Chapter

An Overview on Antiviral Potential of Traditional Medicines

Mehtap Kilic and Bilge Sener

Abstract

Traditional medicines can serve as the source of potential new drug candidates and initial research focuses on the isolation of bioactive lead compounds. Medicinal plants have a combination of secondary metabolites that are naturally occurred by giving different therapeutic benefits. Phytoconstituents have been recognized as an important role in the drug discovery process moreover the other sources. Presently, over hundred natural product-derived pharmaceuticals are being used in modern medicine. Plants and their secondary metabolites, with activity against targets associated with the viral infections could provide valuable leads for the development into drugs for the novel antiviral drugs. Some of them play as important tools in the immune system exhibiting antiviral potentials. The objective of this review is to conduct information regarding the potential of traditional medicines to which have shown antiviral activity against SARS-CoV-2 infection.

Keywords: Antiviral, traditional medicine, medicinal plants, phytoconstituents, SARS-CoV-2

1. Introduction

Medicinal plants produce various secondary metabolites in their normal metabolic pathways and these metabolites play an important role for providing the activities of different therapeutic benefits. Medicinal plants have been considered for many years as an essential source of drugs such as morphine, digoxine, quinine, taxol, galantamine, artemisinine *etc*. for the treatment of several diseases and these natural products are still popular main stream stage for researchers to discovery of novel bioactive compounds with recent advancement in science and technology. Furthermore, FDA-approved antiviral drugs (famciclovir, ganciclovir, sorivudine, zidovudine, didanosine, zalcitabine, stavudine and ivermectin) are originally modeled on a natural product parent. The potential utilization of plant extracts and their secondary metabolites to combat the development of antiviral agents is considered to be one of the most important approaches toward effective therapy for viral infections by inhibiting the replication cycle of various DNA and RNA viruses. Among the viral infections, Human Immunodeficiency Virus type 1 (HIV-1) and 2 (HIV-2) as genetic variabilities that causes *Acquired Immunodeficiency Syndrome* (AIDS) which is one of the most dangerous infectious disease all over the world and has led to the death of many people. The anti-HIV potential of the 717 plant species belonging to 151 families were summarized for 206 HIV-reverse transcription (HIV-RT), 254 HIV-protease (HIV-PR) and 43 species as HIV-integrase (HIV-IN); among them *Calendula officinalis, Justicia gendarussa* and *Sceletium tortuosum* might

be useful potential sources for new lead compounds in the development of new candidates with anti-HIV properties of therapeutic interest reported by Salehi *et al*. [1]. 16 ethanolic extracts of Turkish medicinal plants were evaluated for their antiviral activities against Herpes Simplex Virus (HSV) and Sindbis virus (SINV); according to results, the extracts of *Galanthus elwesii* and *Rheum ribes* showed the most potent anti-HSV activities as well as *Galanthus elwesii* and *Leucojum aestivum* were found to be the most potent anti-SINV [2]. Moreover, 14 herbal products with confirmed clinical safety features were attractive starting material for the identification of new antiviral activities and their identified compounds for the eradication of viral diseases were also reported [3]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Influenza A Virus (IAV), and Noro Virus (NV) are highly pathogens that affected the health of the worldwide community. SARS-CoV-2 is an enveloped RNA virus (genus *Betacoronavirus*, subgenus *Sarbecovirus*) that was originated in December 2019 in patients with infectious pneumonia in Wuhan, China. Despite of intense efforts relevant to experimental and clinical studies since the start of the COVID-19 pandemic, no disease-specific drug is available, yet. Several treatment strategies including already known antiviral drugs, interpherons, interleukin inhibitors, and other drugs acting through different mechanims are being implemented in COVID-19 patients. Moreover, the traditional medicines can serve as the source of potential new drug candidates and initial research focuses on the isolation of antiviral lead compounds. This review particularly presents a survey of recent studies on traditional medicines, medicinal plants and phytoconstituents that have indicated antiviral activity for SARS-CoV-2 infection.

2. Traditional medicines

Traditional medicine is being frequently used all over the world. Treatment with traditional medicine is still esteemed highly, particularly by those who have no access to modern health-care. Traditional medicine is to be understood as the total of the knowledge, practices based on theories and experiences indigenous to different cultures used to maintain and improve health, to prevent and diagnose illnesses. Traditional medicine can be included in medical systems and folk medicine along with health knowledge. The numbers of medicinal plants from various medical systems like Ayurveda, Siddha, Unani, Traditional Chinese Medicine, Kampo, *etc*. could be taken into consideration as an inspiring source for bioactive phytochemicals as drug designing as well as nutraceuticals and functional foods for wellness. Based on Lipinski factors and lower binding energies, numbers of compounds from medicinal plants were analyzed for their pharmacological and biological characteristics. Some selected bioactives were found to have lower toxicity with a higher gastrointestinal absorption rate and potent anti-inflammatory and anti-viral activities against targets of COVID-19 which is an infectious pandemic caused by the SARS-CoV-2 virus. The critical target components of SARS-CoV-2 are the Spike protein (S-protein) and the Main protease (Mpro). Mpro is required for the maturation of the various polyproteins involved in replication and transcription. S-protein helps the SARS-CoV-2 to enter the host cells through the Angiotensin-Converting Enzyme 2 (ACE-2). Since ACE-2 is required for the binding of SARS-CoV-2 on the host cells, ACE-2 inhibitors and blockers have got wider attention, in addition to S-protein and Mpro modulators as potential therapeutics for COVID-19. So far, no specific drugs have shown promising therapeutic potential against COVID-19. Therfeore, several studies were undertaken to evaluate the therapeutic potential of traditional medicinal plants against COVID-19.

2.1 Traditional Chinese medicine

Based on the frequency of appearance of each medicinal herb and their corresponding pharmacological activities from Traditional Chinese Medicines (TCM), one of the TCM formula was reconstructed with the potential of treating COVID-19 infection. This TCM formula contains herbs with evidenced antiviral activity along with reducing fever, removing dampness, expelling phlegm, and arresting coughing. It includes *Bupleurum chinense*, *Ramulus cinnamomi*, *Scutellaria baicalensis*, *Glycyrrhiza glabra*, *Atractylodes macrocephala*, Rhizoma Zingiberis, *Agastache rugosa*, *Stephania tetrandra* root, *Polygonum cuspidatum*, *Rheum palmatum*, Tangerine Peel, Semen Armeniacae Amarum and *Ophiopogon japonicus* root. These herbs have the effect of eliminating dampness, for relieving cough and lung symptoms. In addition, in modern pharmacology, *Rheum palmatum* and *Polygonum cuspidatum* have significant antiviral effects due to their rich emodin content. Full prescription of 12 drugs are evaluated for the clinical treatment of COVID-19 [4]. On the other hand, a medicinal plant library containing 32,297 potential antiviral traditional Chinese medicinal plants compounds were analyzed the 3-Chymotrypsin-Like protease (3CLpro) sequence which plays a critical role in the replication of virus particles and unlike structural/accessory protein-encoding genes constructed its 3D homology model. These analyses revealed that the top nine hits might serve as potential anti-SARS-CoV-2 lead molecules for further optimisation and drug development process to combat COVID-19. The proteolytic processing is mediated by Papain-Like protease (PLpro) and 3CLpro. The 3CLpro cleaves the polyprotein at 11 distinct sites to generate various non-structural proteins that are important for viral replication [5].

In Asian countries, *Saxifraga* species (Saxifragaceae) are used as medicinal herbs for treatment of various types of disorders. With respect to antiviral activities, *Saxifraga melanocentra* inhibited the activity of hepatitis C virus serine protease. The virucidal activity of pyrogallol compounds obtained from *Saxifraga spinulosa* have also suggested against SARS-CoV-2, Influenza A (IAV), as well as Feline Calici Virus (FCV) and Murine Noro Virus (MNV) [6].

2.2 Traditional Persian medicines

In Iran, some medicinal plants have great potential value for treatment of COVID-19 based on the therapeutic approaches of Traditional Persian Medicine (TPM) is one of the most ancient medical doctrines mostly known as “wi”, several of which have also been confirmed by pharmacological studies in modern medicine. Among them, Amla (*Phyllanthus emblica* L.), Chicory (*Cichorium intybus* L.), Clove [*Syzygium aromaticum* (L.) Merr. and L.M.Perry], Damask Rose (*Rosa* × *damascena* Herrm.), Fenugreek (*Trigonella foenum-graecum* L.), Galangal (*Alpinia galanga* (L.) Willd., *A. officinarum* Hance), Garlic (*Allium sativum* L.), Grape and Raisin (*Vitis vinifera* L.), Licorice (*Glycyrrhiza glabra* L., *G. uralensis* Fisch.), Rhubarb (*Rheum palmatum* L., *R. officinale* Baill.) and Saffron (*Crocus sativus* L.) were determined as promising plant species. However, preclinical mechanistic studies as well as clinical trials are necessary to confirm the safety and efficacy of these plants for the management of SARS-CoV-2 infection [7].

2.3 Ayurveda

For nearly 5000 years Ayurveda, an ancient Indian medicine method, has been practiced in India, relying heavily on plants to formulate it. Ayurvedic herbal supplements and immunity boosters showing the way to a broad-spectrum

antiviral drug that is the need of the hour. Antiviral properties of *Glycyrrhiza glabra, Andrographis paniculata, Phyllanthus spp., Zingiber officinale, Withania somnifera*, and *Curcuma longa* have been reported [8]. Whereas, *Tinospora cordifolia* and *Emblica officinalis* have the properties to enhance immunity. It has been shown that *Coptidis rhizome, Meliae cortex, Sanguisorbae radix, Cimicifuga rhizome,* and *Phellodendron cortex* exhibit anti-coronavirus activity. *Sophorae radix*, *Torilis fructus,* and *Acanthopanacis cortex* decreased intracellular viral RNA levels with corresponding viral protein decreases [9]. The antiviral activity of some phytoconstituents present in traditional medicinal plants from Ayurveda were also investigated against spike glycoprotein of SARS-COV-2 as well as its host ACE-2 receptor. Some parameters like drug-likeness, pharmacokinetics, and toxicity were also determined to ensure the safety and efficacy of active constituents. Based on the findings amarogentin, eufoliatorin, α-amyrin, caesalpinins, kutkin, β-sitosterol, and belladonnine were found the top ranked molecules have the highest affinity toward both the spike glycoprotein and ACE-2 [10]. Further, fourthy-one plant-derived compounds from Indian medicinal plants were screened for their inhibitory effect on Main protease (Mpro) of SARS-CoV-2 using the molecular docking approach. Among them amentoflavone, lectin, glycyrrhizic acid, hypericin and torvoside H exhibited high binding energy. Amentoflavone isolated from *Torreya nucifera* showed the highest binding energy of 10.0 kcal/mol with the SARS-CoV-2 Mpro [11]. Furthermore, free energy calculations on these compounds performed by using the molecular docking procedure. The results suggested that amentaflavone, hypericin, and Torvoside H respectively complexed with SARS-CoV-2 Mpro show better binding with stabilizing interactions and provided valuable information in developing new, novel and natural anti-viral drugs for COVID-19 [9]. In addition, taraxerol isolated from *Clerodendrum* species has shown potential antiviral activities with desirable pharmacological features [12]. Withanolide A active constituent of ayurvedic herb from *Withania somnifera* has shown promising antiinfluenza properties by targeting neuraminidase of H_1N_1 Influenza as well as the highest binding affinity with S-protein and ACE-2 receptor [13]. AYUSH Ministry of Health, India, has recommended the use of the aqueous extract of *Withania somnifera* as a preventive and prophylactic for treating COVID-19 infection. Withametelin isolated from *Datura innoxia* plant, has shown a better binding affinity against Mpro, S-protein and ACE-2. However, the pharmacological analysis revealed its toxicity to health. Other compound known as Daturaolone also isolated from *Datura innoxia*, has shown lower toxicity and potent antiviral and anti-inflammatory activities. These compounds can be further developed and assessed as phytoformulations against SARS-CoV-2 infection [8].

2.4 Siddha medicine

During molecular docking and simulation analysis for the prevention and cure of COVID-19 infection on some phytoconstituents of Siddha medicine were determined as potential candidates. Among them orientin, bis-andrographolide, cucurbitacin B, cucurbitacin E, isocucurbitacin B, vitexin, berberine, bryonolic acid, piperine and magnoflorine were identified as potential lead molecules that have been shown to possess the ability to interact with the components that block the viral replication in SARS-CoV-2. Moreover, the immune-enhancing properties of these compounds without any adverse side effects could provide natural immune power to resist COVID-19 infections [14]. Several plants have been found to act on the ACE-2 receptor, which could become promising antiviral agents and can help in combatting COVID-19 pandemic. *Rheum palmatum, Polygonum multiflorum, Cerasus avium, Alcea digitata, Rubia tinctorum, Citrus aurantium, Berberis integerrima, Peganum*

harmala and Allium sativum have the potential to act on the ACE-2 receptor and are well-known for blocking the transmission or entry of Coronoviruses. These plants can possibly be used for the combinational therapeutic management of COVID-19 by inhibiting various protein targets of SARS-CoV-2 (**Table 1**) [15].

Traditional medicines	Medicinal plants	Antiviral compounds	Virus	References
Traditional Chinese Medicine	*Agastache rugosa*, *Atractylodes macrocephala*, *Bupleurum chinense,* *Citrus reticulata*, *Glycyrrhiza glabra*, *Ophiopogon japonicus,* *Polygonum cuspidatum*, *Prunus armeniaca* var. *ansu* *Ramulus cinnamomi,* *Rheum palmatum*, *Saxifraga melanocentra,* *Scutellaria baicalensis*, *Stephania tetrandra,* *Zingiber officinale*	Emodin, Pyrogallol	SARS-CoV-2, Influenza A (IAV), Feline Calici Virus (FCV) and Murine Noro Virus (MNV)	[4–6]
Traditional Persian Medicine	*Allium sativum*, *Alpinia galanga* *Alpinia officinarum* *Cichorium intybus* *Crocus sativus* *Glycyrrhiza glabra* *Glycyrrhiza uralensis* *Phyllanthus emblica* *Rheum officinale* *Rheum palmatum* *Rosa damascena* *Syzygium aromaticum* *Trigonella foenum-graecum* *Vitis vinifera*	—	SARS-CoV-2	[7]
Ayurveda	*Acanthopanax gracilistylus,* *Andrographis paniculata,* *Cimicifuga racemosa* *Clerodendrum* species, *Coptis chinensis* *Curcuma longa,* *Datura innoxia,* *Glycyrrhiza glabra,* *Melia azedarach* *Phellodendron amurense* *Phyllanthus spp.,* *Sanguisorba officinalis* *Sophora flavescens*, *Torilis arvensis,* *Torreya nucifera,* *Withania somnifera*, *Zingiber officinale*	Amarogentin Amentoflavone, α-Amyrin, β-sitosterol, Belladonnine, Caesalpinins, Daturaolone, Eufoliatorin, Glycyrrhizic acid, Hypericin, Kutkin, Lectin, Torvoside H, Taraxerol, Withanolide A, Withametelin	SARS-CoV-2, H_1N_1 Influenza	[8–13]

Traditional medicines	Medicinal plants	Antiviral compounds	Virus	References
Siddha medicine	*Alcea digitata, Allium sativum Berberis integerrima, Cerasus avium, Citrus aurantium, Peganum harmala Polygonum multiflorum Rheum palmatum, Rubia tinctorum*	Berberine, Bis-andrographolide Bryonolic acid, Cucurbitacin B, Cucurbitacin E, Isocucurbitacin B, Magnoflorine, Orientin, Piperine Vitexin	SARS-CoV-2	[14, 15]
Thai traditional medicine	*Boesenbergia rotunda*	Panduratin A	SARS-CoV-2	[16]
African traditional medicine	*Abrus precatorius Acacia senegal, Achyranthes aspera Allium sativum*, *Annona muricata Artemisia afra*, *Azadirachta indica Cryptolepis sanguinolenta*, *Curcuma longa, Euphorbia hirta Garcinia kola*, *Glycyrrhiza glabra*, *Hypoxis hemerocallidea, Moringa oleifera* Lam., *Nigella sativa* L., *Psidium guajava Sutherlandia frutescens, Xysmalobium undulatum, Zingiber officinale*	Arabic acid, Hypoxoside, L-Cnavanine, Uzarine	SARS-CoV-2	[17]
Traditional South American Countries Medicine	*Althaea officinalis*, *Commiphora molmol*, *Glycyrrhiza glabra*, *Hedera helix, Sambucus nigra Uncaria tomentosa,*	3-dihydrocadambine, 3isodihydrocadambine Proanthocyanidin C1, Proanthocyanidin B4, Proanthocyanidin B2 Proanthocyanidin C1, Speciophylline Uncarine acid, Uncaric F	SARS-CoV-2	[18, 19]
Phytoconstituents			SARS-CoV-2, H_1N_1 Influenza	[20–30]
Alizarine, Aloe-Emodin, Amaranthin, Anthrarufin, Calceolarioside B, Curcumin, Dantron, Emodin, Harman, Harmalol, Hypericin, Licoleafol, Lycorine, Methyl rosmarinate, Mycophenolate Mofetil, Myricetin, Myricitrin, Ouabain, Resveratrol, Scutellarein, Silvestrol, Tylophorine, Vasicine, Vasicinone, 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, 3,5,7,3′,4′,5′-hexahydroxy flavanone-3-*β*-D-glucopyranoside, (2S)-eriodictyol 7-*O*-(6″-*O*-galloyl)-*β*-D-Glucopyranoside, 3-*O*-*β*-D-glucopyranoside				

Table 1.
The list of traditional medicines for antiviral activities.

2.5 Thai traditional medicine

Among 122 Thai traditional medicines, *Boesenbergia rotunda* extract and its compound, known as panduratin A exhibited the potent anti-SARS-CoV-2 activity by using the high-content imaging system coupled with the plaque reduction assay. Treatment with *Boesenbergia rotunda* extract and panduratin A after viral infection drastically suppressed SARS-CoV-2 infectivity in Vero E6 cells with IC_{50} of 3.62 μg/mL (CC_{50} = 28.06 μg/mL) and 0.81 μM (CC_{50} = 14.71 μM), respectively. Also, the treatment of panduratin A at the pre-entry phase inhibited SARS-CoV-2 infection with IC_{50} of 5.30 μM (CC_{50} = 43.47 μM). Therefore, Panduratin A exerted the inhibitory effect against SARSCoV-2 infection at both pre-entry and post-infection phases as the novel natural candidate [16].

2.6 African traditional medicine

Fifteen African ethnomedicinal herbs (*Abrus precatorius* L. Gaertn, *Achyranthes aspera* L., *Allium sativum* L., *Annona muricata* L., *Artemisia afra* Jacq. ex Willd, *Azadirachta indica* A. Juss., *Cryptolepis sanguinolenta* (Lindl.) Schltr., *Curcuma longa* L., *Euphorbia hirta* L., *Garcinia kola* Heckel, *Glycyrrhiza glabra* L., *Moringa oleifera* Lam., *Nigella sativa* L., *Psidium guajava* L., *Zingiber officinale* Roscoe) used in African traditional medicine from different countries in Africa were investigated in the prevention, treatment and management of COVID-19 infection [17]. From them, *Glycyrrhiza glabra* was reported to be successful inhibitor for SARS-CoV replication and was recommended for the management COVID-19. Due to the complex nature of SARS-CoV-2 and clinical presentation of COVID-19 disease, combining two or more extracts with various pharmacological activity from these herbs in a standard dosage form such as capsule, tablets, syrups, and injections is necessary in the management of the disease. This combination would improve adherence but care must be taken to ensure that all ingredients in the formulation are compatible otherwise it may lead to therapeutic failure or toxicity. These findings will serve as a source of information for future research in the selection of herbs which could be used in the management of COVID-19 [17].

2.6.1 African medicinal plants

Sixty-two alkaloids and hundred terpenoids isolated from some African medicinal plants were docked to the 3-Chymotrypsin-Like protease (3CLpro) controled coronavirus replication as a promising drug target for combating the coronavirus infection. The twenty alkaloids and terpenoids with high binding affinities to the SARS-CoV-2 3CLpro were further docked to the 3CLpro of SARS-CoV by comparing with the reference inhibitors (Lopinavir and Ritonavir). From them, 10-hydroxyusambarensine, cryptoquindoline, 6-oxoisoguesterin and 22-hydroxyhopan-3-one showed potent activity against SARS-CoV-2 3CLpro [31].

2.6.2 Nigerian medicinal plants

Fifty Nigerian medicinal plants and their 9 phytoconstituents were investigated against symptoms related to COVID-19. Their specific therapeutic actions are administered to combat the key players in the pathogenesis of the disease [32].

2.6.3 Moroccan medicinal plants

The molecular docking studies on sixtyseven phytoconstituents from Moroccan medicinal plants were evaluated for their *in vitro* and *in vivo* antiviral activity against SARS-COV-2 Main protease before clinical trial. The results of molecular docking studies showed that three compounds (crocin, digitoxigenin, and *β*-eudesmol) were proposed as inhibitors against the coronavirus based on the energy types of interaction between these compounds and studied protein [33].

2.6.4 South African medicinal plants

Twentynine phytoconstituents isolated from commonly used South African traditional medicinal plants were examined against SARS-CoV-2 using molecular docking and molecular dynamics. Molecular docking identified arabic acid from *Acacia senegal* and L-canavanine found in *Sutherlandia frutescens* were determined as a potential inhibitor 3C-Like main protease (3CLpro) of SARS-CoV-2. Similarly, hypoxoside isolated from *Hypoxis hemerocallidea* and uzarin from *Xysmalobium undulatum* were also identified as a potential inhibitor of SARS-CoV-2 receptor binding domain and SARS-CoV-2 RNA-dependent polymerase (SARS-CoV-2 RdRp). In addition, these compounds exhibited favorable binding orientations characterized by strong molecular interactions within respective inhibitors binding pockets of the target enzymes [34].

2.7 Traditional medicinal plants of South American countries

Uncaria tomentosa (cat's claw) is traditionally used medicinal plant in South American countries. Twentysix phytoconstituents of *Uncaria tomentosa* were docked on the binding interface of the ACE-2 and SARS-CoV-2 spike protein of novel corona virus. From these compounds namely Proanthocyanidin C1, 3-isodihydrocadambine, Uncarine F and Uncaric acid had a good predicted binding affinity for interface of the ACE-2 as compared to the sulfated Heparin OctaSaccharide (HepOS). Likewise, 3-dihydrocadambine, Proanthocyanidin B4, Proanthocyanidin B2 and Proanthocyanidin C1 had the highest docking score on SARS-CoV-2 spike glycoprotein in their open state. Virtual prediction ADME revealed that Speciophylline, Uncarine F and Uncaric acid presented values of drug ability according to Lipinski rule, demonstrating their potential bioavailability as likely orally active antiviral. *Uncaria tomentosa* can be performed as an herbal supplement with the safety and efficacy parameters at both preclinical and clinical stages to evaluate its effectiveness in the treatment of novel coronavirus disease (COVID-19) [18].

Thirty-nine herbal medicinal plants known in the America and Europe for the management of respiratory conditions, mainly regarding the symptoms cough, pain and fever were studied for their therapeutic potential alongwith the limitations for their use and possible risks. For five out of the 39 herbal drugs a positive benefit/risk assessment was determined. The level of evidence for *Althaea officinalis*, *Commiphora molmol*, *Glycyrrhiza glabra*, *Hedera helix* and *Sambucus nigra* are suggested a potential clinical use as adjuvants in the treatment of early/mild cases of COVID-19. Another twelve herbal medicines were classified as promising plant species [19].

3. Various phytoconstituents

Various phytoconstituents occured in living organisms in a high structural diversity have antiviral activities by inhibiting different stages in the replication

of various viruses. Their different antiviral mechanisms like virus adsorption, virus-cell fusion, reverse transcription, protease and integrase inhibition have been reported in recent studies [20, 21]. Lycorine, hypericin, emodin, tylophorine, ouabain, mycophenolate mofetil, silvestrol, myricetin and scutellarein were also reported for their inhibitory effects against SARS-CoV-2 and other human coronaviruses [22]. Some phytoconstituents such as myricitrin, methyl rosmarinate, 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, 3,5,7,3′,4′,5′-hexahydroxy flavanone-3-*β*-D-glucopyranoside, (2*S*)-eriodictyol 7-*O*-(6′′-*O*-galloyl)-*β*-D-glucopyranoside, calceolarioside B, myricetin, 3-*O*-*β*-D-glucopyranoside, licoleafol, and amaranthin were reported as potential lead candidates to develop novel anti-SARS-CoV-2 drugs [23].

Moreover, anthraquinone derivatives were screened on the basis of binding energy against N-Terminal Domain (NTD) of SARS-CoV-2. Emodin, Anthrarufin, Alizarine, Aloe- emodin, and Dantron showed the good binding affinity at three different active sites of N-Terminal Domain of SARS-CoV-2 nucleocapsid phosphoprotein. These compounds prevent the assembly of virus particles and stop the infection. They are suggested as potential drugs for COVID-19 treatment [24]. From secondary metabolites, curcumin as the main constituent of *Curcuma longa* L. (turmeric), is the reputed compound displaying remarkable biological activities for human health. It has been shown to have an inhibiting effect against SARS-CoV-2 [25]. Synthesized resveratrol derivatives have been shown to suppress SARS-CoV replication and reduce its clinical symptoms [26]. Some *beta*-carboline alkaloids including harman, harmalol and quinazoline-type alkaloids like vasicine and vasicinone have showed antiviral effect against influenza virus [27].

Among the secondary metabolites, essential oils interfere with the virus envelope or masking viral compounds which are necessary for adsorption or entry into host cells. Essential oils have long been known to have antiviral properties and are being proposed to have activity against SARC-CoV-2 virus [28]. Owing to their lipophilic nature, essential oils are advocated to penetrate viral membranes easily leading to membrane disruption. Moreover, essential oils contain multiple active phytochemicals that can act synergistically on multiple stages of viral replication and also induce positive efects on host respiratory system including bronchodilation and mucus lysis. Their antiviral properties were shown by computer-aided docking and *in vitro* studies for anti-SARC-CoV-2 [29, 30].

4. Conclusion

Plants and their secondary metabolites provide valuable leads for the development into drugs for the novel antiviral activities. Ivermectin is the FDA approved drug and inhibited the replication of SARS-CoV-2 [35]. Although there is an increase in the use of traditional medicine worldwide, researches in traditional medicines are insufficient. Assessments of the quality, safety, and efficacy of traditional medicines are needed to provide scientific information that regulations need. In the present review, antiviral activity mainly against coronaviruses of traditional medicines along with their phytoconstituents through the literature data relevant to their enzyme and receptor interactions given by different assays. Pre-clinical studies would provide deep insight into mechanism of actions and also drug ability of the antiviral candidates for the treatment of COVID-19 infection. Besides, vast range of double-blinded clinical studies with strict protocols is required to estimate the accurate potential of antiviral phytochemicals against COVID-19 with the aim of ensuring the fulfillment of international acceptable standards. Therefore, phytoconstituents will play an important role and continue to support in developing potential drugs against SARS-CoV-2.

Conflict of interest

The authors declare no conflict of interest.

Author details

Mehtap Kilic[1] and Bilge Sener[2*]

1 Faculty of Pharmacy, Department of Pharmacognosy, Health Sciences University, Ankara, Turkey

2 H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan

*Address all correspondence to: bilgesener11@gmail.com

References

[1] Salehi B, Kumar NVA, Sener B, Sharifi-Rad M, Kılıc M, Mahady GB, Vlaisavljevic S, Iriti M, Kobarfard F, Setzer WN, Ayatollahi SA, Ata A, Sharifi-Rad J. Medicinal plants used in the treatment of human immunodeficiency virus. Int. J. Mol. Sci. 2018;19(5):1459-1519. DOI: 10.3390/ijms19051459

[2] Hudson JB, Lee MK, Sener B, Erdemoglu N. Antiviral activities in extracts of Turkish medicinal plants. Pharm. Biol. 2000;38:171-175. DOI: 10.1076/1388-0209(200007)3831-SFT171

[3] Sener B. Antiviral activity of natural products and herbal extracts. Gazi Medical J. 2020;31:474-477.

[4] Lee DYW, Li QY, Liu J, Efferth T. Traditional Chinese herbal medicine at the forefront battle against COVID-19: Clinical experience and scientific basis. Phytomedicine 2020;80:153337. DOI: 0.1016/j.phymed.2020.153337

[5] Qamar MT, Alqahtani SM, Alamri MA, Chen, L-L. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. J. Pharm. Anal. 2020;10:313e319. DOI: 10.1016/j.jpha.2020.03.009

[6] Takeda Y, Murata T, Jamsransuren D, Suganuma K, Kazami Y, Batkhuu J, Badral D, Ogawa H. *Saxifraga spinulosa*-derived components rapidly inactivate multiple viruses including SARS-CoV-2. Viruses. 2020;12:699. DOI: 10.3390/v12070699

[7] Bahramsoltani R, Rahimi R. An evaluation of traditional Persian medicine for the management of SARS-CoV-2. Front. Pharmacol. 2020;11:571434. DOI: 10.3389/fphar.2020.571434

[8] Mondala P, Natesha J, Abdul Salam AA, Thiyagarajand S, Meerana SM. Traditional medicinal plants against replication, maturation and transmission targets of SARS-CoV-2: Computational investigation. J.Biomol. Struc. Dyn. 2020;5:1-18. DOI: 10.1080/07391102.2020.1842246

[9] Saravanan KM, Zhang H, Senthil R, Vijayakumar KK, Sounderrajan V, Weia Y, Shakila H. Structural basis for the inhibition of SARS-CoV2 main protease by Indian medicinal plant-derived antiviral compounds. J. Biomol. Struc. Dyn. 2020;1-9. DOI: 10.1080/07391102.2020.1834457

[10] Maurya VK, Kumar S, Bhatt MLB, Shailendra K, Saxena SK. Antiviral activity of traditional medicinal plants from Ayurveda against SARS-CoV-2 infection. J.Biomol. Struc. Dyn. 2020;19:1-17. DOI: 10.1080/07391102.2020.183277

[11] Mishra A, Pathak Y, Tripathi V. Natural compounds as potential inhibitors of novel coronavirus (COVID-19) main protease: An in silico study.ResearchSquare.DOI:21203/rs.3.rs-22839/v1

[12] Sharma K, Zafar, R. Occurrence of taraxerol and taraxasterol in medicinal plants. Pharmacog. Rev. 2015;9:19-23. DOI: 10.4103/0973-7847.156317

[13] Cai Z, Zhang G, Tang B, Liu Y, Fu X, Zhang X. Promising anti-influenza properties of active constituent of *Withania somnifera* Ayurvedic herb in targeting neuraminidase of H_1N_1 influenza: Computational study. Cell Biochem Biophys. 2015;72(3):727-739. DOI: 10.1007/s12013-015-0524-9

[14] Lakshmi SA, Shafreen RMB, Priya A, Shunmugiah KP. Ethno-medicines of Indian origin for combating COVID-19 infection by hampering the viral replication: Using structure-based drug discovery approach. J. Biomol. Struc. Dyn.

2020;1-16. DOI: 10.1080/07391102.2020.1778537

[15] Siddiqui AJ, Danciu C, Ashraf SA, Moin A, Singh R, Alreshidi M, Patel M, Jahan S, Kumar S, Alkhinjar MIM, Badraoui R, Snoussi M, Adnan M. Plants-derived biomolecules as potent antiviral phytomedicines: New insights on ethnobotanical evidences against coronaviruses. Plants. 2020;9:1244. DOI: 10.3390/plants9091244

[16] Phongthon KP, Suksatu A, Manopwisedjaroen S, Munyoo1 B, Tuchinda P, Jearawuttanakul K, Seemakhan S, Charoensutthivarakul S, Wongtrakoongate P, Rangkasenee N, Pitiporn S, Waranuch N, Chabang N, Khemawoot P, Sangiamsuntorn K, Pewkliang Y, Thongsri P, Chutipongtanate S, Hongeng S, Borwornpinyo S, Thitithanyanont A. High-content screening of Thai medicinal plants reveals *Boesenbergia rotunda* extract and its component Panduratin a as anti-SARS-CoV-2 agents. Scientifc Reports. 2020;10:19963. DOI:10.1038/s41598-020-77003-3

[17] Adeleye OA, Femi-Oyewo MN, Bamiro OA, Bakre LG, Alabi A, Ashidi JS, Balogun-Agbaje OA, Hassan OM, Fakoya G. Ethnomedicinal herbs in African traditional medicine with potential activity for the prevention, treatment, and management of coronavirus disease 2019. Future J. Pharm. Sci. 2021;7:72. DOI: 10.1186/s43094-021-00223-5.

[18] Yepes-Pereza AF, Herrera-Calderonb O, Quintero-Saumeth J. *Uncaria tomentosa* (cat's claw): A promising herbal medicine against SARS-CoV2/ACE-2 junction and SARS-CoV-2 spike protein based on molecular modeling. J. Biomol. Struc. Dyn. 2020;29:1-17. DOI: 10.1080/07391102.2020.1837676

[19] Silveira D, Prieto-Garcia JM, Boylan F, Estrada O, Fonseca-Bazzo YM, Jamal CM, Magalhães PO, Pereira EO, Tomczyk M, Heinrich M. COVID-19: Is there evidence for the use of herbal medicines as adjuvant symptomatic therapy? Front. Pharmacol. 2020;11: 581840. DOI: 10.3389/fphar.2020.581840

[20] Taban Akça K, Suntar I. An overview on flavonoids as potential antiviral strategies against coronavirus infections. Gazi Medical J. 2020;31:478-484.

[21] El Sayed KA. Natural products as antiviral agents. Stud. Nat. Prod. Chem. 2000;24:473-572. DOI: 10.1016/S1572-5995(00)80051-4

[22] Jahan I, Onay A. Potentials of plant-based substance to inhabit and probable cure for the COVID-19. Turk. J. Biol. 2020;44:228-241. DOI: 10.3906/biy-2005-114

[23] Erdogan Orhan I, Senol Deniz FS. Natural products as potential leads against coronaviruses: Could they be encouraging structural models against SARS-CoV-2? Nat. Prod. Bioprospect. 2020;10:171-186. DOI: 10.1007/s13659-020-00250-4

[24] Rolta R, Yadav R, Salaria D, Trivedi S, Imran M, Sourirajan A, Baumler DJ, Dev K. In silico screening of hundred phytocompounds of ten medicinal plants as potential inhibitors of nucleocapsid phosphoprotein of COVID-19: An approach to prevent virus assembly. J.Biomol. Struct. Dyn. 2020;27:1-18. DOI: 10.1080/07391102.2020.1804457

[25] Erdogan Orhan I, Senol Deniz FS. Golden pigment curcumin: An inspiring antiviral molecular model for COVID-19 drug design. Gazi Medical J. 2020;31: 469-473.

[26] Huang H, Liao D, Zhou G, Zhu Z, Cui Y, Pu R. Antiviral activities of resveratrol against rotavirus *in vitro* and *in vivo*. Phytomedicine. 2020;77:153230. DOI: 10.1016/j.phymed.2020.153230

[27] Mohammad-Taghi M, Moradi MT, Karimi A, Kopaei M, Fotouhi F. *In vitro* antiviral effects of *Peganum harmala* seed extract and its total alkaloids against influenza virus. Micropath. 2017;110:42-49. DOI: 10.1016/j.micpath.2017.06.014

[28] Asif M, Saleem M, Saadullah M, Yaseen HS, Al Zarzour R. COVID-19 and therapy with essential oils having antiviral, anti-infammatory, and immunomodulatory properties. Infammopharmacology. 2020;28(5):1153-1161. DOI: 10.1007/s10787-020-00744-0

[29] Bakkali F, Averbeck S, Averbeck D, Idaomar M. Biological effects of essential oils. Food and Chem Tox. 2008;46:446-475. DOI: 10.1016/j.fct.2007.09.106

[30] Boukhatem MN, Setzer WN. Aromatic herbs, medicinal plant-derived essential oils and phytochemical extracts as potential therapies for coronaviruses: Future perspectives. Plants. 2020;9:800. DOI: 10.3390/plants9060800

[31] Gyebia GA, Ogunrob OB, Adegunloyec AP, Ogunyemia OM, Afolabid SO. Potential inhibitors of coronavirus 3-chymotrypsin-like protease (3CLpro): An in silico screening of alkaloids and terpenoids from African medicinal plants. J. Biomol.Struc.Dyn. 2020;18:1-1813. DOI: 10.1080/07391102.2020.1764868

[32] Oladele J, Ajayi EI, Oyeleke OM, Oladele OT, Olowookere BD, Adeniyi BM, Oyewole OI, Oladiji AT. A systematic review on COVID-19 pandemic with special emphasis on curative potentials of Nigeria based medicinal plants. Heliyon. 2020;6:104897. DOI:10.1016/j.heliyon.2020.e04897

[33] Khatabia K, Lakhlifia T, El-ldrissia M, Bouachrine M. Moroccan medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. J.Biomol.Struc.Dyn. 2020;6:1-9. DOI: 10.1080/07391102. 2020.1758790

[34] Dwarka D, Agoni C, Mellem JJ, Soliman ME, Baijnath H. Identification of potential SARS-CoV-2 inhibitors from south African medicinal plant extracts using molecular modelling approaches. South African J. Bot. 2020;133:1-12. DOI: 10.1016/j.sajb.2020.07.035.

[35] Calya L, Drucea JD, Cattona MG, Jansb DA, Kylie M, Wagstaf KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res. 2020;178:104787. DOI: 10.1016/j.antiviral.2020.104787