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Effect of Alkaloids on SARS-CoV-2

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ABSTRACT: The use of herbs in treatment has started with the history of humanity and a significant number of effective drugs are being developed from herbal sources. Primary and secondary metabolites, which are natural products produced by plants, are the most basic products of the industry directly or indirectly. One of these groups is alkaloids. Alkaloids show antiviral effects in viral diseases. COVID-19, which started in China and spread to many countries, has become an epidemic that threatens all humanity worldwide as a "Coronavirus Pandemic". No reliable and certified drug has yet been developed for this virus. Recent important research shows that plant-based substances can be potential candidates for developing effective and safe drugs against this virus. Referring to such recent studies, this study primarily shows that the antiviral potentials of some alkaloids especially quinine and artemisinin and its derivatives. In addition, the importance of antiviral plant substances in the development of a broad-spectrum drug for SARS-CoV-2 is emphasized.

Keywords: SARS-CoV-2, COVID-19, Alkaloid, Quinine, Artemisinin

1. INTRODUCTION

COVID-19, which started in China and spread to many countries, has become an epidemic that threatens all humanity worldwide as 'Coronavirus Pandemic'. To date, all coronavirus groups that infect humans have posed a serious risk to public health [1]. The SARS-CoV and MERS-CoV outbreaks that have occurred at certain time intervals over the last two decades have created a global threat to public health and the threat has gradually increased with the recently defined 2019-nCoV. SARS-CoV-2 has a faster propagation profile than previous CoVs that have been defined.

Viral infections caused by coronaviruses are often associated with upper respiratory infections, symptoms may differ depending on the immune responses of patients. Since the virus-host relationship plays a key role in viral infections, it is extremely important to activate the immune response and combat viral infection by increasing the body's combat mechanism, thereby controlling CoV infections. However, immune responses unconformably can cause immunopathology and impaired pulmonary gas exchange in individuals [2-4]. Immune deficiency or misdirection of the immune response may increase viral replication and cause tissue damage; overactive immune responses can also lead to immunopathological conditions.

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SARS-CoV-2 spreads in the respiratory epithelium by binding to angiotensin converting enzyme 2 [5, 6]. The transmission of the disease is through direct contact from person to person. The transmission route of SARS-CoV-2 is similar to influenza. The disease is transmitted mainly through droplets. When a person with an infection coughs, sneezes or talks, the virus in their respiratory secretions can infect another person if they come into direct contact with the mucosa. In addition, it is transmitted to the droplets that are brought out by coughing and sneezing by sick individuals, after contact with the hands of other people, taking their hands to the mouth, nose or eye mucosa. The incubation period ranges from one to fourteen days [5]. COVID-19 presentation can range from a mild disease to pneumonia and even septic shock [7]. COVID-19 can affect many organs such as the brain, kidney, liver, especially the lungs. Generally, fever, cough, fatigue, sputum production, shortness of breath, sore throat, headache and sometimes vomiting Diarrhea and lymphopenia are common [6]. Patients have bilateral multilobar ground-glass opacities with peripheral or posterior distribution [8, 9]. Radiological findings progress with the highest severity around the 10th day of disease [9]. There is no specific drug or vaccine with proven safety and efficacy in the treatment or prevention of the disease yet. Immune response in a viral infection; It aims to destroy both the virus and the host cells that carry or reproduce the virus. With the researches on cell culture and animal models, many antiviral drug candidates have been identified that have an effect on preventing the entry of viruses into the host organ or decreasing the rate of reproduction in the host organ. Medicinal plants contain many different active phytochemical compounds such as glycosides, saponins, flavonoids, proanthocyanidins, terpenoids, phenylpropanoids, tannins, resins, lignans, sulfides, polyphenolics, coumarins, furyl compounds, alkaloids and essential oils. It has been demonstrated in previous studies that some of them show strong antiviral activity against various viruses and some of them are phyto-antiviral agents that have the potential to be used in different types of coronavirus-induced diseases.

2. MATERIAL AND METHODS

2.1. Alkaloids

Nature has been the source of medical agents for thousands of years and people recognized the therapeutic power of plants and used it to live healthily. In addition, primary and secondary metabolites, which are natural products produced by plants, are the most basic products of the industry directly and indirectly. One of these groups is alkaloids. Alkaloids are nitrogen-containing compounds in a heterocyclic ring common to about 20% of all vascular plants. Alkaloids are formed as metabolic by-products. Alkaloids with complex molecular structures usually contain at least one nitrogen atom in the amine structure. Hydrocarbon groups consisting of carbon and hydrogen are attached to the nitrogen atom, and the amine structure is often found in a ring structure on the nitrogen or hydrocarbon groups. Plants containing alkaloids contain more than 0.01% alkaloids [10].

Plants usually have more than one alkaloid in a similar structure. Oxygen-containing alkaloids have a hard crystalline structure, and those that react with acid are in the form of salt. Their salt-forming abilities and their complexity with metal ions facilitate their separation and determination prior to chromatography. Alkaloids are subclassed according to the chemical type of their nitrogen-containing rings. There are about 12,000 alkaloids known for their biological activities. However, with their characteristic bitter taste and concomitant toxicity, they repel insects and herbivores. Alkaloids are used as pharmacological, stimulant, narcotic and poison [11, 12]. Biochemical studies of alkaloids in plants began in 1806 with the isolation of morphine. Due to the stereochemical complexity of the morphine molecule, its structure could

not be explained until 1952. Alkaloid biosynthesis in plants over half a century has been attempted to be understood by chemical, biochemical and molecular research [13].

Alkaloids often cause poisoning in animals and humans. An alkaloid contained in Cotalaria and Heliotropium (balbulus) species causes liver cirrhosis when taken continuously. The alkaloid produced by a type of fungus known as rye mackerel found in grain seeds causes ergotism disease. The physiological effects of alkaloids are important in medicine. For example, morphine obtained from poppy is used as a painkiller in medicine and noscapine is used as a cough suppressant. Intake amounts of alkaloids are also important. Alkaloids taken in small amounts may benefit, while alkaloids taken in excess can be lethal [10]. The poisonous alkaloid which is obtained from the hemlock (*conium maculatum*) causes death by paralyzing the respiratory tract. Misuse of methadone used in medicine also causes addiction. Therefore, the use of the drug outside the doctor's control poses serious dangers to people.

Alkaloids are used as antiviral agents against viruses. Studies have shown that berberine could inhibit viral replication of the Herpes Simplex virus and Chikungunya virus [14, 15]. The isoquinoline alkaloids tetrandrine, fangchinoline and cepharanthine are potential for treatment HCoV- OC43 infection [16]. HCoV-OC43 is similar to SARS-CoV. Palmatine, an isoquinoline alkaloid, suppresses West Nile and Zika virus replication [17, 18]. Chelidonine shows antiviral effect against Herpes Simplex virus, Human Immunodeficiency virus and the influenza virus [19]. Sanguinarine is used for antimicrobial activities and it shows antiviral activity against Human Immunodeficiency virus protease and Herpes Simplex virus [20]. Emetine is a potential antiviral agent against SARS-CoV-2 [21].

2.2. Quinine and it’s Derivatives

Since ancient times, the *Cinchona officinalis* has traditionally been used as an anti-malaria medication to treat various malaria-related health problems. About 40 species of this plant grow in South America. During culture, the lower branches of the plant are pruned so that the crown of the tree grows and the trunk is in the shade. The temperature should not be prevented during the drying of the shells. Because a compound called quinotoxin is formed at high temperature, which is toxic. The shells are yellow when first collected, and become red when dry. This color comes from the grain in the drog. During tanning, the tannins are oxidized and turned into flobafen. The most important feature of the *Cinchona officinalis* is due to the presence of various types of alkaloids. 60% of these alkaloids constitute quinine, quinidine, kinkonin and kinkonidine, and 2/3 of this rate is "quinine" alkaloid. The shell contains minerals such as acids, essential oils and triterpine (quinovic acid), organic (kinic acids), phenolic, flavonoids (psoantycyanidin), phytosterols [22].

Quinine is used as an antimalarial agent because of their effectiveness against P. vivax, P. malariae and P. ovale parasites, especially Plasmodium falciparum. Also quinine demonstrates antiviral effect against Herpes Simplex virus, Dengue and influenza virus [23]. Although other alkaloids found in the composition of the plant also have antimalarial effects, their activities are quite low compared to quinine, so they are not preferred for malaria treatment. Of these alkaloids, quinidine, the stereoisomer of quinine, is used in the treatment of arrhythmia. Researchs show that the combination effects of more than twenty alkaloids, rather than one of them, are a key source of their medicinal property. Studies have been conducted to demonstrate that potassium alkaloids have the potential for anti-obesity, anti-cancer, anti-oxidant, anti-microbial, anti-parasitic and anti-inflammatory activity [22].

Quinine is absorbed by the body both parenterally and orally and reaches peak concentrations within 1-3 hours [24]. It is dispersed throughout the body fluids and bound to a high proportion of protein, alpha-1 acid glycoprotein. Concentration and alpha-1 acid glycoprotein levels determine its binding capacity in plasma. Quinine easily crosses the placental barrier and it is also found in cerebral spinal fluid. The excretion of the body is rapid, 80% of the drug administered is eliminated by hepatic biotransformation, and the remaining 20% is excreted unchanged by the kidney [25, 26]. The half-life of quinine varies between 11-18 hours [27]. Many of the pharmacokinetic properties of quinine vary according to the patient's age. The distribution volume is lower in younger children than in adults, and the elimination rate is slower in older than younger adults. In acute malaria patients, the distribution volume decreases and systemic clearance is slower than healthy individuals; the severity of the disease is proportional to the changes occurring in the body. In malaria patients, the binding of quinine to proteins and the level of quinine in their plasma increase [28]. Quinine is still used in the treatment of chlorine resistant malaria cases. In long-term and high doses, it shows side effects such as sensitization in the heart, hematuria and hearing difficulties. A well-controlled use can help reduce its toxicity. The commercial drug is sold as quinine sulfate. The powdered drug in quinine sulfate is wetted with barium hydroxide or calcium hydroxide and consumed with benzene. The benzene extract is rinsed with 10% sulfuric acid and the alkaloids are taken into the acidic water. Acidic water is neutralized with the help of sodium carbonate. If the neutral solution is left in the refrigerator or in a cold place, quinine sulfate will settle. The collapsed quinine sulfate is filtered, dissolved in hot water, and decolorized with activated charcoal.

The quinolone rings of quinine, chloroquine and hydroxychloroquine molecules are common. Chloroquine and hydroxychloroquine are alkylated 4-4 aminoquinoline compounds. In the process of COVID-19 pandemic, which influenced the world, quinine and its derivatives are frequently mentioned. The effects of chloroquine and hydroxychloroquine substances, synthetic analogs developed based on the chemical structure of quinine, on COVID-19 have been investigated in many studies in the literature. Chloroquine interferes with the glycosylation of SARS-CoV cellular receptors. It also increases the endosomal pH required for virus/cell fusion so it has broad spectrum antiviral activity [29, 30]. Another synthetic analog of quinine, hydroxychloroquine suppresses terminal phosphorylation of Angiotensin-converting enzyme 2 (ACE2) such as chloroquine. Figure 1 shows the key points in the application of natural products against SARS-CoV2. It also increases the pH in endosomes [31]. A significant number of clinical studies have been conducted examining the therapeutic efficacy of chloroquine phosphate and hydroxychloroquine in patients with SARS-CoV-2 infection [32-34]. Chloroquine, a broad spectrum antiviral in vitro experiments, has been reported to show strong antiviral activity against SARS-CoV-2 [35, 36]. Data from 100 patients participating in multiple clinical studies conducted with chloroquine treatment in China until February have been published and chloroquine phosphate has been reported to be superior in suppressing pneumonia exacerbation, improvement in lung imaging findings, and shortening the duration of the disease [37]. But, the results of a study reveal that hydroxychloroquine is potent than chloroquine to inhibit SARS-CoV-2 in vitro [38].

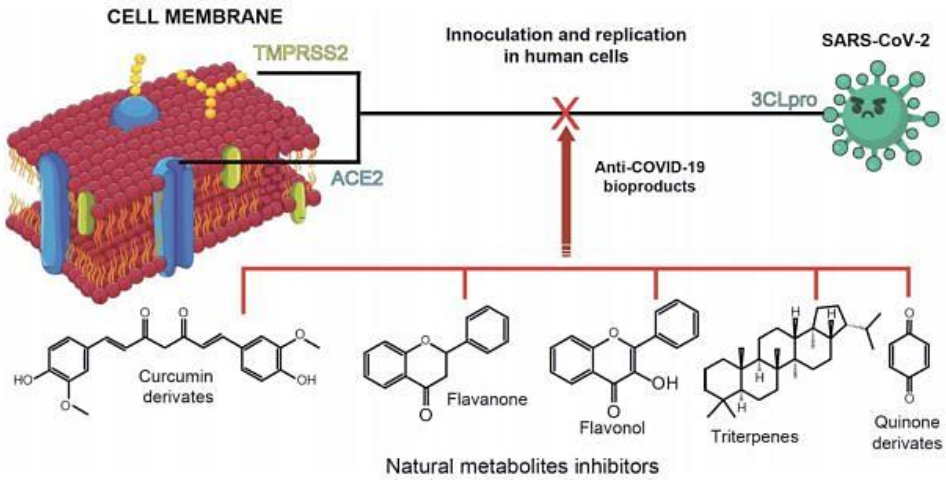

Fig. 1. Schematic representation of key points on the application of natural products against SARS-CoV2 [39]

A study has shown that chloroquine, hydroxychloroquine, and quinine can interact with amino acid residues in the peptidase domain of the ACE2 receptor. According to the results, quinine showed the strongest affinity to the ACE2 receptor (-4.89 kcal/mol) followed by hydroxychloroquine (-3.87 kcal/mol) and chloroquine (-3.17 kcal/mol), respectively. The results showed that quinine, chloroquine and hydroxychloroquine can prevent infection of the SARS-CoV-2 virus by interacting with the Lys353 residue in the peptidase region of the ACE2 receptor [40]. In another study showed that quinine has a higher antiviral effect with a better toxicity profile against SARS-CoV-2 in vitro and a better plasma presence compared to H-CQN and CQN drugs [41]. In patients infected with SARS-CoV-2, high cytokine concentrations have been determined and show that the severity of the disease is associated with cytokine storm [42]. Therefore, besides the direct antiviral activity of hydroxychloroquine, it is also possible to act by suppressing the synthesis of cytokines and especially pro-inflammatory factors with its anti-inflammatory effect. In vitro data show that quinine, chloroquine and hydroxychloroquine inhibit SARS-CoV-2 replication. Since hydroxychloroquine and chloroquine are quinine derivatives and similar chemical structures, it is thought that they can be used as a therapeutic agent in the treatment or prevention of COVID-19.

2.3. Artemisinin and it's Derivatives

The source of Artemisinin is the *Artemisia* species, which contains between 200-400 species, grows in dry or semi-arid climates. Artemisinin is a sesquiterpene with a peroxide group with chemical formulas $C_{15}H_{22}O_5$ and a molecular weight of 282.332 g/mol. The unique endoperoxide bridge supply an active site for the drug mechanism of action [43]. Among the *Artemisia* species, the highest amount of artemisinin is found in *Artemisia annua* [44]. Artemisinin, a sesquiterpene alkaloid, has been used as an anti-malaria drug since 1975. Chinese scientist Dr. Tu Youyou isolated one of the active molecules, antimalarial active substance artemisinin and its derivatives, in 1972 and caused these studies to receive the 2015 Nobel Prize. Artemisinin and its derivatives, artesunate and artemether are used as antimicrobial drugs against Plasmodium falciparum. Antimalarial drug combination therapy proposed by the World Health Organization (WHO) in 2001 includes Artemisinin-based Combination Therapy (ACT). The basis of this treatment is combining artemisinin and its derivatives with existing antimalarial drugs. Combination therapy of Artemisinin is currently one of the most effective ways to treat and reduce the transmission rate of malaria. In the period 2010-2018, an estimated

3 billion artemisinin-based combination therapy was provided by countries. It is reported that approximately 63% of these supplies are made for the public sector [45].

In addition to its antimalarial feature, artemisinin is effective in various diseases in the literature. Artemisinin has been demonstrated to cause cancer cell death very potently and selectively by iron bonding [46]. Due to the high selectivity of cancer cells, positive results have been obtained in cancer studies due to their anti-cancer potential of artemisinin and its derivatives [47]. Kim et al. demonstrated that artemisinin is antimicrobial on various bacteria and also has anti-inflammatory, antioxidant properties [48]. Artemisia annua has antiviral activity against human cytomegalovirus, herpes simplex virus type 1, Epstein Barr virus, hepatitis C virus, dengue fever virus and some HIV-1 strains. It was also successfully tested in patients receiving traditional Chinese medicine as a supplement to traditional treatment during the SARS-CoV outbreak in 2003 [49].

In order to reduce the side effects of chloroquine and hydroxychloroquine, artemisinin can be used as an adjunct cure. Artemisinins can be prescribed with higher doses because it has less side effect. There is a cytokine storm in patients infected with COVID-19 responsible for a major inflammatory response and their very severe progressive clinical state. Artemisinin can be also used to inhibit the cytokine storm. During the COVID-19 infection, chymotrypsin-like protease (CLPro) enzyme has been producing, Artemisia annua pharmacological mechanism inhibit the activity of this enzyme [43]. The effect or interactions of artemisinins on the ACE2 receptor has not been studied yet which is known as a critical binding cellular receptor of SARS-CoV-2 [50]. Artemia can be an alternative treatment for acute respiratory distress syndrome (ARDS) because of having its ability to reduce TNF-a and IL-6 [51].

Artemisia annua can inhibit the androgen pathway and decrease the expression of ACE2 and TMPRSS2 proteins which can slow the entry of viruses into human host cells [49]. Artemisia annua also can slow the transmission of infection in the human body so it can reduce the negative effect of COVID-19 symptoms. Because of these advantages of artemisinin, it can be considered as a potential drug candidate and acceptable treatment for COVID-19 pandemic.

3. CONCLUSIONS

Infectious diseases caused by viruses are among the leading causes of death in the world and can create a wide range of symptoms that affect human health globally. Alkaloids are effective in enhancing the immune response of the host against viral pathogens by enhancing the immune system, therefore it is considered a protective and complementary treatment opportunity. In order to develop effective treatment strategies; the structural features, the biology of the virus and the mechanisms of infection in the host cell must be known exactly. It is emphasized that as the knowledge we have about the COVID-19 genome and infection mechanism increases, potential therapeutics and drugs from herbal origin may occur. Due to the fact that different alkaloids can be tested on different types of diseases, it is thought that a new drug with more potency and significantly reduced toxicity can be designed for COVID-19 and it can be produced as a pioneering drug in the treatment of more diseases with good bioactive potential with an appropriate modification in alkaloids. In particular, quinine and artemisia-based drugs could make a potent drug candidate that can be used as a treatment for a wide range of respiratory diseases and could be an option for emergency treatment for the COVID-19 pandemic.

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