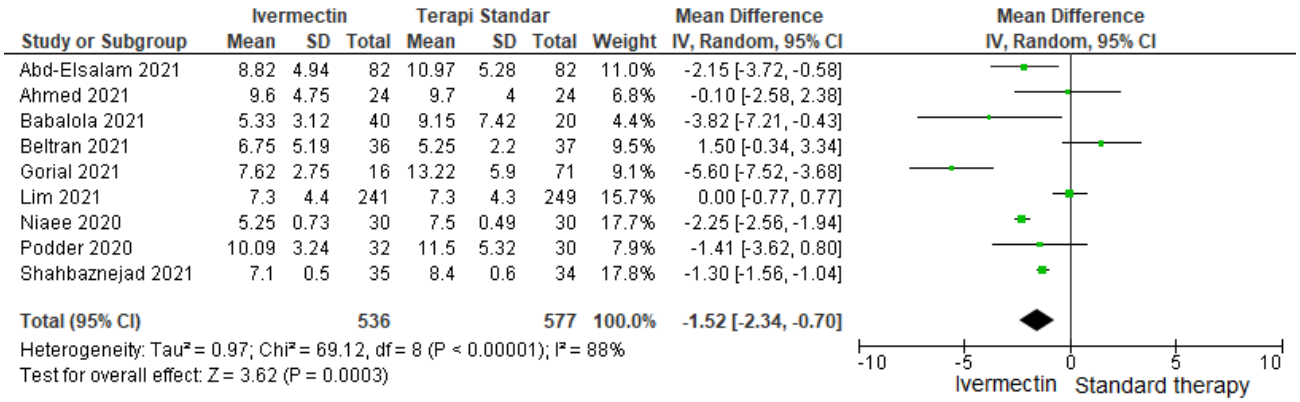

Figure 3. Forest Plot Effectiveness of Ivermectin Use on the Length of Stay in Inpatients of COVID-19

Based on the results of the forest plot in Figure 3 Ivermectin can reduce the duration of hospitalization in COVID-19 patients by 1.52 units compared to standard therapy and this result is statistically significant (SMD= -1.52; 95%CI= -2.34 to -0.70; p=0.003). The heterogeneity of the research data shows I^2= 88% so that the distribution of the data is said to be heterogeneous (random effect model).

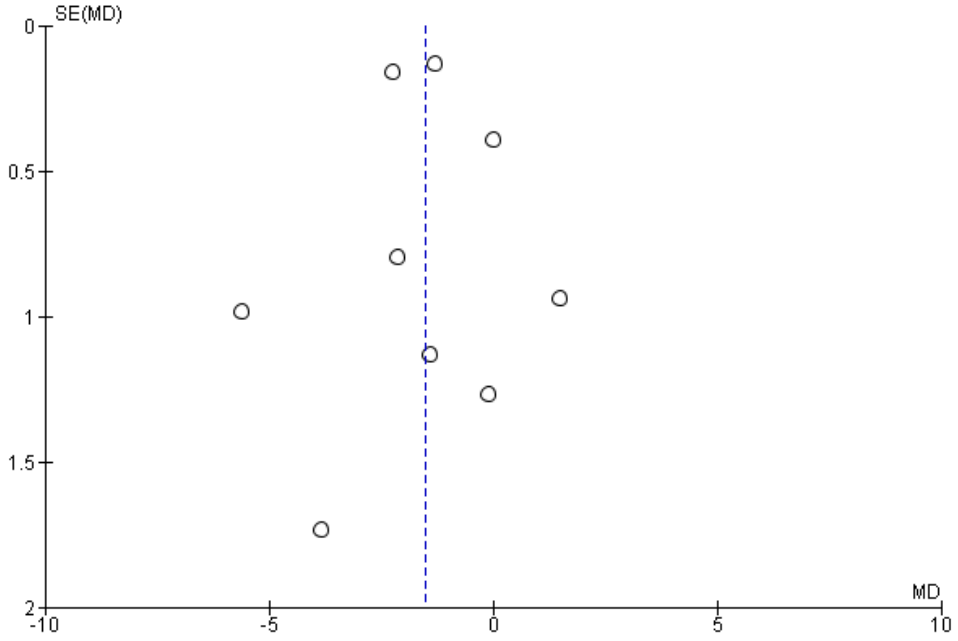

Figure 4. Funnel Plot Effectiveness of Ivermectin Use on the Length of Stay in Inpatients of COVID-19

The funnel plot in Figure 4 shows a publication bias as indicated by not symmetric distribution between the right and left plots. The right side has 5 plots and the left side has 4 plots, that overestimates the true effect of Ivermectin's effectiveness on the duration of hospitalization of patients infected with COVID-19.

DISCUSSION

In this study, there were 9 articles regarding the drug Ivermectin in the treatment of

COVID-19 which were processed using the Revman 5.3 application. The results of the forest plot of research articles with a randomized controlled trial design showed that Ivermectin provided 1.52 times of cure compared to standard therapy and was statistically significant.

Ivermectin, a parasitic agent that has been approved by the FDA, is able to prevent viral proteins from entering the nucleus of host cells. Ivermectin was also shown to accelerate viral clearance in the body compared to the placebo group and showed significant reductions in CRP and LDH levels. Patients receiving Ivermectin also showed a lower incidence of respiratory distress and a shorter duration of hospitallization. Giving Ivermectin as a COVID-19 drug is able to have a positive impact on patients both clinically and in the laboratory (Wijaya et al., 2021).

The mechanism of action of ivermectin against SARS-CoV-2 is actually not known with certainty. This effect is thought to be related to the ability of ivermectin to inhibit /β1 importin, which is a transporter that mediates viral proteins to enter and leave cells. Importin inhibition will reduce the translocation of SARS-CoV-2 nucleocapsid protein from the cytoplasm to the nucleus, thereby interfering with virus propagation (Heidary and Gharebaghi, 2020).

The mechanism is similar to the action of ivermectin in other viruses that have been studied in vitro. Ivermectin has also been reported to bind to the receptor domain that attaches to the angiotensin-converting enzyme 2 (ACE2) receptor, thereby preventing the entry of the virus into host cells (Heidary and Gharebaghi, 2020).

Caly et al. (2020) from the Royal Melbourne Hospital, Australia conducted a study on Vero/hSLAM cells infected with SARS-CoV-2. In this study, infected cells treated with 5 M ivermectin showed a 93% reduction in viral RNA within 24 hours. Within 48 hours, viral RNA reduction was up to 5000-fold without any ivermectin-induced toxicity. This study concluded that a single dose of ivermectin had antiviral properties against SARS-CoV-2 isolated in vitro (Kant et al., 2020). In this study, it was shown that the administration of Ivermectin was effective in reducing the length of stay in the hospital for patients infected with COVID-19 by 1.52 units compared to standard therapy and this result was statistically significant.

Research on the use of Ivermectin and other drugs in dealing with the COVID-19 outbreak is still ongoing. Despite the satisfactory results in several studies both in vitro and in vivo, the use of Ivermectin will continue to be studied to improve the accuracy of previous studies. The limitation of this study is language bias because in this study only articles published in English and Indonesian are used, thus ignoring articles in other languages. In this study, there are limitations in the search for articles. Not many researchers have conducted studies on ivermectin with the duration of hospitallization of COVID-19 patients.

AUTHOR CONTRIBUTION

Masromi Hendria Wijayanto is the main researcher who selects the topic, explores and collects data. Didik Tamtomo and Bhisma Murti played a role in analyzing data and reviewing research documents.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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REFERENCE

Abd-Elsalam S, Noor RA, Badawi R, Khalaf M, Esmail ES, Soliman S, Abd El Gafar MS, et al. (2021). Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study. J Med Virol. 93: 5833-5838. doi: 10.1002/jmv.27122.

Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, Phru CS, et al. (2021). A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 103: 214-216. doi: 10.1016/j.ijid.2020.11.191.

Babalola OE, Bode CO, Ajayi AA, Alakaloko FM, Akase IE, Otrofanowei E, Salu OB, et al. (2022). Ivermectin shows clinical benefits in mild to moderate COVID19: a randomized controlled double-blind, dose-response study in Lagos. QJM. 114(11): 780-788. doi: 10.1093/-qjmed/hcab035.

Beltran-Gonzalez JL, Gamez MG, Enciso EAM, Maldonado RJE, Palacios DH, Campos SD, Robles IO, et al. (2021). Efficacy and safety of ivermectin and hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. medRxiv. doi: 10.1101/-2021.02.18.21252037.

Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 178: 104787. doi: 10.10-16/j.antiviral.2020.104787.

Gorial IF, Mashhadani S, Sayaly HM, Dakhil BD, AlMashhadani MM, Aljabory AM, Abbas HM, et al. (2020). Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial). medRxiv. 7(7): 20145979.doi: doi: 10.1101/2020.07.07.20145979.

Heidary F, Gharebaghi R (2020). Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot. 73(9):593-602. doi: 10.1038/s41429-020-0336-z.

Kant S, Rastogi H, Bajpai J, Aggarwal KK (2020). Ivermectin – A potent weapon in the anti-COVID-19 armamentarium. IJCP. 31(5):413-21.

Lim SCL, Hor CP, Tay KH, Jelani AM, Tan WH, Ker HB, Chow TS, et al. (2021). Efficacy of ivermectin treatment on disease progression with mild to moderate COVID-19 and comorbidities the i-tech randomized clinical trial. JAMA Intern Med. 182(4): 426-435. doi: 10.1001/jamainternmed.2022.0189.

Niaee MS, Gheibi N, Namdar P, Allami A, Zolghadr L, Javadi A, Karampour A (2020). Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. Asian Pac J Trop Med 14:266-73. doi: 10.4103/1995-7645.-318304.

Perhimpunan Dokter Spesialis Farmakologi Klinik Indonesia (2020). Kajian Farmakoterapi Pengobatan COVID-19. Jakarta:Perdafki.

Podder CS, Chowdhury N, Sina MI, Haque WMMU (2021). Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC Journal of Medical Science. 14(2): 11–18.

Rothan HA Byrareddy SN (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity. Elsevier. 109: 102433. doi: 10.1016/-j.jaut.2020.102433.

Shahbaznejad L, Davoudi A, Eslami G, Markowitz JS, Navaeifar MR, Hosseinzadeh F, Movahedi FS, et al. (2021). Effects of ivermectin in patients with COVID- 19: A multicenter, double-blind, randomized, controlled clinical trial. Clin Ther 2021. 43(6): 1007-1019.

Weiss SR, Navas-martin S (2005). Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus. 69(4): 635–664. doi: 10.1128/MMBR.69.4.635.

Wijaya H, Saraswati NAS, Amanda DA (2021). Ivermectin dan Covid-19: Sebuah Tinjauan Literatur. Majalah Kesehatan Indonesia. 2(1): 9–15. doi: 10.47679/makein.202119.

Yuliana (2020). Corona virus diseases (Covid-19) Sebuah tinjauan literature. Wellness and Healthy Magazine. 2(1).