THE EFFECTIVENESS OF POLY-HERBAL AS ADJUVANTS FOR THE STANDARD TREATMENT OF COVID 19 IN PATIENTS WITH MODERATE DEGREE OF SARS COV2 BASED ON CLINICAL AND LABORATORY SYMPTOMS

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Abstract
This study aims to examine the effectiveness of polyherbal (ONOIWA MX) capsules containing 5100mg Channa striata extract, Curcuma xanthorriza 240mg and Moringa oleifera 240mg as adjuvants for standard treatment of Covid 19 in the management of moderate pneumonia.

Method
This is a clinical randomized controlled single blind parallel study conducted during the COVID-19 pandemic on patients having symptoms as well as positive cases, meanwhile, patients were follow-up for 7 days after the last dose of Onoiwa MX. A total of 48 patients were COVID-19 positive and divided into 2 groups namely group I (n = 24) given standard therapy 2x200mg hydrochloroquine, 1x 500mg azithromycin injection, 2x75mg oseltamivir as well as 750mg Levofloxacin injection and Onoiwa MX 3x1 sachet for 7 days. Meanwhile, patients in the second group were given 2x200mg hydrochloroquin, 1x500mg azithromycin, 2x75mg oseltamivir as well as 750mg Levofloxacin injection + C.striata sachet 3 times a day for 7 days. Furthermore, a clinical and vital signs examinations were carried out on the patient daily.

CONCLUSION
The administration of ONOIWA MX sachet as an adjuvant therapy for standard COVID-19 treatment reduce parameters such as D-dimer, CRP and clinical symptoms.

Keywords: ONOIWA MX sachet, COVID-19

Introduction
Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It is a new type of Coronavirus that has never been previously identified in humans. At least two types are known to cause diseases resulting in severe symptoms such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The common signs and symptoms of COVID-19 infection
include acute respiratory problems such as fever, cough and shortness of breath. Furthermore, the mean incubation period was 5-6 days with the longest incubation period being 14 days\textsuperscript{[1,2]}. Severe cases of COVID-19 cause pneumonia, acute respiratory syndrome, kidney failure, and even death\textsuperscript{[2,4]}. Based on data from countries affected by the initial pandemic, 40% of cases experience mild and moderate diseases such as pneumonia respectively, 15% experience serious illness, while 5% experience critical condition. Patients with mild symptoms recovered after 1 week, meanwhile, there were no signs of viral pneumonia or hypoxemia in mild cases based on the criteria for severe cases in adults, while in moderate cases, clinical manifestations of pneumonia were found with symptoms of fever, cough, shortness of breath and rapid breathing with oxygen saturation above 90 mmHg, but no symptoms of severe pneumonia were found. Moreover, in severe cases, saturation decreased below 90 mmHg with symptoms of pneumonia, namely fever, cough, shortness of breath and rapid breathing\textsuperscript{[2,6,7]}. In critical cases, Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock, multi-organ failure, including kidney or acute heart failure are found which ultimately result to death. Meanwhile, COVID-19 severely attacks patients with comorbid factors such as metabolic syndrome, kidney and heart failure, as well as other secondary infections such as Human Immunodeficiency Virus (HIV), tuberculosis and non-COVID-19 pneumonia\textsuperscript{[3,5]}. The WHO has highlighted the appropriate use of natural products as a prime candidate to explore bioactive Moringa oliefera in anti-viral research. This is because there is no effective vaccine and the supply of expensive drugs is insufficient for socio-economic demands\textsuperscript{[9,10]}. Therefore, the problem examined in this study is the role of natural medicines with various properties as adjuvant therapy in the management of COVID19. Patient recovery is very important while treatment is very dependent on the body's immune response and the speed of health workers in handling acute cases or emergencies\textsuperscript{[8]}. This study aims to examine the combination of Channa striata, Curcuma xanthoria and Moringa oliefera, each with properties expected to provide better improvement in the standard treatment of COVID-19 patients. The combination has several properties including immunostimulants, anti-inflammatory, antimicrobial, anti-viral, anti-oxidant and also function as a hepatoprotector, preventing hypoalbunemia and dyslipidemia in metabolic syndrome\textsuperscript{[9]}. 

**Methods**

**Study design**

This is a clinical randomized controlled single blind parallel study conducted during the COVID-19 pandemic on patients having symptoms and as well as positive cases. Patients were follow-up for 7 days after last dose of Onoiwa MX. A total of 48 patients were COVID-19 positive\textsuperscript{[13,15]}.

**Study population**

The inclusion criteria for the sample 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, willing 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, patients with 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 2 groups:

Group I (Intervention) : 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.

Group II (control) : 24 patients were given 2x200mg hydroxychloroquine, 1x500mg azithromycin, 2x75mg oseltamivir, and 750mg Levofloxacin injection + control for 7 days. The patients were subjected to clinical and vital signs examinations daily.

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.

Intervention
This study used the standard therapy for COVID-19 patients as follow:

Onoiwa MX produced by PT Nuswantara Nirmala Nusantara, Bintaro, Indonesia. Each capsule contains *Channa striata* extract 5100mg, *Curcuma xanthorriza* 240mg, and *Moringa oleifera* 240mg as an adjuvant to standard treatment given for the management of Covid-19 patients confirmed with moderate pneumonia with a dose of 3x1 sachet per day orally for 7 days. The treatment results were assessed for improvement in clinical and laboratory symptoms every 5 days of patient care.

Table 1. Criteria for Clinical Symptoms and Manifestations\(^{[1,2]}\)

<table>
<thead>
<tr>
<th>Symptom criteria</th>
<th>Clinical manifestations</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Symptoms</td>
<td>The mildest conditions</td>
<td>The SARS-CoV-2 test results were positive without any clinical signs and symptoms</td>
</tr>
<tr>
<td>Mild ill</td>
<td>Mild pain without complications</td>
<td>Symptomatic patients without evidence of viral pneumonia or hypoxia. Symptoms include fever, cough, fatigue, anorexia, shortness of breath, myalgia. In addition, other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, loss of smell (anosmia),</td>
</tr>
</tbody>
</table>
or loss of taste (ageusia) that appear before the onset of respiratory symptoms are also frequently reported. Aged patients had immunocompromised atypical symptoms such as fatigue, decreased consciousness, and mobility.

| Moderate ill | Mild pneumonia | In adolescent or adult patients: Those with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing), but no signs of severe pneumonia including SpO2> 93% with room air. |
| Severe ill | Severe pneumonia / severe ARI | In adolescent or adult patients: Those with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) and one of respiratory rate> 30 x/second, severe respiratory distress, or SpO2 <93% in room air. |
| Critical | Acute Respiratory Distress Syndrome (ARDS) | Patients experience rapidly progression to acute respiratory distress syndrome (ARDS) or respiratory failure, develop shock, encephalopathy, myocardial damage or heart failure, coagulopathy, acute renal impairment, and multiple organ dysfunction or other manifestations of sepsis. |

Clinical examination was conducted from November 2020 to January 2021 after passing the Ethics review. The study commenced by initially filling in the informed consent, signing it, and thereafter proceeded to the selection, treatment, and post-treatment phase respectively. During the study, clinical symptoms, complete blood count, C reactive protein, D dimer were assessed before and after COVID 19 treatment.
Study treatments
The study framework is presented as follows:

Patients were divided into 2 groups namely:
Group I; given 2x200mg hydroxychloroquine, 1x500mg injection of azithromycin, 2x75mg oseltamivir, and 750mg Levofloxacin injection + ONOIWA Mx 3x1 sachet for 7 days.
Group II: given 2x200mg Hydrocloroquin, 1x500mg azithromycin, 2x75 mg oseltamivir, and 750 mg Levofloxacin injection + control 3x1 sachet for 7 days. The patients were subjected to clinical and vital signs examination daily.

RESULTS

A total of 315 patients were excluded because the data were incomplete while 48 patients were included based on the inclusion requirements. The patients' demographic data and clinical characteristics are presented in Table 1.

Table 1. Demographic and clinical characteristics of the participants at baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 year</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>40-60 year</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>61-79 year</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>87.5%</td>
<td>95.8%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Fever</td>
<td>75%</td>
<td>79.2%</td>
</tr>
<tr>
<td>Anosma</td>
<td>12.5%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>
Based on the table above, majority of the respondents had cough symptoms (87.5% in the intervention and 95.8% in the placebo group), fever (75.0% in the intervention, and 79.2% in the placebo group), and Dyspnea (75.0% in the intervention and 75.0% in the placebo group), while 8.3% of respondents had anosmia symptoms (12.5% in the intervention and 4.2% in the placebo group). Therefore, it was concluded that the majority of respondents have symptoms of cough, shortness of breath (Dyspnea), and fever.

![Figure 1. Co-morbid conditions of patients](image.png)

Based on Figure 1, the most common comorbid suffered by respondents include hypertension (41.7% in the intervention and 54.2% of the placebo group) and Diabetes Mellitus (DM) (20.8% of the intervention and 37.5% the placebo group). Meanwhile, the least suffered comorbid include CKD (4.2% of the intervention and 8.3% of the placebo group) and Asthma (8.3% of the placebo group).

**Table 2. Initial laboratory data of the patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Before treatment</th>
<th>Group I After treatment</th>
<th>Group II Before treatment</th>
<th>Group II After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb (g/dL)</td>
<td>13.43 gm/dL</td>
<td>13.35 gm/dL</td>
<td>13.676 gm/dL</td>
<td>13.518 gm/dL</td>
</tr>
<tr>
<td>Lymphocyte (%)</td>
<td>16.95%</td>
<td>21.20%</td>
<td>18.375%</td>
<td>18.916%</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>55.46 mg/dL</td>
<td>20.33 mg/dL</td>
<td>66.75 mg/dL</td>
<td>18.83 mg/dL</td>
</tr>
</tbody>
</table>
Table 2 shows the laboratory results data of group I administered with polyherbal supplementation (ONIWA MX) compared to group II indicating the values of Hgb, lymphocytes, CRP, D-dimer, NLR, and ALC before and after treatments. The lymphocyte yield in group I before treatment was 16.95%, but after polyherbal supplementation for 7 days, it increased by 21.20%. This result was better than the comparison group II which yielded 18.375% and 18.916% before and after treatment respectively. The CRP value of group I before and after treatment was 55.46 mg/dL and 20.33 mg/kg BW respectively, while in the comparison group, the value was 66.75 mg/dL, and was 18.83 mg/dL. Moreover, the D-dimer value in group I was 1380.58 and 412.60 before and after treatment while in group II, the value was 799.11 and 379.56.

In this study, the use of ONOIWA MX containing *Channa striata* extract, *Curcuma xanthorriza*, and *Moringa oleifera* as an adjuvant for the treatment of COVID-19 was measured for its effectiveness in reducing the length of stay (LOS), C-Reactive Protein (CRP), and D-dimer. By measuring LOS reduction, it was found that the intervention group had a mean LOS of 10.25±5.06 days), while the placebo group had a mean LOS of 9.00±3.96 days). The statistical tests showed that there was no significant difference between LOS in the intervention (Group I) and the placebo group (group II) (p = 0.6480). Although, the intervention and the placebo group had no significant difference and even the placebo group's LOS was shorter, other factors played a role. An example is a non-pharmacological intervention, such as the availability of a ventilator[18]. Measurement of CRP before and after treatment in the intervention (group I) and placebo (group II) showed that there was no significant difference in the mean CRP of the two groups (α> 0.05) using the Mann-Whitney test. Although there was no statistically significant difference, the difference in mean CRP before and after treatment in the intervention and placebo group was 35.12 and 47.92 respectively. Therefore, It was concluded that there was a decrease in the mean CRP in both groups. Inflammation that occurs in COVID-19 is indicated by several signs, including Neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-C-reactive protein ratio (LCR) which shows the systemic inflammatory response in the body. Based on Tan et al. (2020)[17], correlation analysis showed that CRP (R = .62; P <.01) was positively associated with CT severity values. In contrast, the lymphocyte count (R = -.37; P <.01) was negatively associated with the CT severity value. Therefore, a high NLR value and a low LCR reflect an inflammatory process that is indicative of a poor prognosis[16].

**DISCUSSION**

There is currently no treatment for COVID-19, the therapy used including antivirals and antibiotics, only relieves the symptoms. Apart from drugs, preventive measures such as government's efforts to vaccinate the public are underway. Although, the vaccine is being
distributed, other efforts to alleviate the impact of COVID-19 are still needed. This study used clinical observations with the treatment group which received the adjuvant (group I) and the control group which received the placebo (group II). The use of placebo in drugs clinical trials is carried out to test the effectiveness. It is used not as a substitute for standard treatment, but in addition to existing standard treatments. In this study, the use of adjuvants was not a substitute for COVID-19 treatment, but as a treatment supplement\textsuperscript{[15]}. Furthermore, in situations like COVID-19 where there is no effective drug as cure, a placebo is used to improve the patient's condition. Meanwhile, efforts to avoid adverse effects in patients are to be actively carried out.

ONOIWA MX containing extracts of \textit{Channa Striata}, \textit{Curcuma Xanthorrhiza}, and \textit{Moringa oleifera} with information on bioactive compounds and mechanisms of action are shown in Table 2.

\textbf{Table 2. Information of the key ingredients of Onoiwa MX}

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Main active compounds</th>
<th>Known effects and possible mechanisms of actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Channa striata}</td>
<td>Albumin</td>
<td>In COVID-19 patients, the level of serum albumin is decreased and the body requires more serum albumin. SARS-CoV-2 virions bind to albumin and reduce the concentration of glycocalyx, therefore, deplete the endothelial glycocalyx layer\textsuperscript{[11]}.</td>
</tr>
<tr>
<td>\textit{Moringa oleifera}</td>
<td>Quercetin Flavonoid quercetin-3-glycoside, rutin, kaempferol glycosides and chlorogenic acids</td>
<td>In a bioinformatics study, researchers have investigated the potential of compounds derived from Moringa oleifera in inhibiting SARS-CoV-2 proteases and made a comparison with known antiviral drugs. Quercetin-3-\textit{O}-\textit{β}-galactoside binds to SARS-Cov 3 Cl protease and inhibits its proteolytic activity with an \textit{IC}_{50} of 42.79 ± 4.95 \textmu M Que was also identified as being...</td>
</tr>
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able to block SARS-coronavirus entry into Vero E6 cells with a half-effective concentration (EC\textsubscript{50}) of 83.4 µM and low cytotoxicity (CC\textsubscript{50} 3.32 mM)\textsuperscript{[5,6,10,12]}. 

| **Curcuma xanthorrhizae** | **Curcumin Flavonoids** | Curcumin as (1) potential inhibitory agent blocking the host viral interaction (viral spike protein—ACE2 receptor) at an entry site in humans and (2) as an attenuator via modulating the proinflammatory effects of Angiotensin II-AT1 receptor-signalling pathways and reducing respiratory distress in the treatment of COVID19\textsuperscript{[14]}. |

The hypothesis for the SARS-CoV-2 treatment strategy is through the simultaneous targeting of extracellular and intracellular viral particles. Meanwhile, the viral action strategy is through the potential to internalize the effect of drugs on the activity of viral protease enzymes, polymerase, and RNA\textsuperscript{[8,9,11]}. Serum albumin is used as an excellent vehicle for drug action and it is a multifunctional protein i.e both intracellular and extracellular\textsuperscript{[11]}. The highest serum albumin concentration is extracellular, namely in the skin, muscles, intestines, cerebrospinal fluid, pleural fluid, and secretions such as sweat, tears, saliva, and milk. There is a relationship between the level of inflammation and extracellular albumin levels. It is known that infected cells under stress conditions increase the need for albumin, both physiologically and pathologically. Therefore, a combination capsule of *Channa striata*5100mg, *Curcuma xanthorriza* 240mg and *Moringa oleifera* 240mg (ONOIWA MX) is very useful in the treatment of SARS-Cov2. This combination inhibits the fusion and entry of the virus into the cell while the other drug internalizes the target of several viral components and signals the cell to stop the spread of the virus. Recent searches for the treatment of SARS-Cov2 infection on PubMed revealed that the use of traditional medicines in treating COVID-19 showed the high potential of curcumin in neutralizing viral activity. According to recent studies, albumin therapy supports COVID-19 patients due to the complex relationship between albumin concentration and ACE2 receptor expression in cells, and the ACE2 receptor is essential in mediating viral infection\textsuperscript{[11]}. Furthermore, albumin is used to stabilize and transport curcumin to intracellular viral targets.
with a drug combination component that blocks viral fusion and/or entry into cells, this strategy is an effective way of treating SARS CoV-2 virus infection. Curcumin is very effective in treating variety of pathological conditions by increasing the main cellular signal. The inhibition of this main cellular pathway also helps in inhibiting the multiplication of viruses within cells as reported in the case of SARS-CoV\textsuperscript{14}. Apart from its antiviral results, curcumin also has anti-inflammatory, antioxidant, and immunomodulatory effects.

Conclusion

Based on the results, the administration of ONOIWA MX sachet containing a combination of \textit{Channa striata} 5100mg, \textit{Curcuma xanthorriza} 240mg, and \textit{Moringa oleifera} 240mg is an effective adjuvant therapy for the treatment of COVID-19.

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Authors’ contributions

LNS conceptualized and designed the study. LNS, C, SA, NA enrolled the participants and collected the data. LNS and NA analyzed the data. SA wrote the first draft of the manuscript. LNS, C, SA and NA made significant inputs into the final version of the manuscript. SA provided important advice at all stages of the study. All authors read the final version of the manuscript and confirmed it for publication.

Conflict of interests

The authors declare no conflict of interests

REFERENCES


