International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 16, Issue 9, 2024

Review Article

ANTIVIRAL POTENTIAL OF HERBAL MEDICINE IN FIGHTING COVID-19 PANDEMIC, RE-INVESTIGATION OF HERBAL MONOGRAPHS

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Received: 01 Jun 2024, Revised and Accepted: 09 Jul 2024

ABSTRACT

Medicinal herbs have been widely used in traditional medicine for their immune-boosting potential to humans in fighting various ailments, especially viral infections causing severe respiratory diseases such as influenza virus, H5N1, coronaviruses of different types, mainly MERS (Middle East Respiratory Syndrome), SARS (Severe Acute Respiratory Syndrome) and SARS-CoV-2 (COVID-19) that was declared by the World Health Organization (WHO), as a global pandemic. Various efforts are focusing despite the discovery of the vaccine, on finding treatments that can combat the serious complications of COVID-19, but in the absence of confirmed effective drugs, it is crucial to explore various possibilities including herbal medicines approved as antiviral agents. This study aims to identify key medicinal plants rich in bioactive compounds with antiviral activity against SARS-CoV-2., with the correlation regarding the collected information on their efficacy and safety with existing data in published official monographs presented to ensure the proper use of these natural constituents. Accordingly, a comprehensive review of the published literature was conducted using various scientific databases, including Scopus, PubMed, Google Scholar, and Web of Science. The analysis revealed the need to update herbal monographs and establish a globally harmonized approach to health claims associated with herbal medicines.

Keywords: COVID-19, SARS, Phytochemicals, Herbal medicine, Coronavirus-host protein pathways, Monographs

DOI: https://dx.doi.org/10.22159/ijpps.2024v16i9.51681 Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

The COVID-19 outbreak started in late December 2019 in Wuhan, China. The most striking clinical manifestation is a Severe Acute Respiratory Syndrome (SARS) known as SARS COV-2 that causes damage to extrapulmonary tissues and organs, including the kidney, heart, liver, and brain, in addition to multiple injuries in the ocular system, the musculoskeletal system, the gastrointestinal system, the cardiovascular system, and the skin [1]. Coronavirus disease was discovered in 1931, with the first coronavirus isolated from humans in 1965 that was (HCoV-229E). Until late 2002, after the outbreak of severe acute respiratory syndrome, only two human coronaviruses (HCoV) were known HCoV-OC43 and HCoV-229E. Once the SARS Coronavirus (SARS-CoV) had been identified, two further human coronaviruses were described. Three groups of coronaviruses exist: group 1 (HCoV-229E and HCoV-NL63), group 2 (HCoVOC43 and HCoV-HKU1), group 3 (no human CoVs as yet). SARS-CoV is an outlier to all three groups, although some place it in group 2 [2]. SARS-CoV-2 is a virus belonging to the family Coronaviridae having an enveloped RNA. This virus has a single-strand positive sense RNA genome 13. Coronaviruses infect several animals; likewise, they cause respiratory illnesses of various intensities in human beings [3]. The origin of SARS-CoV-2 focuses primarily on two hypotheses: zoonotic transmission and potential laboratory involvement. Various research groups have presented arguments both supporting and contesting the notion of a laboratory origin for the virus. Key to these debates is the examination of genetic similarities between SARS-CoV-2 and other coronaviruses found in bats and pangolins, leading to differing interpretations regarding whether these resemblances imply a natural or engineered origin. Certain scholars stress the importance of impartial investigation and transparent data sharing to determine the virus's origin conclusively. While some studies lean towards a zoonotic origin, others suggest that the evidence remains inconclusive, leaving both scenarios viable. Furthermore, meta-analyses have sought to evaluate the probability of natural spillover versus laboratory incidents in the emergence of new viral agents, resulting in diverse conclusions [4]. Because of the rapid rate of spread and the threat to the lives of billions of patients, the World Health Organization (WHO) declared in January 2021 a Public Health Emergency of International Concern upon the life-threatening global outbreak of COVID-19 [5].

The mechanisms involved in the damaging effects of the novel coronavirus are very complex and include endothelial derangement, direct viral toxicity, imbalance in the renin-angiotensin-aldosterone system, and immune dysregulation. Therefore, it is crucial to develop novel, safe, and effective therapies to fight against this virus and save lives [1]. Traditional herbal medicine plays an important role because the world's alternative and complementary medicine is rich in phytochemicals, and according to the WHO, 80% of the population relies on traditional medicine for their health needs. During the 2003 SAS outbreak, herbal treatments were evaluated in several studies. They showed effectiveness in controlling the contagious disease in addition to the use of herbal medicine to treat various respiratory diseases [6]. Thus, after concerns about the safety of these natural products were raised, the WHO established monographs on herbal medicines to provide scientific information on the quality assurance and quality control of widely used herbal medicines and their safety and efficacy. These monographs provide models for assisting regulatory authorities in developing their monographs [7]. Community herbal monographs are also implemented for European herbal substances by the European Medicinal Agency (EMA) to achieve global standards for medicinal plant regulation [8]. This article aims to highlight the pharmacological importance of previously isolated bioactive compounds from herbal medicines and their relative mechanisms of action in fighting against the SARS-CoV-2 virus, in addition to focusing on the relative monographs of these plant species to assure their use according to the specified standards that guarantee their safety and verify the continuous updating of these monographs based on recent findings in this regard. The objective is to present alternative therapeutic options that are both safe and efficacious, particularly in the context of advancing novel treatments for COVID-19.

MATERIALS AND METHODS

A comprehensive literature review was achieved by searching journals and books accessible in databases such as, Scopus, PubMed, Google Scholar, and Web of Science from 1995 to 2024. This review aims to compile data on toxicity, potential side effects, and herb-drug interactions not extensively covered in established monographs.

RESULTS

The results showed the antiviral potential of bioactive compounds in herbal medicines, such as the antiviral potential of Maca (*Lepidium meyenii*) against human influenza types A and B. The methanolic extract showed significant inhibition of the viral growth by interfering with virus attachment or preventing virus-cell fusion, so the research proved that Maca is rich in phytochemicals such as isothiocyanates, fatty acids, saponins, glucosinolates, alkaloids, and flavonoids that have potential inhibitory effects for Flu-A and Flu-B [9]. Moreover, two antiviral flavons, 7-O-galloyltricetiflavan, 7,4-Di-O-galloyltricetiflavan, and quercetin-3-O-β-D-glucopyranosyl, were extracted from the leaves of *Pithecellobium clypearia* and were active against Flu-A (H1N1) [10]. Tannins isolated from persimmon (*Diospyros kaki*) showed inhibition of 12 viruses, among which influenza viruses H3N2 and H5N3 [11]. Further studies showed that Scutellarein, belonging to the flavone monomer class and isolated from *Erigeron karvinskianu*, is widely used in traditional medicine and is active against pulmonary fibrosis, HIV, and SARS. Quercetagetin, a flavonol isolated from *Tagetes erecta*, in addition to dihydromyricetin, a flavanonol isolated from *Ampelopsis megalophylla*, and Osajin, an isoflavone produced by *Maclura pomifera*, can inhibit SARS-CoV-2 replication. Interestingly, Matrine, a quinolizidine alkaloid isolated from *Sophora flavescens*, is widely used in traditional medicine for its anti-inflammatory effects and its capacity to lower organ injury. Matrine sodium chloride injection proved that it has anti-COVID-19 efficacy [1]. Furthermore, liquorice is a common herb that has been widely used in traditional medicine for centuries. Many bioactive compounds were isolated from liquorice, including around 20 triterpenoids and 300 flavonoids. Studies have shown that they possess many pharmacological effects, such as antimicrobial, anti-viral, anti-inflammatory, and antitumor. In Chinese pharmacopeia, *Glycyrrhiza inflate*, *Glycyrrhiza uralensis*, and *Glycyrrhiza glabra* L. were prescribed as liquorice. Glycyrrhizin, the phytochemical isolated from liquorice, was active against H5N1 [12].

Accordingly, plant secondary metabolites (PSMs) which are intermediary compounds formed in response to stress exposure, aiding plants in adapting to environmental challenges, possess potent antimicrobial, antifungal, and antiviral properties. Recent research indicates the potential antiviral effects of plant secondary metabolites (PSMs) in humans. Investigation into the use of plant-derived active compounds against COVID-19 reveals a variety of bioactive phytochemicals with therapeutic potential against diverse diseases. These compounds may act through immunomodulation, influencing COVID-19 biomarkers, or directly targeting the SARS-CoV-2 virus. Plant secondary metabolites (PSMs) are categorized into four main groups: terpenoids/terpenes, phenolics and polyphenols, glycosides, and alkaloids [13].

Terpenes (essential oils)

Terpenes represent a diverse array of natural organic compounds commonly found in plants, particularly in their essential oils. These lipophilic compounds emit distinct odors that serve to protect plants from various pathogens. Terpenes are recognized as the primary secondary metabolites in over 36,000 plant species and exhibit a wide range of potential medicinal properties, including anti-cancer, anti-inflammatory, antiviral, antioxidant, and antibacterial effects. Lately, there has been increased interest in terpenes due to their notable antiviral activities. Their ability to integrate with the lipid bilayer of viruses disrupts their structure, making terpenoids valuable as specific inhibitors against viral infections. Notably, certain terpenes like celandine-B, betulinic acid, and ursolic acid have demonstrated potent antiviral effects, with IC50 values ranging from 1 to 20 µg/ml. Additionally, research indicates that terpenes exhibit high binding affinities and significant inhibition against various strains of coronaviruses, suggesting potential efficacy against COVID-19. The outer lipid layer of COVID-19 is crucial for its attachment to host cell membranes, and terpenes can disrupt this lipid layer, thereby inhibiting viral binding [13]. Moreover, coronaviruses contain single-stranded RNA, which serves as a messenger RNA upon entering host cells. This RNA triggers the formation of two polyproteins, which further assemble into replication and transmission complexes that regulate RNA synthesis and the formation of structural proteins, while also enhancing protease enzyme activity. Protease enzymes play a crucial role in cleaving the polyprotein. Recent antiviral therapeutic strategies involve identifying protease enzyme inhibitors from natural sources, with terpenes being particularly noteworthy due to their widespread presence in plants, as well as their low IC50 (Half-maximal inhibitory concentration) values [14, 15].

Glycyrrhizin

Glycyrrhizin, a triterpene saponin, possesses diverse biological activities and pharmacological characteristics. Recent investigations have highlighted its therapeutic promise in combating COVID-19. Its actions include binding to angiotensin-converting enzyme II (ACE2), impeding intracellular reactive oxygen species (ROS) accumulation, suppressing proinflammatory cytokines, and inhibiting thrombin. Inhibiting excessive airway exudate production and promoting the production of endogenous interferon are additional effects of glycyrrhizin. Recent reports indicate that the combination of glycyrrhizin and boswellic acids has promising effect onCOVID-19 treatment due to their multi-target approach. This combination demonstrates efficacy in reducing mortality rates, accelerating recovery, and enhancing prognosis [16].

Quercetin

Quercetin, derived from the Latin term "Quercetum," referencing oak forests, is a flavone compound found abundantly in various fruits and vegetables like berries, onions, apples, dill, lovage, capers, and cilantro. It is also available in supplemental form. Known for its polyphenolic properties, quercetin exhibits significant antiviral, pro-metabolic, and anti-inflammatory effects. Recent studies have highlighted its potential in supporting antioxidant, anti-inflammatory, anti-viral, and immune-protective functions. Investigations suggest that quercetin may interfere with SARS-CoV-2 by inhibiting the interaction between the virus's spike protein and ACE2 receptor, thus impeding viral entry into host cells. Additionally, it may hinder viral replication, as evidenced by its inhibition of 3C-like protease (3CLpro), crucial for SARS-CoV-2 replication, with an IC50 of 73 µM. Furthermore, quercetin demonstrates strong interactions with SARSCoV-2 Mpro, a protease essential for viral RNA translation, decreasing the cytokine storm owing to its anti-inflammatory activity [17].

Alkaloids

Alkaloids, a diverse group of secondary metabolites comprising over 12,000 compounds, contain nitrogen in a reduced oxidation state. Found predominantly in flowering plants, fungi, bacteria, and specific animal species, alkaloids are classified based on their biosynthetic pathways into various types such as tropanes, quinolines, indoles, purines, isoquinolines, imidazoles, pyrrolidines, pyrrolizidines, pyridines, and others. These bioactive metabolites exhibit a wide range of pharmacological effects, including antioxidant, antifungal, antimalarial, antibacterial, and antiviral activities. Recent research highlights the potential of certain alkaloids, either alone or in combination with other medications, in combating the COVID-19 pandemic. Several alkaloids have shown promising antiviral effects against SARS-CoV-2, including papaverine, caffeine, berberine, colchicine, crambescidin 786, cryptospirolepine, deoxynortryptoquivaline, cryptomisrine, 10-hydroxyusambarensine, emetine, ergotamine, camptothecin, lycorine, nigellone, norboldine, and quinine. Colchicine, a lipid-soluble tricyclic alkaloid, is currently used to treat inflammatory conditions like gout and familial Mediterranean fever. Its potential against COVID-19 lies in its ability to modulate inflammatory immune responses. By inhibiting neutrophil activity, reducing superoxide free radicals, lowering tumor necrosis factor levels, and indirectly blocking the NLRP3 inflammasome, colchicine helps

manage inflammation and prevent cytokine storms. Moreover, colchicine acts as a microtubule-disrupting agent, inhibiting tubulin polymerization. Since coronaviruses rely on microtubules for various stages of their lifecycle, including entry into host cells and replication of viral genome, colchicine's disruption of microtubules may hinder viral entry and replication. This mechanism suggests its potential as a therapeutic agent against COVID-19 [17]. Table 1 includes some of the most promising herbal medicines fighting against SARS-CoV-2 and related viruses with their relative mechanism of action.

Table 1: Herbal medicine fighting SARS, MERS and other related viruses, their mechanism of action and their relevant monographs

Plant name/family	Monograph	Mechanism of action	Reference
Allium sativum-garlic/liliaceae	WHO/EMA	-Inhibition of viral PDB6LU7 proteins -Inhibition of ACE2 receptor	[5, 8]
Andrographis paniculata/Acanthaceae	WHO/EMA	-Inhibition of TMPRSS2-Inhibition of SARS-CoV 3CLpro	[9, 10]
Artemisia annua/Asteraceae	WHO	Inhibition of virus replication	[9, 10]
Artemisia apiacea/Asteraceae	WHO	Inhibition of virus replication	[11, 12]
Bupleurum chinense/Apiaceae	WHO	Inhibition of virus replication	[32, 68]
Camellia sinensis-Green Tea/Theaceae	EMA	Inhibition of SARS-PLpro Inhibition of SARS-COV RdRp and 3CLPRO	[9]
Cinnamomum verum-cortex Cinnamomi/Lauraceae	EMA-WHO	Pseudovirus infection inhibition	[8, 34]
Citrus aurantifolia/Rutaceae	Globinmed	Inhibition of 3CLpro	[39, 69]
Citrus aurantium(Bitter orange)/Rutaceae	Globinmed	-Inhibition of 3CLPRO, helicase protein, S protein, ACE-2 receptor	[9, 69]
Curcuma longa/Zingiberaceae	WHO/EMA	Inhibition of 3CLpro	[41, 44]
Digitalis purpurea-Foxglove/Plantaginaceae	USP/French	inhibition of SARS-COV-2 replication	[70]
Euphorbia neriifolia/Euphorbiaceae	Globinmed	Inhibition of virus replication	[71, 72]
Forsythia suspensa/Oleaceae	Monograph for quality evaluation of chinese crude drugs	Inhibition of SARS-COV S protein and ACE2 receptor	[5]
Garcinia mangostana-Queen fruit/Clusiaceae	Malaysian	Inhibition of virus replication	[47, 71]
Glycine max (soyabean)/Fabaceae	EMA	ACE-2 inhibition	[73]
Glycyrrhiza radix-Liquorice/Fabaceae	WHO/EMA	Inhibition of virus replication ACE-2 inhibition	[12, 73, 74].
Glycyrrhiza uralensis-Liquorice/Fabaceae	WHO/EMA	Inhibition of virus replication Binding to SARS-CoV S protein Suppression of H5N1-induced apoptosis	[9, 11, 50, 75].
Hibiscus sabdariffa-Roselle Calyx/Malvaceae.	Malaysian	Inhibtion of the SARS-CoV helicase protein	[71, 76]
Isatis tinctoria-dyer's woad/Brassicaceae	NA	Inhibition of 3CLpro	[52]
Lycoris aurea/radiata Amaryllidaceae	NA	Inhibition of virus replication	[21]
Nigella sativa/Ranunculaceae	NA	ACE2 inhibition	[18, 55]
Panax ginseng/Araliaceae	WHO-EMA	Inhibition of 3CLpro	[44, 77]
Peganum harmala L		Inhibition of viral genome	[13]
Plume thistles (Cirsium spp)	NA	Inhibition of the main protease (Mpro) and spike (S)	[78]
Polygonum multiflorum/Polygonaceae	WHO	Blocking of the S protein/ACE-2 interaction	[79]
Rhei radix and rhizome/Polygonaceae	WHO-EMA	Blocking of the S protein/ACE-2 interaction	[9, 44]
Rheum officinale-chinese rhubarb/Polygonaceae	WHO-EMA	ACE2 inhibition	[44, 76]
Scoparia dulcis/Scrophulariaceae	Globinmed	Inhibtion of SARS-CoV helicase	[76]
Scutellaria baicalensis/lamiaceae	WHO	Inhibition of ACE2, inhibiting RdRp and the SARS-CoV Inhibition of activity of SARS-CoV helicase protein	[59, 60, 73]
Stephania tetrandra/Menispermaceae	NA	Inhibition of virus replication	[9]
Tamarindus indica/Fabaceae	Globinmed	Inhibiton of 3CLpro	[39, 71]
Tribulus terrestris/Zygophyllaceae	WHO	Inhibition of SARS-CoV PLPRO	[8, 80]
Tylophora indica/Asclepiadaceae	Globinmed	Inhibiton of viral replication	[69, 71]
Uncaria tomentosa (cat's claw)/Rubiaceae	EMA	Blocking of the S protein/ACE-2 interaction	[60]
Urginea maritima (Drimia maritima)/Asparagaceae	British herbal compendium	Inhibition of SARS-CoV-2 Mpro and 3CLpro	[5]
Vitis vinifera/Vitaceae	EMA	Binding to SARS-CoV S protein and 3CLpro	[76]
Withania somnifera Radix Withaniae (Ashwagandha)/Solanaceae	WHO	Binding with SARS-CoV-2 Main Protease	[29]

DISCUSSION

The literature survey showed different mechanisms of action of medicinal herbs for coronavirus therapies: by acting on specific enzymes in the virus such as papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp), serine protease, main protease (Mpro/3CLpro, also known as 3-chymotrypsin-like protease), and helicase to inhibit the process of viral self-assembly, or by targeting specific proteins in the virus to prevent viral binding to human cells (spike protein and ACE-2 receptor). The homology between SARS-CoV-2 and SARS-CoV gene sequences reaches 80% because of the method of virus entry into human cells and how it binds to ACE-2 receptors in a similar way. Therefore, this similarity suggests that the therapeutic targets against both types of viruses are common [18]. ACE-2 is a receptor considered the entry point for the SARS-CoV-2 virus during the infection process in human cells, so the virus attacks any organ having this receptor, such as the epithelial cells in the lung, ileum, colon, upper esophagus, and heart muscle cells; urothelial cells in the bladder, and proximal tubules in the kidneys [19]. Then the virus enters the circulation through the interaction between ACE-2 and the viral S-protein [20]. Therefore, the reduction in the infection will be by interfering with this interaction, and this is one of the mechanisms of some phytochemicals in fighting against COVID-19, as demonstrated by molecular docking studies, among

which the study showed the binding potential of baicalin, hesperidin, scutellarin, nicotianamine, and glycyrrhizin to the ACE-2 enzyme with ΔG (kcal/mol) of-8.46, ΔG (kcal/mol) of-8.3, ΔG (kcal/mol) of 14.9, ΔG (kcal/mol) of 5.1, and ΔG (kcal/mol) of-9, respectively. So, these bioactive compounds are promising candidates for blocking the 2019-nCoV infection [21]. Moreover, many edible plants rich in emodin and luteolin inhibit COVID-19 infection by preventing the interaction between the S-protein in the virus and the ACE-2 receptor [18]. Another target for anti-corona treatments is the spike protein pathway. The family of coronaviruses has multiple similar spike proteins. The interaction of S-protein with the host cells as the epithelial cells of the lungs causes the SARS-COV-2 infection through the epithelial cell membrane [22]. Hence, this protein is essential for the fusion of the virus with the target cell membrane through the host ACE-2 receptor since the S-protein serves as a key that allows the virus penetration into the target cell via fusion with the cell membrane. Moreover, the rapid transmission of coronavirus is explained by the easy binding of the S protein on the surface of the virus with the ACE-2 receptor inside human cells [18]. Molecular docking studies showed many phytochemicals such as hesperidin, cannabinoids, Herbacetin, Rhoifolin, morin, Pectolinarin, Epigallocatechin gallate, and kaempferol that have S-protein binding potential and can be used as an alternative treatment for SARS-COV-2 infection [23]. In addition, active ingredients extracted from essential oils such as terpenoid phenols, phenylpropanoids, and monoterpenes isolated from the essential oils of plants belonging to families *Lauraceae*, *Myrtaceae*, *Lamiaceae*, *Geraniaceae*, *Apiaceae*, and *Fabaceae* proved effective in the inhibition of the SARS-CoV-2 viral spike protein [24]. Recently, most of the vaccines approved for immunization against COVID-19 are directed towards the spike-S glycoprotein and lead to antibody production that results in blocking receptor binding and viral genome uncoating [25]. Pfizer/BioNTech and Moderna vaccines contain modified RNA to encode the virus S protein, which leads to the spike protein locking into a 3-D shape just before it binds to the ACE2 receptor on human cells, with which the antibodies neutralizing the virus must interact [26]. Other enzymes are also involved in coronavirus inhibition, such as 3CLpro (3-chymotrypsin-like cysteine protease) because it directly mediates the Nsps (Non-structural protein), which is necessary for the virus cycle. Small molecular inhibitors and peptides contain SARS-COV2 3CLpro inhibitors [27]. The papain-like protease PL proenzyme is also essential for coronavirus replication since it helps in cleaving polyproteins into smaller products that are utilized in the novel viruses' replication [28]. Additionally, The RNA helicase enzyme is crucial for coronavirus replication and proliferation. Many natural compounds are potent inhibitors of the helicase enzyme, such as myricetin and scutellarin [29]. An additional role is that of serine protease enzyme activity that is required by a transmembrane glycol (TMPRSS2) to allow the entry of the virus to the target cell. Serine protease inhibitors (SPIs) are candidate alternatives to stop the life cycle of the virus, and many medicinal plants are a rich source of SPIs, such as plants of the leguminous family (*Poaceae*, *Fabaceae*, and *Solanaceae*) [30, 31]. In this article, the most promising medicinal herbs having anti-corona potential were collected in table 1. Most of these plant species have well-established monographs, mainly WHO and EMA monographs, except for some plant species, *Stephania tetrandra*, *Lycoris radiata*, *Isatis tinctoria*, and *Plume thistles*, but our review of these monographs showed the need for updates to assure the safe use of these plant species. *Allium sativum* is rich in organosulfur compounds and proved to be effective against COVID-19 [32].

After a review of the literature on its interaction with some drugs, like warfarin, which causes bleeding, and with chemotherapy drugs, mainly docetaxel, garlic was found to minimize the clearance of docetaxel, which may lead to the accumulation of docetaxel. Thus, an update on the monograph of this plant species to alert cancer patients on chemotherapy and those taking warfarin about the risk of this herb-drug interaction is necessary [33]. Studies about *Andrographis paniculata,* rich in diterpene lactones, showed its great potential against SARS-CoV-2 [34], but a study has shown the risk of combining this medicinal herb with *Aspilia Africana* because of the resulting cytotoxicity of this combined extract, as proved in a study done in vitro on murine cells. So, further investigation is needed to confirm this herb-herb interaction [35]. Moreover, some studies indicated the herb-drug interaction between *Andrographis paniculata* and the drugs eliminated via CYP3A4 and UGT2B7-catalyzed metabolism, such as morphine, because the andrographolide derivatives are potential selective inhibitors of UGT2B7 and CYP3A4 [36, 37]. Therefore, it would be beneficial to the patient to be aware of these warnings before taking this plant species as an anti-corona treatment. The addition of these warnings to the plant monograph is crucial to protect individuals and to inform drug manufacturers about the risk of mixing these two plant species in the same formulation, especially since both have anti-fertility potential [38]. Moreover, *Artemisia annua* is a plant species rich in sesquiterpenes, artemisinin, and its derivatives, artesunate that were approved for medical use, and it is on the WHO list of essential medicines for the treatment of malaria. Many studies showed the efficacy of these phytochemicals against SARS-CoV-2 [39], but the long-term use of artemisinin and derivatives causes toxicity which is related to each derivative and its route of administration, mainly neurotoxicity and embryotoxicity [40], hence, an update on the section concerning the safe use of Artemisia in its monograph is needed to alert about this toxicity. Besides the beneficial effect of *Bupleurum chinense* rich in triterpene saponins against HCoV-22E9 [41], it has shown cardiotoxicity and hepatorenal toxicity in studies done in vivo and in vitro, especially on long-term use [42]. Moreover, after revision of the WHO monograph of *Radix Bupleuri*, the results of the recent studies need to be included in the monograph for better monitoring of patients taking this plant species, mainly the kidney and liver markers in the blood.

Similar cases are found with other medicinal herbs such as *Camellia sinensis* (green tea), which is rich in caffeine and has phytochemical potential in fighting the SARS virus [34]. Since many patients suffering from cardiovascular diseases drink green tea because they are persuaded of its beneficial effects on health, it is crucial to inform individuals about the herb-drug interactions that have been demonstrated in several studies and need to be updated in its official monograph, mainly with sildenafil, tacrolimus, rosuvastatin, nadolol, simvastatin, and warfarin, which may cause a risk of drug toxicity or reduced drug efficacy [43]. Interestingly, *Cinnamomum verum* (Cortex Cinnamomi) was previously mentioned as a SARS-COV inhibitor [44] but since an article showed the risk of hepatotoxicity in individuals on statin treatment, so further studies are needed to confirm these results [45].

Concerning *Citrus aurantium* (bitter orange), it has shown efficacy in the SARS-COV-2 treatment due to the presence of flavanone glycoside [34], but being rich in synephrine alkaloid, precautions should be taken when taken with caffeine-containing products such as energy drinks or other medicinal plants rich in caffeine because of the risk of hypertension and serious heart side effects, so the dose taken should not be more than 60 mg of p-synephrine alone or 40 mg in combination with 320 mg caffeine. Such information about the safe use of *Citrus aurantium* needs to be updated in the plant monograph [46]. Furthermore, *Curcuma longa* has proven to be beneficial in SARS-CoV, being rich in phenols and a potent inhibitor of 3CLpro [47], but a warning was not revealed in its official monograph about safety issues related to potential inflammatory hepatic effects in patients taking curcumin in combination with statins [48], in addition to its interaction with some chemotherapy drugs such as etoposide, vincristine, vinblastine, doxorubicin, daunorubicin, epirubicin, methotrexate, and melphalan because of its influence on the protein MRP-1 (ABCC-1) responsible for the transport of these drugs [49]. Besides all the medicinal herbs discussed previously, *Digitalis purpurea* (Foxglove) has shown efficacy against SARS-COV-2 due to digoxin and ouabain presence [50], but the use of these cardiac glycosides should be used carefully, and patients should be monitored for signs of digoxin toxicity. The measures to be taken should be clarified in the plant monograph, such as monitoring electrolyte levels, digoxin serum levels, and interactions with many drugs such as verapamil, thyroid hormones, and antineoplastics [51]. Additionally, *Garcinia mangostana* is rich in xanthones and effective against COVID-19 [52], but the major risk from this herb should be highlighted, mainly the bleeding side effect, particularly during concomitant use of herbs or drugs that increase such risk [53]. *Glycine max* also should be taken carefully in cancer patients taking some chemotherapy drugs along with this herb since it influences the protein BCRP (ABCG-2,

MXR) responsible for the transport of these drugs, such as epirubicin, topotecan, and etoposide, besides its interaction with drugs metabolized by cytochrome P450 [49, 54]. Liquorice was proven to be a potential inhibitor for SARS-CoV and related viruses by different mechanisms, such as ACE2 inhibition, binding to the S protein of the virus, and inhibition of viral replication [21, 55] but besides the major side effects and interactions mentioned in its WHO and EMA monographs, the liquorice interaction with warfarin was proven and should be highlighted for the safety of patients taking this medication [56]. More care should be taken also while using *H. sabdariffa* rich in flavonoids of great potential in fighting coronavirus [18] because, in addition to the drug interactions mentioned in its official monograph, the focus should be on the interaction of this medicinal plant with captopril since coadministration of *H. sabdariffa* with captopril could modify the pharmacokinetic profile of this drug, so, their coadministration is forbidden [57]. In addition, the aqueous beverage of *Hibiscus sabdariffa* showed significant herb-drug interaction with simvastatin, so the coadministration of this beverage with simvastatin should be avoided until further clinical data are available [58]. *Nigella sativa* L., also known as Kalwanji in Pakistan, is a native medicinal plant belonging to the Ranunculaceae family. Renowned for its therapeutic properties and recognized for its antiviral and antimicrobial significance. Research on this plant's nutraceuticals reveals that the essential oils extracted from its seeds contain notable levels of steroids, saponins, terpenoids, and tannins which serve as potential medicinal agents, particularly against viral infections such as COVID-19 and other viral strains. Notably, tannins, a constituent of *Nigella sativa* L., have garnered attention for their antiviral properties. Therefore, the investigation into the antiviral potential of tannins derived from *Nigella sativa* L. could contribute significantly to the development of therapeutics against coronaviruses. Given these promising attributes, it is recommended that further research be conducted to explore the pharmacological importance of *Nigella sativa* L. in the question of an effective medicinal remedy against COVID-19 [13]. Interestingly, *Panax ginseng is* used in traditional medicine for coronavirus treatment by inhibiting 3CLpro [59]. It should be taken with precaution, not only as mentioned in its monograph with antidepressants, mainly MAO inhibitors, but also with the imatinib drug since it has been proven to cause hepatotoxicity if taken together [49]. Besides this herb-drug interaction, Panax *ginseng* interacts with warfarin, so its co-administration should be avoided [56]. In addition, *Peganum harmala* L., commonly referred to as Hermal Booti, is an herbal plant belonging to the Nitrariaceae family rich in secondary metabolites (PSMs), including alkaloids, flavonoids, polysaccharides, and anthraquinones. Notably, the alkaloids found in *Peganum harmala* have demonstrated intriguing antiviral antifungal, and antibacterial properties. Given its rich concentration of PSMs, particularly alkaloids, *Peganum harmala* presents itself as a compelling candidate for exploration as a potential therapeutic agent against COVID-19, especially considering its historical use in treating respiratory and inflammatory conditions. The notable PSMs present in the plant have the potential to disrupt the viral genome's structure, thus impeding viral replication [13]. Concerning *Scutellaria baicalensis, which is* rich in flavonoids responsible for its potential against COVID-19 via inhibition of multi-target pathways [29, 60], special care should be taken in patients using benzodiazepines since wogonin, baicalin, and scutellarein bind to the benzodiazepine receptor, the GABAA receptor, so, this warning should be mentioned in the WHO monograph of *Scutellaria baicalensis*, for safer use of this herbal medicine [61]. *Tribulus Terrestris*, proven as an herbal medicine rich in phytochemicals active against coronavirus and working through the inhibition of SARS-CoV PLpro mechanism [62], should be avoided in patients suffering from renal injury since this plant species induces kidney injuries such as nephritis, kidney stones, and nephrotic syndrome. This warning should be present in the official monograph for patient safety, especially for those suffering from renal problems or taking medications affecting the kidneys [63]. *Withania somnifera* showed potential by binding with SARS-CoV-2 Main Protease [64]. Many articles have demonstrated that it causes inhibition of CYP2B6 and induction of the CYP3A4 metabolism pathway, so it may cause herb-drug interaction [65].

Accordingly, based on the current review, it is advised that individuals use natural alternatives for the prevention of various ailments, mainly the COVID-19 disease, the most widely spreading infection in the world, especially after the similarity shown between the mechanisms of action of the vaccines approved for immunization against this virus and some herbal medicines discussed in our article previously. However, the major concern about the safety of these herbal medicines cannot be solved without continuous and regular updates on their monographs that assure all the necessary information concerning the side effects, uses, and interactions of these plant species since misuse or abuse of these natural compounds may lead to a catastrophic impact on health. Finally, although quality is not addressed in detail in the Community herbal monographs, the quality of herbal medicines must be controlled and monitored to ensure the safety of the product. The best example of herb contamination is the risk of the presence of toxic pyrrolizidine alkaloids, which becomes a challenge for manufacturers and growers regarding the quantification and identification of these contaminants and work on their reduction. Measures should be taken to minimize the level of pyrrolizidine alkaloids (PA) in herbal drugs according to the required standards [66]. *Jacobaea vulgaris* in Europe and *Ageratum conyzoides* in Ethiopia are examples of a significant problem of contamination of these plants with PA alkaloids [67]. So, herbal contaminants should be limited according to the Pharmacopoeia requirements concerning their levels as well as the methods for determination, such as the presence of heavy metals, aflatoxins, pesticide residues, and microbiological contamination in herbal drugs [66]. A significant problem is that of mycotoxins, among which are ochratoxins, fumonisins, aflatoxins, and tricothecene. The most studied and classified as group 1 human carcinogens are aflatoxin B1, B2, G1, and G2, which are highly toxic contaminants in any herbal products as per the WHO guidelines for quality assessment of herbal medicines (Annex 4). Moreover, *Stephania tetrandra* should be free of aristolochic acids (AA) that cause urothelial carcinoma before use due to FDA concerns about adulteration of this species with the nephrotoxic *Aristolochia fangchi,* which is rich in AA [67].

Therefore, the quality-safety-efficacy triangle should be the main driver for the registration of herbal medicines before allowing their use, and community herbal monograph implementation will play a significant role in protecting public health.

CONCLUSION

This article illustrates the most promising herbal medicines effective in preventing and controlling SARS-CoV and related viruses, mainly COVID-19, the global pandemic that is threatening the whole world because no efficient treatment has been discovered yet to eradicate the serious complications it causes to health.

Seeking natural alternatives with great synergistic potential with drugs because of the various mechanisms of action of the phytochemicals found in these plant species is an opportunity that should be encouraged in all countries. However, these herbal drugs should fulfill all the necessary guidelines that ensure their efficacy, safety, and quality. To achieve this goal, our analysis suggests promoting the design of community monographs for medicinal plants that proved to have potential in SARS-CoV-2 treatment, such as *Stephania tetrandra*, *Isatis tinctoria*, *Plume thistles*, *Nigella sativa,* and *Lycoris radicata,* since the use of these species should be according to pre-evaluated standards that specify the dose to be used, the restrictions in case of herb-drug interactions, or medical conditions that may worsen upon the use of these herbs.

Since this article focused especially on the significance of updating herbal monographs on the use of medicinal plants to fight different types of viruses, the results of recent studies done on these plant species should be incorporated regularly in the published monographs under the supervision of national and international authorities and under the umbrella of WHO to assure the global harmonization of natural products' health claims.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors are responsible for concept, design and critical revision of the manuscript, data analysis/interpretation are done by Mayssaloune kanso, Maha Aboul Ela, Zeina Omeiche and Abdalla El Lakany. Drafting of manuscript is achieved by Mayssaloune Kanso.

CONFLICT OF INTERESTS

Declared none

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