Abstract
The infectious disease from Coronavirus Disease 2019, or COVID-19, has quickly spread world-wide since 2019. Therapies for managing COVID-19 have yet to be confirmed as medication for the severe sickness that the disease may cause. This study aimed to review the previous research of the efficacy of trial therapy and treatment to the patients in the hospital with COVID-19. Using PRISMA guidelines as a method for conducting a systematic literature review, a total of 67 articles were collected from several online journal databases. Various therapies were found that are effective in the treatment and management of COVID-19. In accordance with the inclusion and exclusion criteria of this study, a total of 8 articles were selected. The study showed that several therapies are effective in managing the severe illness, can be used as COVID-19 treatment. Combination of medicine have shown the effectiveness of clinical improvements and recovery rate in a short time compared to single medicine. Nevertheless, further study into effective therapies for COVID-19 must be continued to find the best therapy and treatment.

Keywords: Clinical improvement, COVID-19, effective therapy, management treatment

Introduction
The emergence of the infectious disease known as Coronavirus Disease 2019 (COVID-19) began in Wuhan at the end of 2019. The causative agent of COVID-19 is the same as the virus from severe acute respiratory syndrome (SARS) disease. The first infection of SARS was found in the South China last month in 2002. The virus has spread rapidly worldwide, and was reported by the World Health Organization (WHO) in January 30, 2020. Thus far, as of June 2020 the coronavirus has affected 215 countries and territories, with over 6,190 confirmed cases, and over 376,300 deaths. In Indonesia, cases confirmed by the Ministry of Health are over 28,200 and confirmed deaths over 1,600 cases. COVID-19 is a respiratory disease which can cause fatigue, fever, dry muscle aches, coughs, shortness of breath and in some instances lead to pneumonia. The most common means of transmission occurs person to person, including amongst family members, and also from healthcare workers. There is no agreed medication to help recovery from COVID-19; the management of medication is based on each patient’s sign and symptoms. The WHO advises to apply empiric antimicrobial therapy and to implement mechanical ventilation based on the clinical diagnosis of patients. The purpose of this study was to review the previous research of the efficacy of trial therapy and treatment to the patients with COVID-19. The study emphasizes that effective therapy for COVID-19 to the patients should be able to accelerate the recovery of patients and the symptoms of COVID-19 suffered by patients are not getting worse in Indonesia.

Method
The research used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting a systematic literature review. Authors chose relevant study published from January 2020 to March 2020, by searching Pubmed, Science Direct and Google Scholar, with a total of 67 articles found. The search terms used were "Coronavirus Disease 2019", "Novel Corona Virus 2019", "The Therapy for Coronavirus Disease", "The Treatments for Severe Acute of COVID-19". Only articles written in English were considered. The study was focused on the treatment of...
SARS, virus MERS-Cov and SARS-CoV. Inclusion criteria for this study are only articles on therapy and treatment of COVID-19 given to patients in hospitals or health services. While the exclusion criteria of this study are articles on COVID-19 prevention treatments in the community. The screening was conducted by reading the title, abstract, and full text of the articles.

Eligible studies on therapies and treatment for managing COVID-19 to the patients were performed in a systematic review table. This table showed the author and year; country of publication of the trial therapy or treatment; population/data source; efficacy measure; adverse events; and lessons learned. Interpretation of the data is done by using qualitative and quantitative approach. The qualitative approach involved interpreting tables and learning the lessons, while the quantitative approach included assessing the efficiency rate of the therapy and treatment reviewed.

**Results**

A total of 67 articles were obtained from three sources (Figure 1); 16 articles from Google Scholar, 24 articles from Pubmed, and 27 articles from Science Direct. Three articles from these sources were copied articles. After screening by reading 64 abstracts, 28 articles were excluded since they discussed preventive therapy in the community, such as physical distancing, use of face masks, or the symptoms of COVID-19. After screening by reading the whole 36 articles, 28 articles were excluded since they only discussed the contain of medicines recommended for therapeutic use or treatment for COVID-19. Therefore, the included articles according to the inclusion and exclusion criteria of this study were eight quantitative studies.

Table 1 shows the systematic literature review of the efficacy of therapy for managing COVID-19, while Table 2 shows the review of the efficacy of treatment for managing COVID-19. A total of eight studies were selected for the review, showing that various therapies and interventions were effective in handling COVID-19.

Based on Table 1, a combination of medicines was better than one type of medicine. The level of clinical patient improvement on day 14 was higher in the Lopinavir (LPV) - Ritonavir (RTV) group than in the standard care group (45.5% vs 50.0%). In the study of Arbidol combined with LPV/r (Lopinavir/Ritonavir), after 14 days in 15 (94%) out of 16 patients, COVID-19 could not be detected at p-value of less than 0.05. After six days of treatment, all the six patients (100%) at the group of Hydroxychloroquine combined with Azithromycin were tested negative of COVID-19.

Table 1 also shows the evaluation of the adverse events of the reviewed studies. Study Cai, *et al.*, found Favipiravir (FPV) patients had two cases of diarrhea, one liver injury case, and one poor diet case), while study Chen, *et al.*, found that FPV increased serum uric acid (16 /116), with OR = 5.52 at p-value of less than 0.005. LPV/RTV patients had five cases of diarrhea, five vomiting cases, six nausea cases, four rash cases, three liver injury cases, and two cases of chest tightness and palpitation. Two patients in the group of Arbidol was diagnosed with leukopenia (white blood cell count < 4 x 10^9/L). In one study which combined Arbidol with LPV/r, 68.7% of patients demonstrated elevated levels of bilirubin, with a top mean of 25.26 μmol/L (10.61 μmol/L).

Not only the use of drugs, but also treatment by progressive muscle relaxation and sunbathing can also increase healing (Table 2). Progressive muscle relaxation is useful in reducing stress for COVID-19 patients, especially in hospitals.

**Discussion**

Based on the results of this study, it appears that there are drugs that can be used to cure patients of COVID-19; for example, antiviral and antimalarial medicines, such as Lopinavir/ Ritonavir, Favipiravir, Arbidol, and Hydroxychloroquine. The study results of Zhu, *et al.*, show that the side effects that need to be considered in-
Table 1. Systematic Literature Review the Efficacy Therapy for Managing COVID-19

| Author       | Year | Country | Population / Data Source | Therapy | Efficacy Measure | Adverse Event | Lesson Learn                          |
|--------------|------|---------|--------------------------|---------|------------------|---------------|---------------------------------------|
| Cao et al., 15 | 2020 | China   | When adult patients have under treatment of COVID-19: RTV and LPV with standard care group 99 patients. Only standard care 100 patients. | Lopinavir (LPV) – Ritonavir (RTV) versus standard care | Clinical improvement at day 14: The LPV and RTV are 45.5 % and standard care only are 30%. | Lopinavir/Ritonavir: four serious gastrointestinal. Standard care: respiratory failure, acute kidney injury, and secondary infection common in the Diagnosed with leukopenia: Lopinavir/Ritonavir group: 1 patient; Arbidol group: 2 patients | Lopinavir-Ritonavir treatment more effective beyond standard care only. |
| Zhu, et al., 16 | 2020 | China   | After laboratory checked, 50 patients confirmed with COVID-19. They are divided into two groups: including lopinavir/ritonavir group (34 cases) and Arbidol group (16 cases). | Arbidol monotherapy versus Lopinavir/ Ritonavir | On day 14, viral load Arbidol group was detectable in all the patient. Lopinavir / Ritonavir was found in 44.1% | FPV patients had (2 diarrhea, 1 liver injury, 1 poor diet). LPV/RTV patients had (5 diarrhea, 5 vomiting, 6 nausea, 4 rashes, 3 liver injury, 2 chest tightness and palpitation). | Arbidol monotherapy more effective than Lopinavir |
| Cai, et al., 17 | 2020 | China   | Patients of COVID-19 were screened in The Third People’s Hospital on Shenzhen. FPV (35 Patients), LPV/RTV (45 patients) | Favipiravir (FPV), versus Lopinavir (LPV)-Ritonavir (RTV) | Viral clearance and chest imaging rate: FPV (4 day, 91.43 %), LPV/RTV (11 day, 62.22%) | FPV patients had (2 diarrhea, 1 liver injury, 1 poor diet). LPV/RTV patients had (5 diarrhea, 5 vomiting, 6 nausea, 4 rashes, 3 liver injury, 2 chest tightness and palpitation). | FPV more effective treatment for SARS-Cov-2 patients during the growth and settlement of viral virus. |
| Gautret, et al., 18 | 2020 | France  | The population located in Marseille at the University Hospital. Hydroxychloroquine group (14 patients), Hydroxychloroquine with Azithromycin (6 patients), control patients (16). | Hydroxychloroquine only versus combined with Azithromycin | After 6 day of inclusion, a number of negative patients: Hydroxychloroquine with Azithromycin (6/6 patients, 100%) Hydroxychloroquine only (3/13 patients, 23.1%), control patients (2/16 patients, 12.5%). | Potential risk has not been established yet | Hydroxychloroquine treatment is significantly associated with the reduction of the virus disappearance and Azithromycin reinforced its effect. |
| Deng, et al., 19 | 2020 | China   | Included adults (age ≥ 18 years old) with laboratory-confirmed COVID-19 without invasive ventilation and patient were given oral Arbidol and LPV/r in the combination group and oral LPV/r only in the monotherapy group. | Arbidol combined with LPV/r versus LPV/r alone | After 14 days, the SARS-Cov-2 was not detected in therapy using Arbidol combined with LPV/r in more than 94% patients. While Arbidol monotherapy only worked in 52.9% patients. Improving the chest CT scans. 11(69%) of 16 patients in the combination group after seven days, compared with 5 (29%) of 17 in the Monotherapy group. | The proportion of patients who demonstrated elevated levels of bilirubin were 68.7%, with a top mean bilirubin was 25.26 μmol/L. 43.7% of patients demonstrated digestive upsets, such as mild diarrhea and nausea, but all patients had no premature discontinuation secondary to adverse effects. | The apparent favorable clinical response with Arbidol and LPV/r supports further LPV/r only. |
| Chen, et al., 20 | 2020 | China   | An entire data of 240 patients with COVID-19 pneumonia were hired from the three hospitals (120 from Zhongnan Hospital of Wuhan University (ZNUW), 88 from Leishenshan Hospital (LSH), and 32 from The Third People’s Hospital of Hubei Province (HBTH) | Favipiravir against Arbidol | After 7 days of the clinical recovery rate of Favipiravir group 71 from 116 patients, the Arbidol group only 62 from 120. Favipiravir controlled to petile latent to relief for two of pyrexia and cough. | The highest frequently observed Favipiravir - coalition adverse event was elevated serum uric acid (16/116). | Favipiravir equaled to Arbidol, did not importantly to improve the medical recovery rate on day 7. Favipiravir importantly recover the latency to respite for pyrexia and cough. |

clude two patients who had leucopenia when using Arbidol. Another effect found in the study by Cai, et al., 17 was that using FPV that can cause diarrhea and liver injury. The advice to medical personnel in Indonesia is that they should also pay attention to these side effects if some of these therapies will be prescribed to patients
Table 2. Systematic Literature Review the Efficacy Treatment for Managing COVID-19

| Author          | Year | Country | Population / Data Source                                      | Therapy                        | Efficacy Measure                                                                 | Adverse Event | Lesson Learn                  |
|-----------------|------|---------|----------------------------------------------------------------|-------------------------------|----------------------------------------------------------------------------------|---------------|-------------------------------|
| Liu, et al.     | 2020 | China   | 51 patients from Hainan General Hospital, China                | Progressive muscle relaxation  | The anxiety (STAI) score after a 5-day intervention was significant (p-value < 0.001). | No adverse event was found in this study. | Progressive muscle relaxation can reduce anxiety and improve sleep quality in patients with COVID-19. |
| Asyary, et al.  | 2020 | Indonesia | 8% of hospitals are available to care for COVID-19 patients, being emergency hospitals in Jakarta. | Exposed directly to sunlight   | After daily sunlight exposure for a minimum of 3 hours, deaths due to COVID-19 decreased. | No adverse event was found in this study. | Direct exposure to sunlight was connected significantly to recovery from COVID-19 among patients in Jakarta, Indonesia. |

Notes: STAI: The Spielberger State-Trait Anxiety Scale; SRSS: Sleep State Self-Rating Scale

of COVID-19.

The results of this study show that a combination of drugs works better. In the research conducted by Deng, et al.,19 it was shown that the combination of Arbidol and Lopinavir/Ritonavir could accelerate healing for patients of COVID-19. On the 14th day of treatment, 94% of patients receiving combination therapy showed negative signs of the SARS COV 2 virus. In research Gautret, et al.,18 also combined Hydroxychloroquine with Azithromycin in their study. On day 6 post-inclusion, the number of negative patients was 6/6, 100%. The study by Cao, et al.,15 which combined Lopinavir and Ritonavir showed an improvement in the patient’s health condition at 45.5% on day 14. The effects that need attention are serious gastrointestinal adverse events with Lopinavir and Ritonavir, elevated levels of bilirubin, and digestive upsets, such as mild diarrhea and nausea in combined Arbidol with Lopinavir/Ritonavir therapy.

Apparently, progressive muscle relaxation can help reduce stress for COVID-19 patients. Based on medical diagnosis, some coronavirus disease patients have sleep disturbance and anxiety after isolation therapy. Anxiety due to psychological stress could become a trigger of decreased immunity and physiological disorders.23 Progressive muscle relaxation (PMR) training reduced the effect of anxiety on the patients, which might happen due to the balance between the hypothalamic nucleus and anterior. By reducing the activity of the sympathetic nervous system, stress and anxiety can be prevented, and physical and mental relaxation can be increased.24 Sunlight can also be applied to increase healing in patients COVID-19 as triggers the production of vitamin D, which strengthens the immune system.25

Recently, to help progress in the study of the effectiveness of several therapies, WHO developed the solidarity clinical trial project for COVID-19 treatments.26 The project aims to obtain strong and valid clinical evidence for four potential therapies that have been tried. In March 2020, the government of Indonesia joined the trial.

In Indonesia, there is some development of pharmaceutical drug research in herbal trials. Universitas Indonesia and the IPB University (Institut Pertanian Bogor) research teams are also developing this line of study with regard to antibodies and antivirals accessed from guava, moringa leaves, and orange peel. These compositions include hesperidin, rhamnetin, kaempferol, quercetin, and myricetin from the mixture of guava (pink fruit skin), orange peel, and moringa leaves.27 The study discusses research against the protein, and gathering herbs related to the work of the virus, obtained several related groups to prevent the SARS-CoV-2 virus (corona-virus).27

The limitation of this study is to limit studies that have been reviewed because there are still many trial therapy studies that are being conducted in several other countries. This study also did not involve an additional population variation, such as pregnant mothers and children, so the efficacy and occurrence of adverse events for pregnant women and children could not have been explored more in this study.

Conclusion

Several studies have shown the effectiveness of several trial therapies and treatment for COVID-19. These used a single drug or a combination of drugs, mostly from the antiviral class. Progressive muscle relaxation and sun-bathing treatment can also improve the healing process. Medical personnel is expected to implement the results of this study to COVID-19 patients in Indonesia. Nevertheless, research about the effective therapies for COVID-19 must be continued to find the best therapy and treatment. Future studies on the treatment of COVID-19 could be related to varying ages and condi-
tions, such as pregnant women and children.

Abbreviations
COVID-19: Coronavirus disease 2019; SARS: Severe Acute Respiratory Syndrome; WHO: World Health Organization; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; LPV: Lopinavir; RTV: Ritonavir; LPV/r: Lopinavir/Ritonavir; FPV: Favipiravir; ZNWU: Zhongnan Hospital of Wuhan University; LSS: Leishenshan Hospital; HBTH: The Third People’s Hospital of Hubei Province; STAI: The Spielberger State-Trait Anxiety Scale; SRSS: Sleep State Self-Rating Scale; PMR: Progressive Muscle Relaxation.

Ethics Approval and Consent to Participate
Not Applicable

Competing Interest
The authors declare that they have no competing financial interest.

Availability of Data and Materials
The authors confirm that the data supporting the findings of this study are available within the article.

Authors’ Contribution
Halma Zahro Mukhilda, Hilma Hasro Maulida, Gunanti Khairunnisa, Margarethha Josephine Mantrono, Rindu, Eka R W Purnamasari, and Risky Fajar Meirawan created the manuscript. Halma Zahro Mukhilda, Hilma Hasro Maulida, Gunanti Khairunnisa, and Margarethha Josephine Mantrono collected the literature data. Rindu, Eka R W Purnamasari, and Risky Fajar Meirawan reviewed and revised the Manuscript. Risky Kusuma Hartono supervised and discussed the final result.

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