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Alkaloids group as medicinal compounds for treatment of COVID-19: A short review

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Abstract
Corona Virus Disease 2019 (COVID-19) is a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus. Exploiting the potentials of phytocompounds is an integral component of the international response to this pandemic. Alkaloids are group of natural products known to have wide pharmacological activity and have great potential for the development of new drugs to treat a wide array of pathologies. Some alkaloids have antiviral activity and/or have been used as prototypes in the development of synthetic antiviral drugs. Several mechanisms for the known anti-coronavirus effect of alkaloids were discussed, showing that the alkaloids are interesting compounds with potential use as bioactive agents against SARS-CoV-2.

Keywords: COVID-19, alkaloids, medicinal compounds

Introduction
Alkaloids are a wide group of naturally occurring organic compounds being a major part of the largest group of plant secondary metabolites. Alkaloids are a class of naturally occurring nitrogen-containing compounds that have at least one nitrogen as a heteroatom, usually in a heterocyclic ringwith basic properties and produce pronounced physiological response. Currently, more than 8000 natural compounds are classified as alkaloids. Current drug recommendations for the treatment of coronavirus disease-2019 (COVID-19) are based on historical reports from various severe acute respiratory syndrome coronavirus and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) studies [1]. Some evidences from these studies suggest that the use of an integrative approach, such as the use of western medicine with herbal medicines and/or medicinal plant-based natural compounds, is good in controlling the coronavirus infection and in reducing the number of deaths [2]. Natural products have always played a crucial role in drug discovery and development process against various diseases, many groups in the world, are now trying to find new or repurposed natural or naturally originated drugs against viruses and CoVs. Secondary metabolites of the plants, particularly alkaloids and terpenoids have been exhibited strong antimicrobial and anticancer activities besides synthetic drugs and other natural compounds (nucleosides and nucleotides and bacterial and fungi originated ones). The first isolated secondary metabolites have been converted into important drugs since 1800's such as morphine, codeine, cocaine, and quinine have alkaloid skeleton as well as some of the recent anticancer drugs vinblastine, vincristine, taxol, etc. This review includes the last two decades of publications about natural alkaloids rather than their plant extracts which showed some promising results against CoVs. The present review article gaves some examples of alkaloid compounds as anti COVID-19.

Alkaloids as Potential Coronaviruses' Inhibitors
Many alkaloids are used in human diet, both in food and drinks, such as alkaloids available in coffee seeds (caffeine), cacao seeds (theobromine and caffeine), tea leaves (theophylline and caffeine), tomatoes (tomatine), and potatoe (solanine) [3]. In addition to their edible uses, alkaloids also play a prominent role in human medical history and are widely used for the treatment of various diseases such as neurological disorders [4], cancer [5], metabolic disorder [6], and infectious diseases [7]. *Lycoris radiata* of Amaryllidaceae is known for its antiviral potential against influenza virus type A. Four alkaloids, lycorine, hippeastrine, hemanthamine, and 11-hydroxyvittatine, showed antiviral activities against avian influenza virus H5N1 after virus entry into cells. Lycorine and hemanthamine also exhibited more potent antiviral activities, due to their inhibitory effects on nuclear-to-cytoplasmic export of the viral ribonucleoprotein complex, which play important roles in viral generation us,

Amaryllidaceae alkaloids seem to be potential anti-influenza agents [8]. The methanolic extract of the root bark of Schu manniophyton magnificum from Rubiaceae family was tested to evaluate its antiviral activities against HIV and HSV, resulted in finding schumannificine 1 and other chromone alkaloids and acyl and methyl derivatives. Among those alkaloids, schumannificine 1 exhibited the highest anti-HIV activity due to its structural existence of piperidine ring and unsubstituted hydroxy groups, while a number of its derivatives exhibited anti-HSV activities [22]. In another study, two new and six known carbazole alkaloids from Clausena anisum-olens (Blanco) Merr. (Rutaceae) were evaluated on the HIV. The highest antiviral activity against HIV virus for one of the new carbazole alkaloids [10]. Four pairs of enantiomers named β myrifabral A, (±)-α-myrifabral A, (±)-β-myrifabral B, and (±)-α-myrifabral B were derived from Myrioneuron faberi Hemsl.ex F.B.Forbes & Hemsl. (Rubiaceae) as a Chinese herbal plant. ,ese cyclohexane-fused octahy- droquinolizine alkaloids exhibited inhibitory effects on hepatitis C virus [11]. 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 proved antiviral effect against Herpes Simplex virus, Dengue and influenza virus [12]. 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, antimicrobial, anti-parasitic and anti-inflammatory activity [13].

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. Another synthetic analog of quinine ,hydroxychloroquine suppresses terminal phosphorylation of Angiotensin-converting enzyme 2 (ACE2) such as chloroquine. Chloroquine, a broad spectrum antiviral in vitro experiments, has been reported to show strong antiviral activity against SARS-CoV-2 [14, 15]. 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 [16]. But, the results of a study reveal that hydroxychloroquine is potent than chloroquine to inhibit SARS-CoV-2 *in vitro* [17].

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. Artemisinin has been demonstrated to cause cancer cell death very potently and selectively by iron bonding [18]. 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 [19]. Kim *et al*. demonstrated that artemisinin is antimicrobial on various bacteria and also has anti-inflammatory, antioxidant properties [20]. 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 [21].

Conclusion

Some promising natural products were determined having alkaloid or terpenoid or phenolic structures. Among natural compounds tested for antiviral activity, about 100 alkaloids were found to be potent anti-viral agents, at least. This number will be increased by searching marine organisms. Microbes, especially bacteria and fungi are other resources to produce new drugs as well as nucleosides, nucleotides, and nucleic acids. Arbidol which is a small indol derivative which has been previously tried to use in the treatment of a bench of viral diseases including coronaviral ones and even now in COVID-19, but still more clinical trials are needed. Several indol alkaloids are also promising antiviral drugs.

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