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Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-COV-2) Inhibition and Other Antiviral Effects of Ethiopian Medicinal Plants and Their Compounds

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Abstract

Since the outbreak of coronavirus disease 19 (COVID-19), so many people were dying in the world. Treatment modalities have not been developed yet although repurposing of different drugs is done swiftly. None of the repurposed drugs has been approved for treating this pandemic to date. To this effect, herbal medicines are getting a lot of attention in many developing countries since they have a long history of utility to prevent and treat viral infection. Up on extending this knowledge several compounds isolated from herbs are on the pipeline of in silico studies to investigate their inhibitory effects on COVID-19. Most of them exhibited promising effects, although *in vitro, in vivo,* and clinical studies are needed to substantiate their therapeutic implications. This review focuses on herbal medicines of Ethiopia and their compounds potential complementary effects for the treatment of this disease and other viral infections that need prompt further investigations. Most of the medicinal plants and their compounds mentioned herein are investigated for their anti-COVID-19 activities in different molecular docking studies.

Keywords: Antiviral; COVID-19; Medicinal herbs; SARS-COV-2

Abbreviations: ADV: Adenovirus; COVID-19: Coronavirus Disease 2019; CB1V: Coxsackie B1 Virus; CMV: Cytomegalovirus; HIV: Human Immunodeficiency Virus; HSV: Herpes Simplex Virus; PIV: Para-Influenza Virus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; VSV: Vesicular Stomatitis Virus

Introduction

The coronavirus disease 19 (COVID-19) pandemic is contagious and unique in several aspects and has impacted health care systems around the world [1]. Since December 2019, the outbreak of COVID-19, which originated from China, has become a global public health threat [2]. As of May 09, 2020, 4, 029,543 coronavirus cases and 276, 543 deaths were reported almost from all countries of the world [3]. Based on the current knowledge, the disease couldn`t be cured by specific new and already available clinical drugs despite the presence of continuous efforts to repurpose drugs and identify potent novel compounds. In the face of all these challenges, different countries have been reported the use of herbal medicines in preventing and treating COVID-19, though world health organization warns the countries on the safety profiles of the traditional medicines. Traditional chines medicines are one of the herbal preparations getting a lot of attention although clinical shreds of evidence are strictly needed to evaluate the efficacy of these remedies [4].

Besides, Ethiopia is one of the countries endowed with plant biodiversity that have numerous medicinal values. From the medicinal herbs available in Ethiopia; *Nigella sativum*, *Allium sativum*, *Allium cepa*, *Brassica junce*, *Curcuma longa*, *Zingiber officinale*, *Capsicum annum*, and *Citrus sps* are mentioned in different literature for their antiviral activities [5,6]. Despite incomplete studies performed so far, the promising efficacy of *N. sativa* against Human Immunodeficiency Virus (HIV) can be explored as an alternative option for the treatment of this disease after substantiating its full therapeutic efficacy [7]. Quercetin which is isolated from *Allium cepa* can inhibit RNA polymerase; thereby affects entry, attachment, and replication of enterovirus and influenza virus on the host cell. It also alters the process by which virus affect signalling pathway in the host cell. On the other hand, organosulfur compounds like ajoene, diallyltrisulide, and allicin are the main chemicals that impart antiviral property to *A. sativum* [6].

Traditional Medicines for COVID-19 Treatment

Moreover, different ethnobotanical and molecular studies recently revealed that compounds isolated from these herbs exhibited inhibition of coronavirus infection [8]. In different Insilco studies, many compounds from these herbs showed inhibition of SARS-COV-2 main (M) protease, spike (S) glycoprotein, chymotrypsin-like protease (3CLpro), and angiotensin converting enzyme-2 (ACE2) receptor. Therefore,

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the main objective of this review is to suggest some insights to researchers to do further *in vitro, in vivo*, and clinical investigations on the compounds isolated from the following plant species, but not to recommend the communities to use these traditional medicines for COVID-19 treatment **Table 1.**

Table 1: SARS-COV-2 inhibition and other antiviral effects of medicinal plants and their compounds.

Sr. no.	Scientific name	Vernacular name (Amharic)	Isolated compounds with potential anti-COVID-19 activities	Literatures supporting SARS-COV-2 inhibition	Other viral infections treated
1	*Allium cepa*	Key shin kurt	Quercetin epigallocatechin gallate	In silico study showed that quercetin and epigallocatechin gallate isolated from this plant found to be potential inhibitors of COVID-19 main (M) protease [9,10]. The latter one has high oral bioavailability	Enterovirus 71 (EV7, influenzas virus, and avian influenza virus (AI- H9N2) [6,11]
2	*Allium sativum L* (tm 15)	Nech shinkurt	Allicin diallyltrisulide ajoene apigenin	Essential oils, Allicin, diallyltrisulideajoene, and apigenin have strong interactions with the host receptor of ACE2, and exhibited M protease inhibition by 70% [12]	Herpes Simplex Virus (HSV-1 and 2) [13], Influenza A and B virus [14], HIV, Common cold virus, Coxsackie Bl virus (CB1V), Infectious Bronchitis virus, CytomegaloVirus (CMV), Dengue virus, Vesicular Stomatitis Virus (VSV), Para-Influenza Virus type 3 (PIV), and vaccinia virus, [13-22]
3	*Aloe barbadense miller*	Eret	Aloenin aloesin aloe-emodin aloin chrysophanol catechin isoaloresin aloin A	Aloenin extracted from this plant showed a greater binding affinity for COVID-19 protease (6LU7) using in silico study [23]	Influenza virus, Avian Paramyxo Virustype-1 (APMV-1), AI-H5N1, Newcastle Disease Virus (NDV), HSV-1 and 2, H1N1, and Egg-Drop Syndrome Virus (EDSV) [24,25]
4	*Artemesiaannua L*	Chigugn	Artemisinin	In china *Artemesi aannua* ethanolic extract exhibited a potent inhibitory effect against SARA-COV [26]. In addition, according to a study done in Algeria, artemisinin was found to be more effective than hydroxychloroquine against SARS-COV-2 [27]	Influenza virus, tobamoviruses, HSV-6, and HIV [14,28,29]
5	*Bambusa vulgaris*	Shembeko		In chines traditional medicines preparation "yinqiao san", this plant is combined with other plants for the treatment of mild COVID 19 [30]	Measles virus, HSV-1, and yellow fever virus [31,32]
6	*Brassica juncea*	Senafch	Kaempferol glucobrassicin	Glucobrassicin isolated from these plants showed a greater binding affinity for SARS-COV-2 6LU7 and 6Y2E proteases [33]. Kaempferol extracted from *Brassica oleraceavar.* italic showed inhibition of SARS-CoV-2 M protease (Mpro) and Spike (S) glycoprotein [10]	Influenza A/H1N1 Virus [34,35]
	Brassica oleraceavar italic	Broccoli			
	Brassica oleracea	Gomen			
7	*Camellia sinensis*	Shay kitel		Epigallocatechin gallate with high oral bioavailability is also isolated from *Camellia sinensis* and endowed with good binding affinity for SARS-COV-2 S-glycoprotein and M Protease [10]	ADV, HBV, HCV, Influenza Virus, HIV, Bovine Coronavirus, Epstein-Barr virus, EV71, HSV, Chikungunya Virus (CHIKV), Laryngotracheitis Virus (ILTV) [36, 37]

8	*Capsicum annum*	Berbere	Apigenin	Apigenin is isolated from this plant and other species exhibited a good binding affinity for 6LU7 and 6Y2E proteases in molecular docking study [33]	HSV-1 and 2, Poliovirus 1 [38,39]
9	*Citrus aurantium L.*	Behire lomi	Apigenin ethyl cholate nobiletin tangeretin chalcone	The study showed that citrus fruit has many active compounds that have anti-SARS-CoV-2 effects [10]	Respiratory Syncytial Virus (RSV), rotavirus infection [40,41]
10	*Citrus sinensis*	Birtukan	Rhoifolin	----------	Hepatitis A Virus (HAV), Rabies virus and HIV [42,43]
11	*Citrus limon*	Lomi	Hesperidin	Computational studies suggest that hesperidin, a flavonoid abundant in citrus peel, binding with the three main cellular receptors of SARS-CoV-2 virus can act as prophylaxis and treatment of COVID-19 [44]	Common cold, HAV, HCV [14,45]
12	*Curcuma longa*	Erd	Curcumin	Curcumin interacts with SARS-COV2 viral S-glycoprotein and ACE2 of the human cell membrane [46]	PIV-3, Feline Infectious Peritonitis Virus (FIPV), VSV, HSV, flock house virus (FHV), RSV, HIV, HBV, HCV, and HPV [47-59]
13	*Lycopersicones culentum*	Timatim	Rhoifolin	Rhoifolin is a compound extracted from this plants that showed inhibition of SARS-COV-2 Spike and M protease [60]	----------
14	*Musa spp.*	Muz	Rhoifolin	Rhoifolin from this plant species exhibited SARS-COV-2 3CLpro inhibition in molecular docking study [61]	Influenza virus [62]
15	*Nigella sativa*	Tikur azmud	Hederagenin nigelledine a-Hederin	Hederagenin is a constituent of *N. sativa* and several Cucurbitaceae vegetables including *luffa cylindrvica* and *Momordica dioica*, making it again a potentially useful candidate for SARS-COV-2 treatment [33]. Among the different compounds isolated from this plant a-Hederin and nigelledine also exhibited promising effects against SARS-COV-2. Moreover, nigelledine docked into 6LU7 active site gives energy complex about which is close to the energy score given by chloroquine and better than energy score given by hydroxychloroquine and favipiravir [63]	HIV [7], CMV, Avian Influenza (H9N2), Chistosoma Mansoni Infection, Broad Bean Mosaic Virus, HCV, Laryngo Trachiets Virus (ILTV) [64,65]
16	*Ocimumbasilicum*	Bessobila	Ursolic acid	Ursolic acid; a compound isolated from this plant binds with SARS-COV-2 6LU7 and 6Y2E proteases and expected to inhibit the activity of the enzyme and hence restrain viral replication [33]	HSV-C and B, Adenoviruses (ADV), CVB1 and EV71 [66]
17	*Olea europea L*	Woira	Oleanolic acid	Oleanolic acid extracted from *Olea europea L* is mentioned as one of the promising compounds and could serve as potential candidates for further research [33]	Viral Haemorrhagic Septicaemiarhabdo Virus (VHSV), herpes mononucleosis, hepatitis virus, rotavirus, bovine rhinovirus, canine parvovirus, and feline leukaemia virus [67,68]
18	*Phaseolus vulgaris*	Bakela	Kaempferol	Flavonoids like Kaempferol Inhibit SARS-CoV 3CL protease [69]	HIV1, RSV and HSV-1 [70,71]

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19	*Phragmitesaustralis*	Ketema		Phragmites Australis, mint, Chinese bellflower, and licorice mixed and boiled together with 1000 ml pure water for about 15 minutes after boiling to get about 600 ml tincture. Each tincture may be subdivided into three doses and taken 200 ml orally once, three times a day for COVID 19 [30]	Bovine Herpes Virus type 1 (BoHV-1) [72]
20	*Piper nigrum*	Kundo berbere	Piperine	Piperine isolated from this plant exhibited inhibition of chymotrypsin-like protease of COVID-19 virus in molecular docking studies [73]	VSV, PIV, CVB3 [74]
21	*Prunus dulcis*	Lewuz	Almond oil	Almond oil in combination with mulberry leaf, chrysanthemum, and forsythia is considered as one of the components of chines traditional medicines for mild case COVID 19 treatment [30]	HSV-1 and 2 [75,76].
22	*Rosmarinus officinal*	Tibs kitel	Rosmarinic acid	Rosmarinic acid is isolated from this plant and other species endowed with a good binding affinity for 6LU7 and 6Y2E protease in molecular docking study [33]	RSV-A and B [77]
23	*Spinaciaoleracea*	Kosta	Kaempferol	Kaempferol isolated from this plants and other species has low to good oral bioavailability, exhibited a better binding affinity for SARS-CoV-2 Mpro and Spike (S) glycoprotein [10]	
24	*Syzygiumaromaticum*	Kirnfud	Essential oil oleanolic acid	Like Influenza, SARS-COV-2 infection results in "cytokines storms", which are dramatic and damaging increases in levels of chemokines and pro-inflammatory cytokines, often complicated further by pneumonia. The study suggests that this plant essential oil mitigates the "cytokine storm", inflammation-based on in vivo, and in vitro studies [78]. Oleanolic acid is an integral component of clove oil and again used extensively in culinary preparations reported to inhibit SARS-CoV-2 M protease [79]	Feline Calicivirus (FCV), HSV-1 and 2 [80]
25	*Vitis vinifera*	Weyin fire	Resveratrol rhoifolin	Resveratrol effectively inhibits MERS-CoV infection [81].	HSV-1, PIV [82].
26	*Withaniasomnifera*	Gisewa	Withanolide withanone withaferin A	Withanone from *Withania somnifera* inhibits novel COVID-19 entry by disrupting interactions between viral S-Protein receptor binding domain and host ACE2 receptor [83]	H1N1, HSV 1 and 2, CHIKV [84]
27	*ZingiberOfficinale*	Zinjible	Gingerol shogaol	Gingerol showed potential inhibition of protease enzymes [85]	RSV, H5N1, FCV [86,87]

Conclusion and Prospects

In general, there are several documented in silico and ethnobotanical studies recently on the above-mentioned plants on their activity against COVID-19. All these plants constitute many compounds which have inhibitory effects against coronavirus through modulating viral proteins function and host cell surface receptors. Among the compounds isolated from the aforementioned plants; epigallocatechin gallate, quercetin, hesperidin, luteolin, rhoifolin, kaempferol, curcumin, and apigenin showed better inhibitory effects against SARS-COV-2. Ethiopian herbal medicines are good candidates for the treatment of different viral infections. However, further in vitro, in vivo, and clinical investigations of these plants and compounds isolated from them are needed to substantiate their effects. We expect fast and continuous

efforts on traditional medicines to discover drugs and combat with the COVID-19.

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Author Contributions

All authors wrote and reviewed the manuscript and approved its submission.

Conflict of Interest

The authors declare no competing interests. This manuscript/data, or parts thereof, has not been submitted for possible publication to another journal or previously been published elsewhere.

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