(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 6, Page No: 855-865
November-December 2021

IJMSCR

Treatments against SARS-CoV-2

Mr. Jittithorn Prousoontorn
32/1 Phahonyothin 7, Phayathai, Samsen nai 10400

***Corresponding Author:**
Mr. Jittithorn Prousoontorn
32/1 Phahonyothin 7, Phayathai, Samsen Nai 10400

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

SARS-CoV-2, a virus that has brought forth the current Covid-19 global pandemic has so far infected approximately 219 million people worldwide, not to mention spreading to 221 countries globally causing the death of over 4.55 million people as recorded by the WHO (World Health Organization) as of September 2021. It is apparent that SARS-CoV-2 is nonetheless a deadly virus impacting the countless lives of global citizens, hence the ongoing discoveries of treatment for Covid-19. This paper evaluates the various treatments for SARS-CoV-2 including the use of herbal medicine: andrographolide, the use of anti-viral drugs: remdesivir, chloroquine, hydroxychloroquine, azithromycin; and the utilization of monoclonal antibodies

Keywords: NIL

Introduction

The Coronavirus disease widely known as Covid-19 is an acute respiratory illness manifested from the virus SARS-CoV-2. Its severely contagious properties have led to the current ongoing

covid-19 global pandemic. As of September, 2021, there have been an overwhelming 219 million covid cases worldwide, and is still increasing at an alarming rate. With regards to the Coronavirus, reported illnesses have been categorized into four distinct stages depending on the clinical manifestation; mild, moderate, severe, and recovery stages. Symptoms commonly present in the mild phase include fever, coughing, and fatigue as such. Covid-19 symptoms gradually evolve to breathing difficulties, disrupted senses of smell and taste, and failure in respiratory systems once in the 'severe' phase. Transmission of the disease primarily occurs when individuals are exposed to the virus through respiratory droplets or airborne particles. While there are developed vaccines which tremendously help to reduce the spread of the disease as well as the prevention of serious illnesses once exposed to the disease, the number of vaccines is undeniably very limited and has not been distributed globally yet. The first subsidiary of the Covid-19 pandemic was the Beta Coronavirus which was initially discovered in Wuhan, Hubei province China [1]. The Beta Coronavirus possessed onset symptoms involving fever, shortness of breath, cough, fatigue, diarrhea as well as vomiting.

Currently, there are an extensive variety of pharmacologic therapies for adult patients with Covid-19 or the coronavirus. Primary treatments for Covid-19 that are available for use, include anti-viral drugs, for example, remdesivir, anti-SARS-CoV-2 monoclonal antibodies such as bamlanivimab/etesevimab and casirivimab/imdevimab. More treatments for SARS-CoV-2 consists of anti-inflammatory drugs (e.g. dexamethasone), immunomodulatory agents such as baricitinib and tocilizumab which are explicit to be used for emergency cases only; under the FDA or the Food and Drug Administration [23]. The clinical utilization of these medications depends on the

severity of the illnesses in specific cases. The early phase of the clinical progression of Covid-19, has the highest replication rate of SARS-CoV-2 which commonly occurs before or right after the exhibition and presence of Covid-19 symptoms [26]. Anti-viral drugs, as well as antibody-based therapies, are presumably most effective during this phase of the clinical development of Covid-19. The later phase of the disease is periodically caused by the hyper-inflammatory state, originating from the release of cytokines.

Therefore, anti-inflammatory drugs would be more likely to help treat patients rather than utilizing anti-viral therapies in this specific phase of the illness [24].

Background on Andrographis paniculata

Given the current circumstances, the demand for treatment continues to rise at a significant rate. However, not all have access to Covid-19 vaccines as well as adequate healthcare, which led to populations in many developing countries relying on the use of traditional medicinal plants such as Andrographis paniculata. The ongoing Covid-19 pandemic has called forth the scientific community in exploring new treatments for SARS-CoV-2 in relation to plants and herbal medicine. Plant compounds have been found to be an ideal, nonetheless significant component for constructing drugs as possible cures for SARS-CoV-2. Conducted research has shown that two thirds of the population in numerous developing countries resort substantially to the use of medicinal plants to meet primary healthcare needs as well as standards [11]. A.paniculata belonging in the acanthaceae family is a traditional medicinal plant which essentially is used for the treatment of a wide range of various diseases, including cancer, diabetes, high blood pressure, influenza, skin diseases, malaria, for instance. The plant itself contains multiple photochemical constituents with fascinating biological properties. The genus andrographis is composed of an estimated 40 different species and of the 40 species, A.paniculata is well recognized for its outstanding medicinal properties for healthcare treatments. A.paniculata is commonly known as Kalmegh or King of bitters which is native in Srilanka, but later expanded in countries within Southeast Asia [12]. Studies have shown that a large percentage of traditional medical practitioners have utilized A.Paniculata for the treatment of diverse illnesses such as stomachaches, inflammation, and fevers [13],[14],[15],[16]. The plant has been utilized and applied to construct many other various cures such as antidotes for snake bites, poisonous stings as well as Malaria, dyspepsia and respiratory infections [16],[17].

Table 1: Medicinal uses of Andrographis Paniculata

Table 1

Medicinal uses of *A. paniculata*.

Part	Medicinal uses	References
Whole Plant	Snakebite and insect sting treatment, dyspepsia, influenza, dysentery, malaria and respiratory infections.	[6],[7]
Leaf	Fever, colic pain, loss of appetite, irregular stools and diarrhea, common cold, cough, fever, hepatitis, tuberculosis, mouth ulcers, bronchitis gastro-intestinal disorder and sores.	[10],[14], [16]
Aerial part	Common cold, hypertension, diabetes, cancer, malaria and snakebite, urinary tract infection.	[10],[11], [16]
Root	Febrifuge, tonic, stomachic and anthelmintic.	[6]

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Multiple compounds within the aerial sections and roots of Andrographis paniculata are frequently used in the extraction of specific properties of the plant. Phytochemical studies on A.paniculata have resulted in the isolation of numerous plant metabolites [17],[18]. Scientists based in Asia have begun the study on pharmacological properties of A.Paniculata as well as corroborating if the plant is potent and fit for uses regarding the therapeutic substances for the treatment of illnesses. Multiple studies have established that A.Paniculata contains properties involving a wide variety of biological activities such as anti-inflammatory, anti-oxidant, anti-diabetic, anti-infective, anti-microbial, anti-angiogenic, immune modulatory, and liver enzyme modulatory. The plant also possesses compounds of different lactones, flavonoids, and miscellaneous compounds as well [19],[20]. Extracted proteins, andrographolide and arabinogalactan from A.paniculata were tested to find out its anti-microbial activity. Results from the screening revealed that the aqueous extract of the arabinogalactan compound in A.paniculata have anti-bacterial activity as well as properties against Bacillus subtilis (B. subtilis), Escherichia coli (E. coli), Pseudomonas aeruginosa. Whilst the compound andrographolide was reported to only be active against B. subtilis. Furthermore, both compounds were proclaimed to have anti-fungal activities against Candida albicans as well [21]. A.paniculata, in response to anti-diabetic activity; studies have shown that the aqueous extract of A.paniculata did not display a compelling reduction in blood glucose levels in normoglycemic rate [22].

Extensively known as the concept of repurposing natural phytomolecules which will accelerate new drug discoveries accordingly. A possible indicative plant as a potential inhibitor of SARS-CoV-2 is Andrographis paniculata. The plant itself was found to contain antiviral properties once examined. The primary fundamental compound for inhibiting SARS-CoV-2 in Andrographis paniculata is andrographolide, which is evident of possessing anti inflammatory, anti cancer, anti, obesity as well as anti diabetes [5]. Additionally, andrographolide was established in having antiviral properties for an extensive range of viral infections [6]. The andrographolide was then tested to see the efficiency of inhibiting SARS-CoV-2. In this particular study, the main protease of SARS-CoV-2 was used as the receptor as the preparation process was done by utilizing molecular docking as seen in Figure 1

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Figure 1: Docking of SARS-CoV-2 main protease [7]

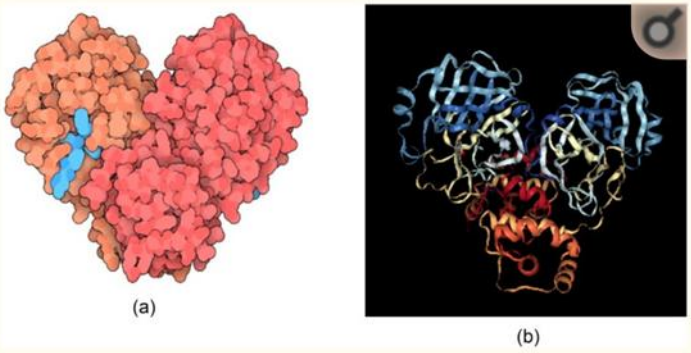

Figure 1.

(a) SARS- CoV-2 main protease with inhibitor in turquoise; (b) Crystal structure of SARS- CoV-2 main protease with inhibitor.

While the ligand preparation method was simulated by using a 3-dimensional molecular structure of andrographolide which played the role of an inhibitor, accordingly in Figure 2

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Figure 2: 3D structure of andrographolide

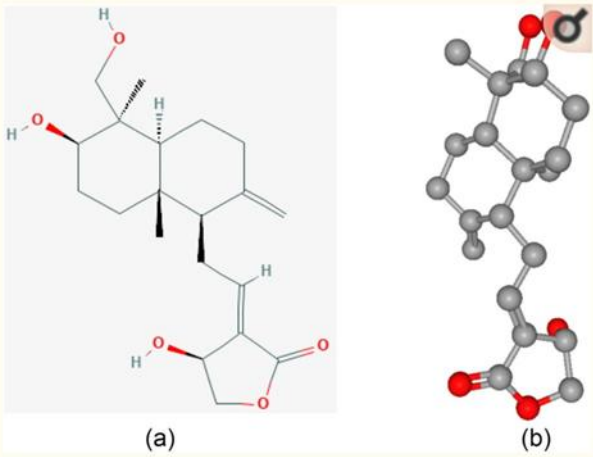

Figure 2.

(a) 2D structure of andrographolide; (b) 3D structure of andrographolide.

The docking process simulates the inhibition of SARS-CoV-2 main protease using andrographolide. Molecular target studies including molecular dockings are essential to discovering phenotypical features as well as effects which are caused by biomolecules. Data from the results of this docking analysis strongly suggested that the compound containing protease from SARS-CoV-2 displayed a negative value of -3.094357 KJ/mol. This can further be implied that there is a significantly high affinity in the binding site between the inhibitor and the receptor as shown in Figure 3 [7].

Figure 3: Ligand in protein binding site

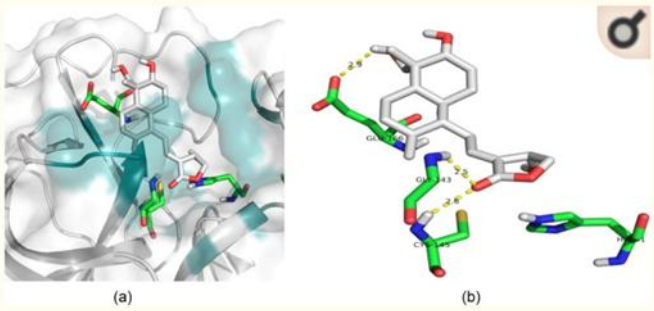

Figure 3.

(a) Docked Ligand in the binding pocket of the protein. The binding pocket of the protein is in light blue and the surface of the protein in white; (b) Residues interacting with the ligand and their hydrogen bonds distance. The Ligand is given in white, interacting residues in green and hydrogen bonds in yellow.

Primary toxicity prediction indicates that a potential inhibitor of SARS-CoV-2, andrographolide does not contain AMES toxicity otherwise known as chemicals that can cause mutations in the DNA of organisms. Further toxicity predictions showed that the use of andrographolide on humans does not

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produce any sort of hepatotoxicity or damages in the human liver.

After the compound, andrographolide was analyzed conscientiously, scientists have discovered that the compound successfully docked against the primary protease of SARS-CoV-2 within the inhibitor region. andrographolide is also capable of oral and intestinal absorption due to its unique properties regarding the permeability through membranes as well as being able to maintain consistency amidst both strong and weak solute and solvent interactions. The toxicity prediction of andrographolide also demonstrates that the compound itself is safe for human consumption without harming side effects.

Treatments for Covid-19 Anti-viral therapies:

Remdesivir

The anti-viral agent, remdesivir is a prodrug, originated from remdesivir-triphosphate (RDV-TP) which is an adenosine analog that performs the role of an inhibitor of

RNA-dependent RNA polymerase. Remdesivir is a broad spectrum anti-viral agent which was recently established to contain anti-viral properties against SARS-CoV-2 [27]. Although numerous healthcare industries have been utilizing the drug remdesivir and seeing definitive results, there is still currently inadequate amount of evidence to officially recommend the use of remdesivir for patients with Covid-19 within the early to moderate stages. However, the use of remdesivir is encouraged as well as recommended for hospitalized Covid-19 patients who require additional levels of oxygen. (133) The results from three randomized clinical tests exhibited that remdesivir was proved to be highly sufficient to placebo in reducing the length of the recovery period in adults who were diagnosed with early stages of Covid-19. The U.S. Food and Drug Administration (FDA) previously permitted the approval for medical use of remdesivir in adults as well as pediatric patients with the Coronavirus or Covid-19 [28],[29],[30]. On the contrary, results which arose from a trial conducted by the World Health Organization (WHO), involving 40 countries and 11,330 patients with Covid-19. The patients were randomly separated into two distinct groups, the first receiving remdesivir for treatment while the other receiving no drug. It was brought to light that the overall results from this clinical trial had no effect that was evident in reducing the majority rate of mortality as well as the length of hospital stay [31]. Ongoing clinical trials for remdesivir molecules are currently underway for a more precise assessment of the antiviral drug remdesivir as conducted by Gilead sciences; in order to provide and implement an efficient and effective cure for the coronavirus outbreak in the near future.

Chloroquine

Another anti-viral drug considerably used as treatment during the current epidemic is chloroquine. chloroquine contains strong inhibitor mechanisms for viral enzymes as well as viral DNA and RNA polymerase. The FDA however, has not permitted the normalized use of chloroquine for treating Covid-19 patients, since studies have shown that the potential benefits of chloroquine does not outweigh the health risks. Furthermore, the National Institutes of Health or the NIH Covid-19 treatment guidelines are in fact, also against the use of chloroquine for Covid-19 inpatients. Nonetheless, In vitro data from preclinical trials have proven that chloroquine has activity against SARS-CoV-2. Further researches and studies on chloroquine have also suggested that there are potential benefits regarding its inhibiting properties on patients experiencing severe pneumonia with infection of SARS-CoV-2, more specific data however, is not yet available. On the contrary, observational cohort study from multi centers evaluated the overall rate of death on patients with Covid-19 along with patients with moderate through to severe cases of Covid-19 in the ICU whom were receiving chloroquine treatment whereas the other trial group received no treatment of chloroquine.

Results unexpectedly showed that there was no significant evidence regarding the difference in mortality rates between the two clinical test groups. Likewise, there were also no compelling differences with regards to the ICU patients' clinical health between one group that was treated with chloroquine compared to the controlled group whom did not receive chloroquine for treatment. Research has also proven that the use of chloroquine and hydroxychloroquine are not suitable and admissible for patients diagnosed with diabetes, hypertension as well as other cardiac illnesses. The tremendous lack of availability of treatments for SARS-CoV-2 has

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convinced the scientific community to investigate on the possible compounds which may serve as an effective treatment for SARS-CoV-2. More research is still in the process of accessing the efficiency of chloroquine in Covid-19 patients.

Hydroxychloroquine

Hydroxychloroquine was initially proposed as an anti-viral drug against severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2. The antiviral drug was discovered to possess in vitro activity against SARS-CoV-2 or mechanisms that hold properties for the inhibition of viral processes and metabolisms, as well as possibly containing immunomodulating properties. The acidification of the cell membrane within hydroxychloroquine prevents the entry of viruses as well as the modification of immune systems through respective cytokine release [3]. More recent studies have shown that the antiviral drug hydroxychloroquine can possibly cause severe drug poisoning in patients.

Further research in hydroxychloroquine suggests that the drug has characteristics for inhibiting pro-inflammatory cytokines which could consequently lead to acute respiratory distress syndrome or ARDS [4]. The anti malarial drug is directly being used for emergency cases in Covid-19 patients only. Recent studies on hydroxychloroquine have shown that the drug's mechanisms involve the inhibition of viral enzymes as well as DNA and RNA processes. Given its useful anti-SARS-CoV-2 properties, hydroxychloroquine however, is not currently approved by the FDA for treatment of Covid-19 patients. As of June 15, 2020, the FDA has made a statement invalidating the EUA or the Emergency Use Authorization's statement, stating that the use of hydroxychloroquine was ineffective in treating patients with Covid-19. Furthermore, the National Institutes of Health (NIH) Covid-19 treatment guidelines are against the use of hydroxychloroquine for treatment of the virus SARS-CoV-2. Results from in vitro trials also suggest an unclear and inconclusive data on the effectiveness of hydroxychloroquine. One multi-center, open-label, parallel randomized trial involving 150 adult inpatients with Covid-19 were treated with hydroxychloroquine and results were later compared to the control group where Covid-19 patients received standard treatment without the presence of hydroxychloroquine. The overall results from the randomized trial over a 28-day time span revealed that there were negative viral conversion rates unresponsive between the two clinical groups. Additionally, results from the controlled randomized trial assessing the effectiveness of hydroxychloroquine, with and without azithromycin in

Covid-19 patients had little to no effect in improving the patients' clinical health as well as the overall mortality rate [31],[32]. Furthermore, data from another randomized controlled trial regarding the effectiveness of hydroxychloroquine as postexposure, suggested that it did not prevent infection from SARS-CoV-2 [33],[34]. In regards to other crucial antiviral drugs as possible cures to Covid-19, the combination of azithromycin and hydroxychloroquine; studies have proven that increasing the pH of the protease in hydroxychloroquine and azithromycin compounds is expected to serve as a potent inhibitor of SARS-CoV-2 [8],[9],[10]. The use of a combined therapy of hydroxychloroquine and azithromycin were demonstrated to be effective in treating patients with the Beta Coronavirus consist of principally, However, given its efficiency, the FDA or the Food and Drug Administration still does not approve the use of the combined therapy involving hydroxychloroquine and azithromycin for treatment of

Covid-19 patients [2]. In a similar manner, the alarming side effects on patients are still a substantial obstacle as to utilizing hydroxychloroquine and azithromycin as a treatment for SARS-CoV-2.

Anti-SARS-CoV-2 neutralizing antibody products

Another possibly potent treatment for SARS-CoV-2 is convalescent plasma therapy.

Convalescent plasma was first established during the SARS, MERS, and Ebola pandemics as a therapeutic agent. Convalescent plasma interventions from recovered patients who were diagnosed with viral diseases such as SARS, MERS, Ebola, and influenza; containing ample amounts of antibody was inclined to an overall reduction in disease mortality rates [42]. The convalescent plasma therapy, however, lacked a sufficient amount of randomized control trials for its efficiency evaluation. Nonetheless, the FDA has

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recently approved the medical use of convalescent plasma therapy on patients in more severe phases of Covid-19 [35],[36].

Additionally, one study based on the US national registry, showed that in-patients with Covid-19 in early stages with lower severity, who received convalescent plasma infusion had an overall lower risk of death as well as a lower risk of the illness further developing into more severe stages of its clinical course. Contrarily, the data received from three minor randomized trials demonstrated that there was no compelling evidence that transfusion of convalescent plasma in hospitalized patients was able to improve the patients' clinical conditions overall. An in vitro study on the convalescent plasma received from individuals

who were infected with SARS-CoV-2 strains, concluded that there was a significant reduction in neutralization against the variant in SARS-CoV-2. Further in vitro analysis have also displayed that there was a compulsorily higher resistance to neutralization by the infusion of convalescent plasma extracted from previously infected Covid-19 patients [37],[38],[39].neutralizing monoclonal antibodies for treatment of COVID-19.

The role of neutralizing antibodies against SARS-CoV-2 has been increasingly significant as therapeutic agents in treating Covid-19, while being comprehensively studied in various clinical trials. To this day, there are several monoclonal antibodies or mABs that are being developed as well as currently undergoing clinical trials for the neutralization of SARS-CoV-2. The US Food and Drug Administration (FDA) has granted permission for the use of mABs in non-hospitalized patients in the mild phases of Covid-19. Further studies on the neutralization of mABs on SARS-CoV-2 have shown that several monoclonal antibodies have properties allowing them to bind as well as neutralize infected patients with the SARS-CoV-2 virus, the process being known as antiviral intervention [40],[41].

Neutralizing monoclonal antibodies predominantly consists of recombinant proteins extracted from

β-cells in patients or humanized mice. Scientists have conducted thorough screening of the derived

β-cells which allows for the identification for certain antibodies regarding its specificity as well as the cell's affinity to correspondingly match and bind with SARS-CoV-2 in order to prevent the entry of the virus. Similarly, mAbs or monoclonal antibodies can also limit immune mediated damage as well as reducing mortality by presuming the role as immunosuppressive agents [43]. In a similar manner, monoclonal antibodies (mABs) also provide efficient therapeutic interventions against certain diseases, acting as passive immunotherapy. Furthermore, mAbs are widely known for its specificity and precision as well as the ability to localize the virus SARS-CoV-2 when compared to conventional plasma therapy, since monoclonal antibodies can easily be separated from the blood of patients infected with the disease which can be further developed in the laboratory [44]. Although, with regards to Covid-19 vaccines, they are often proven to be an effective and highly safe means for battling against the ongoing pandemic, mAbs or monoclonal antibodies remains as a supportive and accessible treatment for covid-19 patients isolated at home or areas with large clusters of covid-19 patients [45]

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