

# THE EFFECT OF ADJUVANT THERAPY WITH POLYHERBAL FORMULAS ON IMPROVING THE mMRC SCORE OF PATIENTS WITH MODERATE- GRADE SARS COV-2 PNEUMONIA

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**Keywords:**

COVID 19, *Channa striata*,  
*Curcuma xanthorrhiza*,  
*Moringa oleifera*

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**ABSTRACT**

Natural Medicines with anti-inflammatory and anti-oxidant potentials act as adjuvant therapy to increase the effectiveness of standard COVID-19 treatment. The combination of *Channa striata*, *Curcuma xanthorrhiza*, and *Moringa oleifera* (Onoiwa Mx) administration can complement the treatment of COVID-19 as adjuvant therapy, especially for patients with mild and moderate pneumonia. Therefore, this study aims to assess the combined administration of *Channa striata*, *Curcuma xanthoria*, and *Moringa Oliefera* extracts as adjuvant therapy in standard COVID-19 treatment. The benefits and efficacy to improve the C reactive protein value, length of stay, and better scoring of the shortness scale were provided, and clinical observation was conducted with a prospective cohort study design. Furthermore, the subjects were patients with probable/positive PCR confirmation with moderate COVID-19 pneumonia after fulfilling the inclusion criteria. A total of 48 subjects were obtained and divided into control and treatment groups of 24 patients each. Three variables were analyzed bivariate, namely the LOS, MMRC, and CRP. The results showed that males (62.5%) had the most characteristic of the sample characteristics with an average age of 50.-54 years old, accompanied by symptoms of cough (91.7%), fever (77.1%), and shortness of breath (75%). Furthermore, the most common comorbid disease of the two groups was hypertension (47.9%). In conclusion, each fever symptom in the treatment group had a median of 3, which means, 50% recovered after experiencing fever symptoms for 3 days. Meanwhile, the control group had a median of 4, which means, 50% recovered after experiencing fever symptoms for 4 days. Shortness of breath and cough each had a median of 4, which means 50% recovered after 4 days of symptoms. Therefore, the improvement in fever is consistent with that of CRP value, which increases the lymphocyte in the treatment group.

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## 1. INTRODUCTION

COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was previously unidentified in humans. There are at least two types of coronavirus known to cause disease with severe symptoms, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Common signs and symptoms of COVID-19 infection include acute respiratory disorders such as fever, cough, and shortness of breath. Furthermore, the average and the longest incubation period is 5-6 and 14 days respectively [1]. In severe cases, it can cause pneumonia, acute respiratory syndrome, respiratory failure, and even death. The increase in COVID-19 cases was quite fast and has spread to different countries in a short time. In July 9, 2020, WHO reported 11,84,226 confirmed cases with 545,481 deaths worldwide (Case Fatality Rate/CFR 4.6%). Meanwhile, Indonesia reported its first case on March 2, 2020, then it increased and spread rapidly throughout the country. On July 9, 2020, the Ministry of Health reported 70,736 confirmed cases with 3,417 deaths (CFR 4.8%) [2]. The COVID-19 situation at the global and national levels is still at very high risk. The world faces the reality of preparing to coexist with COVID-19 while vaccine development is still ongoing. Currently, the treatment management regarding the agreement reference from each professional organization depends on the empirical therapy in several countries and clinical trials recorded at the World Health Organization (WHO) such as recovery and solidarity. In a meta-analysis study, the combination of natural and modern medicine results in better efficacy and safety in management [3]. WHO and the Indonesian Ministry of Health through the Ministry of Health Regulation Number 413 of 2020 strongly support scientific study on Natural Medicines (OBA) to support the current management of COVID 19 treatment [4]. Furthermore, ONOIWA MX, which contains *Chana striata*, *Moringa oleifera*, and *Curcuma xanthorrhiza* extracts are prepared in oral liquid dosage from blueberry flavor and can be used as a therapeutic supplement in COVID-19 patients. This study aims to add data on the use of Onoiwa Mx as an adjuvant of Covid-19 therapy to improve the mMRC scoring of patients with moderate-grade SARS Cov-2 pneumonia.

## 2. METHODS

This is a clinical controlled single-blind parallel study conducted during the COVID- 19 pandemics on patients with symptoms. They were follow-up for 7 days after the last dose of Onoiwa MX, and a total of 48 patients were COVID-19 positive.

## 3. STUDY DESIGN

The inclusion criteria include patients confirmed to have COVID-19 through positive PCR, aged 18–60 years, no comorbid factors, not pregnant/breastfeeding, patients with compos mentis awareness/no loss of consciousness, willingness to take part in the study after signing the informed consent, not hypersensitive, and do not have a history of allergies to certain drugs, ingredients or food. In contrast, the exclusion criteria include patients with other pulmonary infections such as tuberculosis, bacterial pneumonia, as well as pregnant/lactating women, hypersensitivity to certain drugs, substances, or food, decreased consciousness or mental disorders, and under 18 or over 60 years. Based on the inclusion and exclusion criteria, a total of 48 patients were recruited and divided into control and treatment groups. In the treatment group, 24 patients were given 2x200mg of hydroxychloroquine, 1x500mg injection of azithromycin, 2x75mg of oseltamivir, and 750 mg of Levofloxacin + Onoiwa MX 3 times a day, 1 sachet for 7 days. In the control group, 24 patients were given 2x200mg hydroxychloroquine, 1x500mg azithromycin, 2x75mg oseltamivir, and 750mg Levofloxacin injection + control for 7 days. Furthermore, the patients were subjected to clinical and vital signs examinations daily.

### 3.1 Consent and ethical approval

This study was approved by the Institutional Ethics Committee and registered prospectively at Sentra Medika Hospital (001/Suket/KEPK/III/2021). The patients were recruited based on the inclusion and exclusion criteria after the eligible patients submitted a written informed consent.

## 4. RESULTS AND DISCUSSION

### 4.1 Demographic Characteristics.

The mean age for the intervention group was 50,2914.39 years and the age limit was between 18 and 79 years. In the treatment group, 4 people were 40 years old, 16 were 40-60 years old and 4 were 61-79 years old. In the control group, 6 people were 40 years old, 15 were 40-60 years old and 3 were 61-79 years old (Table 1).

**Table 1.** Demographic characteristics of the patients on presentation

Characteristic	Treatment Group (n=24)	control Group (n=24)
<b>Age (range), y</b>	18-79	18-78
<b>Gender</b>		
Male	13	17
female	11	7
<b>Chronic medical illness</b>		
Diabetes	5/24 (20,8%)	9/24 (37,5%)
Acute Kidney Injury	1/24 (4,2%)	2/24 (8,3%)
Heart Failure	4/24 (16,7%)	2/24 (8,3%)
Coronary Artery Disease	2/24 (12,5%)	4/24 (16,7%)
Asthma	0	2/24 (8,3%)
COPD	2/24 (8,3%)	2/24 (8,3%)
Hypertension	10/24 (41,7%)	13/24 (54,2%)
<b>Symptoms</b>		
Fever	18/24 (75%)	19/24 (79,2%)
Cough	21/24 (87,5%)	23/24 (95,8%)
Anosmia	3/24 (12,5%)	1/24 (4,2%)
Nausea	17/24 (70,8%)	13/24 (54,2%)
Rhinorrhea	7/24 (29,2%)	1/24 (4,2%)
Chest pain	6/24 (25%)	5/24 (20,8%)

Most of the patients showed the first symptom of dry cough (95.8%), followed by difficulty in breathing (75%), fever (79%), anosmia (12.5%), Other symptoms, including rhinorrhea and chest pain, were rare (4.8%). For the duration of prehospital pain, the intervention and control groups had an average of 4,631.83

and 5,422.32 days. Furthermore, the need for oxygen during treatment in the intervention and control group had an average oxygen level of 8,884.68 and 7,334.08 lpm. Oxygen is needed when treating moderate COVID 19 pneumonia even though the criteria has an oxygen saturation above 93% during diagnosis. Moreover, knowing the prehospital time is to ensure that the patient has experienced the viremia or the acute phase, which is approximately 7 days before the pulmonary phase as seen from the radiological assessment.

#### 4.2 Laboratory Examinations.

Table 2 showed the laboratory results with the most significant changes between before and after treatment, namely lymphocytes, platelets, ESR, D dimer, and urea levels. The treatment group had an average lymphocyte count before treatment of 16.95 to 21.21 after the use of Onoiwa Mx.

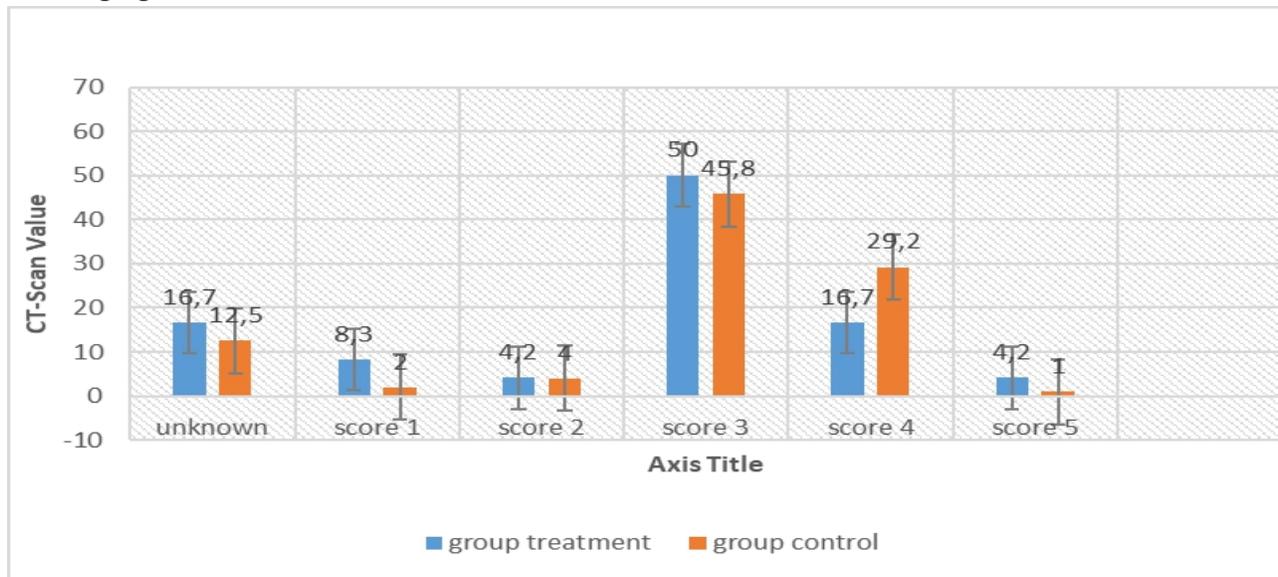
**Table 2.** Laboratory test before and after Onoiwa Mx

Laboratory test	Treatment Group		Control Group	
	before	after	before	after
Leucocytes	10,97 (9,93-11,04)	11,09(10,90-11,08)	8,93(8,90-8,95)	9,31(9,30-9,34)
HB (g/dl)	13,82 (13,45-14,06)	13,13(12,98-13,12)	13,74(12,90-13,76)	13,15(12,90-13,20)
Hematocrit %	39,95 (38,75-40,23)	38,20(37,90-38,05)	40,33(39,90-40,45)	38,75(37,90-38,75)
Platelets	314,83(312,56-315,45)	364,37(363,50-364,12)	295,25(294,50-295,30)	362,87(361,34-362,1)
LED	32,45 (32,30-33,56)	27,21(26,50-27,30)	36,95(35,90-37,20)	44,17(43,24-45,34)
Lymphocytes	16,95(16,86-17,56)	21,21(21,20-22,05)	18,37(17,90-18,38)	18,92(17,80-19,02)
ALC	1,48 (0,98-1,56)	1,76(0,98-1,79)	1,51(0,95-1,56)	1,54(0,98-1,78)
NLR	6,26 (5,68-6,45)	7,69(6,90-7,89)	4,96(3,98-4,98)	5,47(4,98-5,80)
D-Dimer	1131,39 (1130,45-1132,50)	412,60(411,45-412,60)	732,52(731,50-732,50)	379,56(378,78-379,1)
Ureum	40,02(39,90-40,04)	44,0(43,89-44,0)	47,62(47,50-47,90)	31,86(30,76-33,24)
Creatinine	1,09(0,98-1,19)	1,22(1,15-1,23)	2,12(1,90-2,26)	1,05(0,98-1,10)
SGOT	28,27(27,50-28,90)	34,25(33,20-34,26)	55,22(55,20-56,30)	52,33(51,90-53,67)
SGPT	52,77(51,50-52,80)	30,08 □ 8,53(29,89-30,09)	53,78(52,45-53,90)	55,67(54,23-56,76)

Meanwhile, the control group had an average lymphocyte count before treatment of 18.37 to 18.92 after treatment. Furthermore, there was an increase in the lymphocyte value of the treatment group which was a positive assessment towards the improvement response of the COVID-19 patients' immune system. The albumin in *C. striata* prevents hypoalbuminemia, which is important in the treatment process, also improves lymphopenia which correlates with a high risk of death in patients with severe COVID-19. Also, it prevents the systemic inflammatory process which results in increased capillary permeability, and the release of serum albumin into the interstitial space [5]. The average LED treatment group before and after treatment was 32.45 to 27.21. Meanwhile, the control group has an average LED of 36.95 and later became 44.17. After the treatment, there was an increase and decrease in the control and experimental group respectively. Onoiwa Mx contains extracts of *C. striata*, *C. xanthorrhizae*, and *M. oleifera*, and the combination has anti-inflammatory, anti-microbial, antioxidant, and anti-viral effects. For the D dimer variable, the normal D

value was 500, and the treatment group had an average D dimer of 1131.39 and 412.60 before and after treatment. Meanwhile, the control group had an average D dimer of 732.51 to 379.56 after treatment. The difference from the large and significant decrease in the D dimer value was in the treatment group, and the decrease was influenced by the role of albumin in inhibiting thrombus formation, anti-thrombosis, and as an antioxidant. It is known that hypercoagulability due to an excessive body inflammatory response or cytokine storm is a worsening of the Covid disease degree. This can be prevented by maintaining albumin stability and thrombus formation in blood vessels, as well as preventing vasculitis and injury to other organs. SGPT values in the control and treatment groups increased by 53.78 and 52.77 at the beginning of treatment due to liver injury in Covid infection. This caused nausea and reduced appetite at the beginning of hospitalization. There was no improvement in ALT in the control group with a value of 55.67 after being given treatment. In contrast, there was an improvement in the intervention group with a value of 30.08. This is because *Moringa oleifera* performs a hepatoprotective function by inhibiting TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 can repair injury to the liver caused by COVID-19. Furthermore, curcumin stimulates liver cells to make bile, prevents hepatitis and liver disease, lowers blood levels SGOT and SGPT, and acts as antihepatotoxic. It increases appetite and stimulates pancreatic function as well as the body's metabolic hormone system and physiology.

### 4.3 Imaging Features

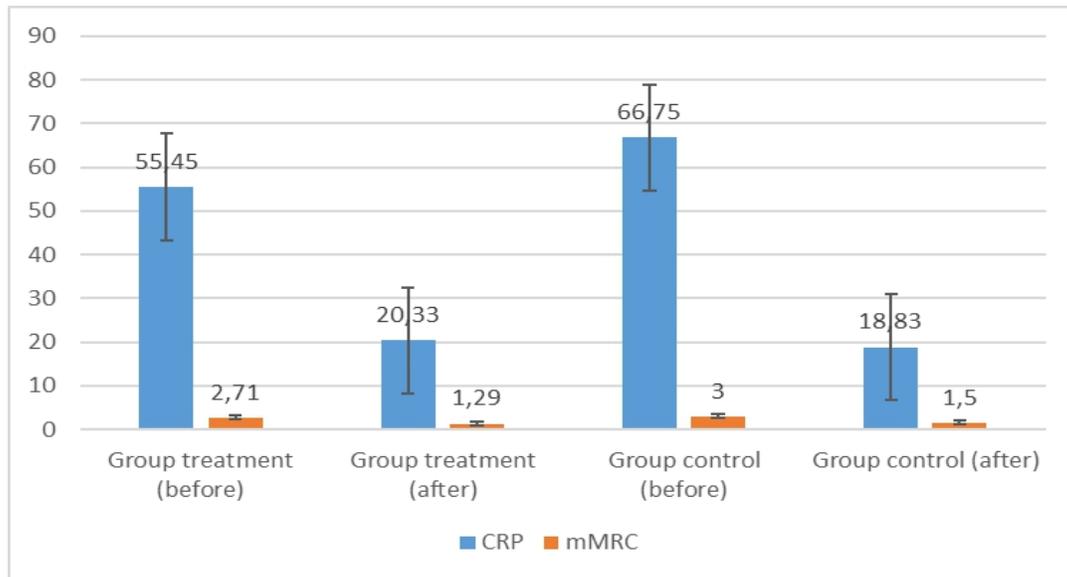


**Figure 1** Patients had a CT scan

Figure 1 showed that in the treatment group, the majority of patients had a CT scan value of 3 (26-50%) by 50.0%. Meanwhile, in the control group, the majority had a CT scan value of 3 (26-50%) by 45.8%. It can be said that most of the patients had CT scan values of 3 (47.9) and 4 (22.9%). Furthermore, there were 14.6% of patients with an unknown CT scan value of 50.0%. In the control group, the majority of patients had a CT scan score of 3 (25 – 50%) which was 45.8%. The extent of the GGO lung lesion infiltrate was assessed, where the higher the score, the more severe the degree of COVID cases and abnormalities in laboratory results. This explained that the area of pneumonia in the intervention group caused a longer LOS than the placebo group. Based on this study, knowledge about the large area of pneumonia lesions will be useful in determining the speed of service and treatment to prevent the worsening of its severity.

The severity of the CT score corresponds to a high CRP and a decreased Lymphocyte value. The intervention group had a CT score of 3 which was higher than the placebo. The mean difference in

lymphocyte means value in the intervention group increased after treatment from 16.95 to 21.21 when compared to that of placebo which only increased to 18.92 from 18.37. Furthermore, the large increase in the lymphocyte value difference in the intervention group with a higher CT score of 3 causes the effectiveness of Onoiwa MX adjuvant therapy containing a combination of *Channa striata*, *Curcuma xanthorrhiza*, and *Moringa oleifera*.



**Figure 2.** The Average CRP

Figure 2 showed that in the treatment group, the average CRP was 55.45 before treatment and became 20.33 after. The results of statistical tests using the Wilcoxon test showed a p-value of 0.008, at  $\alpha$  5% p-value  $<0.05$ , meaning that there was a significant difference in the CRP value in the treatment group between before and after treatment. In the control group, the average CRP was 66.75 and became 18.83 after treatment. Meanwhile, the results of statistical tests using the dependent T-test showed a p-value of 0.001, at  $\alpha$  5% p-value  $<0.05$ , meaning that there was a significant difference in the CRP value in the control group between before and after treatment. Furthermore, the inflammatory process in Covid infection is influenced by insulin-like growth factor 1 (IGF-1) and oxidative stress [6]. The IGF-1 pathway can regulate the immune response through the interaction of cytokines (interferons) and immune cells such as T lymphocytes, macrophages, and bone marrow. Also, high concentrations of IGF-1 are associated with a low risk of death from Covid, and the role of snakehead fish albumin extract can regulate the inflammatory process or cytokine storms that can cause immune response failure and increase the risk of death [7]. The treatment group given Onoiwa Mx containing curcumin has a mechanism of inhibiting inflammatory cytokines by blocking important signals that regulate the expression of pro-inflammatory cytokines including the factor- $\kappa$ B pathway and nuclear MAPK [8]. Furthermore, it has anti-inflammatory and antifibrotic effects by reducing the expression of important chemokines and cytokines involved in lung infections such as IFN MC, MCP-1, IL-6, and IL-10. [9]. Preclinical assay of Curcumin inhibits inflammatory response cells by attenuating cytokine/chemokine expression through the NF- $\kappa$ B pathway and fibrotic response during the regeneration phase of the disease through attenuation of the TGF- $\beta$  pathway in a virus-induced ARDS mouse model.

For the MMRC variable, the treatment and control group had an average MMRC of 2.71 and 3.00 respectively. The results of the statistical test with Mann Whitney showed a p-value of 0.088, at  $\alpha$  5% p-value  $>0.05$ , meaning that there was no significant difference in the MMRC value before treatment between

the two groups. Meanwhile, the treatment and control group has an average MMRC of 1.29 and 1.50 in the post-treatment condition. The results of statistical tests with Mann Whitney showed a p-value of 0.199, at  $\alpha$  5%  $p\text{-value} > 0.05$ , meaning that there was no significant difference in the MMRC value after treatment between the intervention and the placebo group. In the Wilcoxon test, it was found that there was a significant difference in MMRC values in the two groups (intervention and placebo) between before and after the intervention. This is due to the Onoiwa Mx sachets containing extracts of *C. striata*, *C. xanthorrhizae*, and *M. oleifera* phytochemicals that improve function. Furthermore, the albumin extract of *C. striata* can downregulate the expression of ACE2 receptors to increase the arterial partial pressure ratio of oxygen/fraction of inspired oxygen (ratio PaO<sub>2</sub>/FiO<sub>2</sub>) in patients with acute respiratory distress syndrome due to Covid for seven days [10]. The administration of albumin can also improve vascular osmotic blood pressure in patients with pneumonia due to COVID 19. Therefore, there is no seepage of fluid through the blood vessels which can cause pulmonary edema. Albumin can also significantly prevent pulmonary capillary endothelial leakage and alveolar damage in the hyperinflammatory secondary phase to cytokine storm [5]. Curcumin prophylaxis can reduce the inflammatory process by preventing the entry of fluid into the lungs of rats under hypoxic conditions. Furthermore, it causes downregulation of angiogenic molecules such as VEGF followed by reduction of pulmonary edema and albumin extravasation in rat bronchoalveolar lavage fluid [11].

## 5. CONCLUSION

Adjuvant therapy with polyherbal formula (Onoiwa Mx) caused an improvement in the mMRC score of patients with moderate to 2-degree SARS Cov pneumonia. This was evident from the decrease in the mMRC score.

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