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Review

Current Update of Phytotherapeutic Agents in the Treatment of COVID-19: *In-Silico* Based Virtual Screening Approach for the Development of Antiviral Drug

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Abstract

COVID-19, caused by the severe acquired respiratory syndrome coronavirus-2 (SARS-CoV-2), is a highly contagious disease that has emerged as a pandemic. Researchers and the medical fraternity are working towards the identification of anti-viral drug candidates. Meanwhile, several alternative treatment approaches are being explored to manage the disease effectively. Various phyto-drugs and essential oils have been reported to have antiviral activity, but this has not been well studied in the context of SARS-CoV-2. The main focus of this review is on the biology of infection and the different therapeutic strategies involved, including drug repurposing and phytopharmaceuticals. The role of phytochemicals in treating COVID-19 and various other diseases has also been emphasized.

Keywords: SARS-CoV-2; COVID-19; essential oils; phyto-drugs; ethnomedicine; ACE II receptors

1. Introduction

Coronaviruses are single-stranded positive-sense RNA viruses that circulate between humans and animals [1,2]. This century has observed the worldwide spread of the three previously unknown coronaviruses. In 2002, the first case of severe acquired respiratory syndrome coronavirus (SARS-CoV) was reported in China and later spread globally across Vietnam and Canada [3]. The World Health Organization (WHO) established a network of research laboratories in 2003 to combat SARS-CoV. It has been reported that the SARS-CoV replicates in individuals due to the delayed interferon 1 expression [3] and further induce fibrosis in the lungs by triggering the overexpression of the EGFR signaling pathway [4]. A sex bias was observed in the SARS infection, and males were found to be more susceptible to the virus than females, as estrogen signalling provides a protective effect against the virus [5]. Later, the pandemic came to an end in 2004 by infection control measures. However, studies have reported the presence of SARS-CoV-like viruses in bats that affect humans and predicted the re-emergence of SARS in the future [6]. In 2012, a decade after SARS-CoV occurrence, a novel coronavirus infection was identified in Saudi Arabia that spread across 27 Middle East countries by nosocomial transmission [7,8]. It was later diagnosed as the Middle East respiratory syndrome coronavirus (MERS-CoV) [9]. SARS and MERS coronaviruses were reported to share the same host cell receptor for entry [10]. MERS was prevalent across countries until 2016. Soon after the infection was brought under control, SARS-CoV-2 infection occurred in 2019 [11]. These viruses are known to significantly affect an individual's upper respiratory tract and lungs (Fig. 1).

SARS-CoV-2 is a novel strain of coronavirus that was first reported in late 2019 in Wuhan Province, China. The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is highly contagious and spreads rapidly through droplets released on coughing and sneezing, and through touch. The initial spread of this disease is believed to have occurred via bats, pangolins, or turtles [12,13]. SARS-

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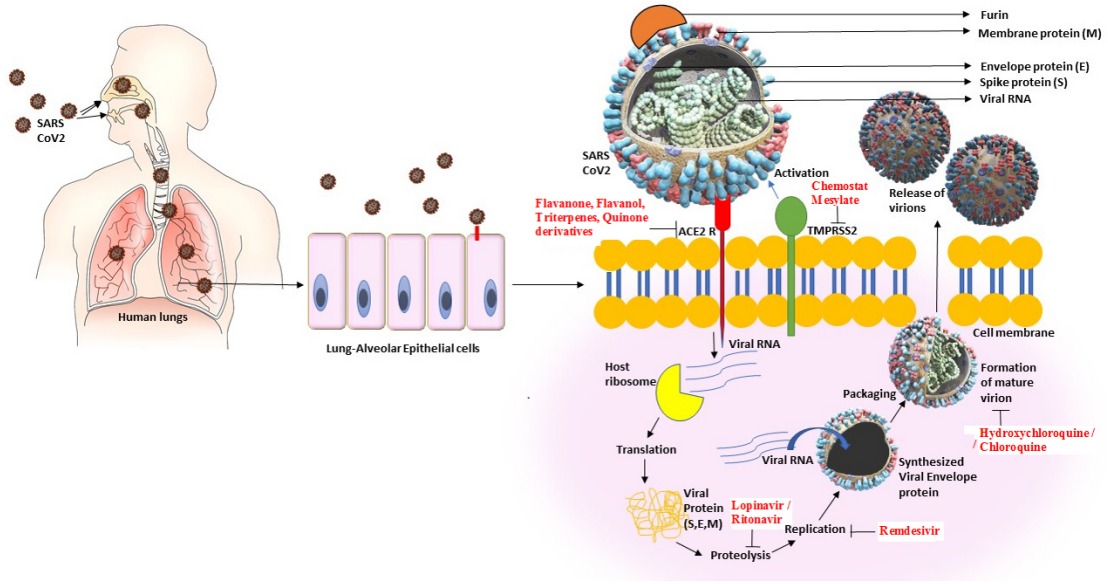

Fig. 1. COVID-19 enter human lungs. The structure and binding of COVID-19 virus to ACE2.

CoV-2 enters the host through a nasopharyngeal route and infects lung cells by targeting the angiotensin-converting enzyme 2 (ACE2) receptor protein on the outer surface. The ACE2 mechanism is altered upon infection, and the host cells are repurposed to participate in viral replication (Fig. 1). Under severe conditions, the host undergoes acute respiratory distress syndrome (ARDS) and develops hypoxia that leads to death [9].

The swiftness of the pandemic has weighed scientists, clinicians, and pharmaceutical industries globally to accelerate the development of treatment strategies, including drug discovery, deployment of experimental drugs, and repurposing the medicines that are already available in the market. Amidst the countless number of treatment options available, repurposing antiviral drugs has gained popularity, but it is still insufficient for treating COVID-19 patients. The advancement of potential broad-spectrum antiviral drugs is impeded by viral diversity because SARS-CoV-2 pliantly surpasses the negative selection pressure and neutralizes the drug action by proofreading exoribonuclease [14]. Although synthetic lead compounds are being tested against SARS-CoV-2, the therapeutic potential of the phytocompounds is still underrated [15]. This review will explain how SARS-CoV-2 infects the host and discuss a possible approach to counteract the condition using natural drug molecules, including phyto-drugs, essential oils, and medicinal herbs that are abundant in nature. This alternative approach may serve as an effective treatment against SARS-CoV-2 with minimal side effects.

2. SARS-CoV-2—Host Interactions

The solution to curbing SARS-CoV-2 is to understand the mechanism by which it enters the host. SARS-CoV-2 has specialized glycoproteins called spike proteins (S) on its outer shell that mediates its entry into host cells [16]. These spike proteins use human ACE2, present in the lung alveolar epithelial cells, as entry receptors and bind through its receptor-binding domains (RBD). The spike protein is reactivated by proprotein convertase furin, which improves spike-RBD binding affinity for efficient cell entry [16]. These mechanisms sneak viral RNA into the host cell while evading immune surveillance. Once inside the cell, viral RNA translates into virulent proteins with the help of RNA-dependent RNA-polymerase [17]. The viral proteins are then packaged into the virus and released from the host cell to infect other healthy cells. During the initial stages of virus replication, the host does not show any disease symptoms, which is known as the incubation period. Although incubation periods differ among viruses, SARS-CoV-2 reportedly has an incubation period of approximately 13 days [9]. Most COVID-19-affected patients develop successive ARDS, which results in inflammation of the lungs and, consequently, fluid leakage into the tissue space [12]. It causes further damage to capillaries, allowing proteinaceous fluid to enter the alveolar space, causing a blockage in oxygen transfer to the blood vessels. As a result, it becomes difficult to pump oxygen, resulting in hypoxia or respiratory distress [12]. Intervention strategies should be meticulously designed to target SARS-CoV-2 virulence and its evasiveness to battle the COVID-19 disease successfully.

3. Viral Genome

The SARS-CoV-2 viral genome is about 29 kb, which encodes structural and non-structural proteins (NSPs) for replication, transcription, structural assembly and pathogenesis. CoV family viruses have long an overlapping two open reading frames (ORF1a and ORF1b) at 5′ position of the genome, translated two long precursor polyproteins 1a

(pp1a) and 1ab (pp1ab) were further proteolytically cleaved to produce 16 mature non-structural proteins [18]. Viral spike (S) proteins are present on the outer membrane of SARS-CoV-2 [19]. The S protein is further divided into two subunits. The S1 subunit, RBD, is involved in its attachment to the host ACE2 receptor, and the S2 subunit helps in the membrane fusion of viral components. This mechanistic framework is conserved among all the *Coronaviridae* species. The S residues have coding regions from residues 27 to 1146, after which there are flexible heptad repeat 2 domains [19].

In addition, there are other target proteins in SARS-CoV-2, including M^{pro}, non-structural protein 15 (NSP15), ADP ribose phosphatase (ARDP), and RdRp. M^{pro} is a cysteine protease that processes the translated polypeptide from the SARS-CoV-2 RNA [20]. Similarly, NSP15 is an endoribonuclease that cleaves the viral RNA at uridylate and enables a successful infection. On the other hand, ADRP is an ADP-ribose1″-monophosphate (Appr-1″-p) converter that generates ADP-ribose (Appr) and enables further viral replication with the help of the RNA dependent RNA polymerase (RdRp) catalyst [20].

The main difference between earlier known coronaviruses and SARS-CoV-2 is that the SARS-CoV RBD is firmly attached to the nearby promoter's N-terminal domain (NTD), whereas SARS-CoV-2 RBD in its down conformation is positioned near the central cavity of the trimer while exhibiting a high degree of structural homology. SARS-CoV-2 has been reported to show high sequence similarity with the bat coronavirus RaTG13, with 29 variant residues (17 related to RBD), along with an insertion mutation in the S1/S2 protease cleavage site leading to RRAR furin recognition, instead of a single arginine (A) in previously known coronaviruses [21,22]. In plasmon resonance studies on interaction kinetics, the RBD of SARS-CoV-2 was reported to bind to the ACE2 receptor with ~15 nM binding affinity, which is ~10–20-fold higher than that of previously known SARS viruses [23]. In addition, two different mutations, D614G and G614, in SARS-CoV-2 have been identified. Individuals infected with G614 have shown more viral load but less disease severity than that of D614G infected individuals [14]. These findings suggest that the selective mutation in SARS-CoV-2 occurred recently, which can be targeted to discover potential drug(s).

4. Therapeutic Strategies

4.1 Drug Repurposing

Drug repurposing is a powerful strategy in which the already FDA-approved drugs on the market are repurposed for different clinical indications than prescribed. It is performed by pharmacophore modelling combined with virtual screening to retrieve new molecules from the FDA drug database [24–30]. This approach can also help pharmaceutical companies reduce the time and resources required to develop new chemical entities. Since all earlier known coronaviruses are genetically similar, preliminary work on drug repurposing could help scientists develop drugs against COVID-19. It is performed on a trial basis to overcome the time required to create a specific drug or antibody against SARS-CoV-2. No specific antiviral medication has been proven to treat COVID-19, although several trials are ongoing worldwide. Many such drugs have been tested, and a few are currently being used as prophylactic drugs for SARS-CoV-2 (Table 1, Ref. [23–29]).

4.2 Phytopharmaceuticals—A New Era of Drug Discovery

Traditional medicine has been in practice for many decades before the emergence of western medicine. Various phytocompounds are known for their therapeutic effects [31]. Although medicinal plants are abundant in nature, only a few herbs have been recognized and scientifically evaluated for their potential in medical treatment. Several herbal medicines are poorly regulated in many countries, primarily due to their lack of efficacy and uniformity of results. Hence, their safety remains a significant concern [31]. However, many phyto-drugs have proven to have extraordinary therapeutic potential and less toxicity compared to synthetic drugs.

Phytochemicals are unlimited resources for the development of potent drug molecules and are being highly explored in the current scenario against various diseases, especially in the case of COVID-19 [32,33]. Phytochemicals from Indian medicinal plants were explored to a larger extent for their inhibitory potential against COVID-19 targets.

4.2.1 Traditional Medicine—TCM and Ayurveda

A phyto-drug called diammonium glycyrrhizinate is known to have anti-inflammatory activity, is administered to human subjects along with vitamin C and has been proposed for COVID-19 therapy on humans [34]. AYUSH 64, an ayurvedic medicine was initially developed in 1980 by the Central Council for Research in Ayurvedic Sciences (CCRAS) for the treatment of malaria and now it has been repurposed for human subjects in Ayurveda centres for the treatment of COVID-19 [35]. In addition, arsenic album 30 an herbal immune-booster recommended by AYUSH as the preventive source for COVID-19 infection [36]. *Kabasura kudinner* (ingredients such as Ginger, Piper longum, Clove, Dusparsha, Akarakarabha, Kokilaksha, Haritaki, Malabar nut, Ajwain, Kusta, Guduchi, Bharangi, Kalamegha, Raja pata, and Musta) chooran a traditional formulation used by Siddha practitioners on human subjects for the prevention and control of COVID-19 infections [36]. Extracts of *Andrographis paniculata*, *Cordia myxa*, *Cydonia along*, and *Zizyphus jujube* showed improved efficacy as an antioxidant, immune booster, and support anti-viral activity in COVID-19 [36–38]. Currently, traditional Chinese medicine (TCMs) practices use herbs such as *Lianhua qingwen* [39], Scutellariae radix, *Astragalus membranaceus,* Lonicerae japonicae Flos, *Fructus forsythia* in humans, for

Table 1. Drugs repurposed for COVID-19.

S No.	Drug	Function	Earlier Prescribed for	Reference
1.	Hydroxy chloroquine	Inhibits viral infection-induced cytokine storm in the host	Parasitic Infections	[24]
2.	Chloroquine and Zinc	Inhibits the viral polymerase		
3.	Remdesivir (GS5734)	Halts viral replication by binding to uracil and inhibits viral RNA polymerase	MERS CoV	[25]
4.	Ribavirin	interacts with the viral synthetase and ribonucleoproteins to inhibit viral replication	human RSV	[26]
5.	Camostat Mesylate/TMPRSS2-Serine Protease Inhibitor	Prevents the viral entry into the host cell by inhibiting the spike protein attachment to host receptors.	MERS CoV	[27]
6.	Oseltamivir	Inhibits viral neuraminidase and prevents virion release from host cells, subsequently reducing viral dissemination into the respiratory tract	Influenza A and B	[28]
7.	Favipiravir (T-705)	RNA polymerase inhibitor that interrupts viral replication inside the host cell	Ebola and Influenza	[29]
8.	Ivermectin	Inhibiting IMPα/β1-mediated nuclear import of viral proteins by activating the signal-dependent nucleocytoplasmic shutting and further inhibiting the host cell division	parasitic infections	[23]

the treatment of Covid-19. These medicines are also known to help alleviate coughing, weakness, digestive disorders, and anxiety caused by the disease [39]. However, further research on this sector is required to would open a wide range of options for efficient medical treatment.

4.2.2 *In-Vitro* Studies on Phytocompounds against SARS-CoV-2

Many therapeutic strategies are developed in the alternative medicine system, and it is high time we consider them. Many *in-vitro* studies have been done on phytocompounds against SARS-CoV-2 (Table 2, Ref. [40–42]). Table 2 lists the various phytocompounds that have been studied against COVID-19. *In-vitro* studies using SARS-CoV2 infected Vero cells has approved the usage of western medicines such as hydroxychloroquine obtained from cinchona bark at a concentration of EC_{50} = 0.72 μM [25] and oseltamivir containing shikimic acid derived from the spice star anise [29] to treat COVID-19. Two alkaloid derivatives namely Emetine and homoharringtonine at a concentration (EC_{50}) of 2.55 μM and 0.46 μM showed significant viral replication inhibition activity in Vero E6 cells. It is also found that the Emetine (0.195 μM) synergistically work with remdesivir (6.25 μM) to inhibit 64.9% of viral yield [43]. Based on a review, the herbal extracts from the medicinal plants such as *Sephorasubstrata radix*, *Cimicifuga rhizome*, *Phellodendron cortex*, *Meliaecortex Corptidis,* and *Coptidis rhizoma* which was earlier found to inhibit the Mouse Hepatitis Virus in humans, could be used to treat SARS-CoV2 at an effective concentration of EC 27.5 μL [44]. *In-vitro* studies have shown that the emodin or kaempferol derivatives- juglanin compounds inhibit the 3a ion channel of SARS-CoV-2 and could potentially prevent the viral release from the infected cells [45].

4.2.3 *In-Silico* Studies on Phytocompounds against SARS-CoV-2

Several phytochemicals have shown promising inhibitory activity in computational and experimental studies against SARS-CoV-2 molecular targets. The majority of the phytochemicals identified were targeted towards the vital enzymes of SARS-CoV-2 such as M^{Pro}, Spike, RdRp and PL^{Pro} [46]. Few of the reports are available on the phytochemical blockers targeting Non-structural proteins and accessory proteins of SARS-CoV-2 [33,46,47] (Table 3). Hesperidin, a flavonoid present in citrus peels at a concentration of 50 mg mL^{-1} and theaflavin were reported to bind to $3CL^{pro}$ SARS-COV-2 cellular receptors and inhibit viral attachment to host cells [46]. *In-silico* studies show that the phyto-drug compounds 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone obtained from *Psorothamnus arborescens* and myricitrin obtained from *Myrica cerifera* binds to SARS-CoV-2 $3CL^{pro}$ and interferes with SARS-CoV-2 replication [48].

The molecular docking approach has revealed that the compound neo andrographolide from *Andrographis paniculata* binds to the RdRp region of the SARS-CoV-2 that is involved in viral RNA replication, with a free energy of binding of –24.1 kcal/mol [37]. It is also reported that the compound shows allosteric interaction with spike protein of SARS-CoV-2 indicating that the compound neo andrographolide could be used as a treatment strategy due to its multi-targeting character [37].

Table 2. *In-vitro* studies of phyto-compounds against SARS-CoV2.

S No.	Phyto- compounds	Classification	IC50 (µM)	Experimental set-up	Reference
1	epigallocatechin-3-gallate (EGCG)	flavanols	0.874	Synthetic FRET substrate (Dabcyl-TSAVLQ↓SGFRKMK-Edans)	[40]
2	ellagic acid	hydroxybenzoic acid derivatives	11.8	Synthetic FRET substrate MCA-AVLQSGFR-Lys (Dnp)-Lys-NH2	[41]
3	curcumin	curcuminoids	11.9		
3	resveratrol	stilbenes	16.9		
4	quercetin	flavanols	23.4		
5	1,2,3,4,6-pentagalloylglucose		3.66	(ED) FRET substrate DABCYL-TSAVLQ↓SGFRKME-EDANS	[42]

4.2.4 Phytochemicals Predicted by *In-Silico* and Supported by *In-Vitro* Studies

Flavonoids are secondary plant metabolites, which are derived from Phenylalanine or 3, Malonyl CoA and is differentiated into various sub-classes like anthocyanins, flavanols, dihydroflavonols, flavanones, flavones, flavonols, isoflavonoids, chalcones, and dihydrocalcones [49]. The maize bioflavonoid synthesis pathway involves the production of naringenin chalcone by condensation of coumaroyl-CoA with 3-malonyl-CoA in the presence of chalcone synthase, which is later transformed to Naringenin. This is in turn converted into dihydrokaempferol which drives the production of pelargonidin, kaempferol, quercetin by incorporating the enzymes dihydroflavonol reductase (DFR), flavonol synthase (FLS), flavanone 3-hydroxylase (F3′H). These compounds are also reported to be heat sensitive above 100 °C in the presence of oxygen >85% [49].

The compound Quercetin, a natural antioxidant from Allum cepa and Paulownia tomentosa Steud, belongs to the family of aglycone flavonols. It is also found in many fruits, vegetables and herbs including *Capparis spinosa* L, *Fagopyrum tataricum* Gaertn, Karmen onions, radicchio *etc.* [49]. *In-silico* studies on Quercetin showed to interfere with various stages of the SARS-CoV-2 entry, replication cycle such as PL^{pro}, $3CL^{pro}$, and NTPase/helicase and shown to Inhibit ACE2 by competing with the substrate N-[3-(2-furyl) acryloyl]-L-phenylalanyl glycylglycine with an IC50 between 5.0 and 14.4 μM [50]. It is also shown to have anti-inflammatory activity that reduces the IL1β and TNFβ along with prophylactic and antioxidant activity, and it is currently under clinical trial for COVID-19.

Similarly, the compound Naringenin, which is seen in the form of Naringin and prunin, belongs to the class of flavonones. Several studies have reported the antioxidant activity of Naringenin, that prevents DNA damage by removing free radicals [51]. It is also reported to show anti-inflammatory activity, that inhibits NF-kB to inhibit the production of inflammatory proteins [52]. Although it is abundantly found in many fruits including grapefruit, tangerines, oranges, and tomatoes, the absorption of the compound in human intestines is very less [49] and thus, an alternative method is required to increase the bioavailability. *In-silico* studies have shown that the compound Naringenin is successfully involved in silencing the two-pore channel 2 (TPC2) at 48- and 72-hours post-infection by inhibiting the COVID-19 viral replication [50].

On the other hand, the compound Kaempferol, which is found in capers, saffron, kale, common bean, cabbage, broccoli, endive, and leek, is found to have antioxidant, antiviral, anti-inflammatory, anticancer and neuroprotective activities [49]. A docking study on Kaempferol revealed that the Kaempferol-7-O-rutinoside, Kaempferol-3-O-glucuronoside and Apigenin-7-O-glucoside compounds showed high affinity against the two 3CLprotease binding pockets 6LU7 and 6M2N with a binding energy of –12.10, –11.80 and –11.52 against 6LU7 and –11.83, –11.34 and –11.01 kcal/mol against 6M2N indicating that these three compounds could be considered as a potential target for therapeutics but the results are yet to be verified experimentally [53].

4.3 Essential Oil—A Hidden Treasure for Respiratory Health

Medicinal herbs are a rich source of secondary metabolites, and few are known to potentially block viral protein function and prevent them from replicating inside the host cells [54]. They include alkaloids, essential oils, terpenoids, phenolic acids, flavonoids, tannins, lignin, coumarins, stilbene, and other plant extracts. The chemical composition and secretion of these secondary metabolites are determined by environmental factors, to an extent [54]. Among these, the essential oils have not been extensively explored for medical treatment. Essential oils can be obtained from various plant parts and are generally odoriferous and contain volatile compounds [55]. They consist of a wide range of essential oil components, including α-pinene, thymol, estradiol, β-pinene, γ-terpinene, sabinene, trans-anethole, caryophyllene, limonene, linalool, myrcene, disulfide, trisulfide, gingerol, myrcene, camphor, camphene, carvacrol, myrtenol, verbenone, and others. They possess antimicrobial, antifungal, antibacterial, and antiviral activities against several pathogens and are classified under Generally Regarded as Safe (GRAS) for medical treatments [55]. This broad spec-

Table 3. Plant based phytochemical and their potential SARS-CoV-2 targets/mode of action.

Classification	Phytochemicals	Source	Target of action in SARS- CoV-2
Monoterpenoids	Geraniol	*Ceolus ambonicus*	M^{pro}
Triterpenoids	Acetoside	Clerodendrum serratum, Scrophularia ningpoensis, Byblis liniflora	
	Ursolic acid	Vaccinium spp.	
	Betulin	*Betula pubescens, Ziziphus mauritiana*	
	Betulinic acid	*Etula pubescens, Ziziphus mauritiana*	
Triterpenes	Maslinic acid	*Olea europaea*	
	Glycyrrhizin	*Glycyrrhiza glabra*	
Sesquiterpenoids	Nootkatone	Cypreus rotundus	
Diarylheptanoids	Gingerenone A	Zingiber officianle	
Flavonoids	Luteolin 7-rutinoside	*Hygrophila auricualata*	
	Rutin	*Tragia involerta*	
	Andrographidine C	*Andrographis paniculate*	
	Myricetin	*Syzygium aromaticum*, *Ceratonia siliqua*, *Vaccinium* spp.	
	Quercetin	*Allium cepa*, *Vaccinium* spp.	
	Dihydromyricetin	*Ampelopsis grossedentata*	
	Quercetagetin	*Tagetes erecta*	
	Scutellarein	*Scutellaria* spp.	
Tannin	Chebulagic acid	*Terminalia chebula*	
Annonaceous acetogenins	Acanthoside	*Sida acuta*	
Lignan	Syrigaresinol	*Sausurea lappa*	
-	Violanthin	*Adhatoda vasica*	
Sennosides	Sennoside B	*Cassia fistula*	
-	Tinosporinone	*Tinospora cordifolia*	
Benzophenones	Maclurin	*Garcinia pedunculata, Gnidia involucrate*	
Quinic acids	Chlorogenic acid	*Terminalia chebula*	
-	Asarianin	*Piper longum*	
Stigmastanes	Gamma sitosterol	*Anacyclus pyrethrum*	

Table 3. Continued.

Classification	Phytochemicals	Source	Target of action in SARS- CoV-2
Alkaloid	Rutaecarpine	*Tylophora indica*	SARS-CoV-2 Spike Protein
Gallate ester	3-O-Galloylepicatechin-(4Beta-6)-Epicatechin-3-O-Gallate	*Camellia sinensis*	
Psoralens	Daucosterol	*Justicia adhatoda*	
Sesquiterpenoids	Caryophyllene	*Ocimum temiflorum*	
Dehydroellagitannin	Geraniin	*Zingiber officinale*	
Curcuminoids	O-Demethyl demethoxycurcumin	*Curcuma longa*	
Benzodioxoles	Myristicin	*Myristica fragrans*	M^{pro} & S protein
Allylbenzene	Eugenol	*Syzygium aromaticum*	
Benzoate ester.	Bis (3,5,5-trimethylhexyl) phthalate	*Pangium edule*	
Benzenoids	Ethyl cholate	*Pangium edule*	
Cannabinoids	Cannabinoids	*Cannabis* spp.	
Flavonoid	Hesperidin	*Linaria vulgaris*	
	Rhoifolin	*Citrus auratium, Vitis vinifera, Musa* spp., *Citrus limon, Citrus paradisi, Lycopersicon esculentum*	
	Tangeretin	*Citrus* spp.	
	Kaempferol	*Brassica oleracea, Spinacia oleracea, Camellia sinensis, Phaseolus vulgaris, Brassica oleracea*	
	Nobiletin	*Citrus* spp.	
	Herbacetin	*Eupatorium perfoliatum, Equisetum arvense, Rhodiola* spp. *Gossypium hirsutum*	
Flavonols	Morin	*Psidium guajav, Prunus dulcis, Maclura pomifera, Chlorophora tinctoria*	
Shogaols	6-Shagaol	*Zingiber officinale*	
Chalcones	Chalcone	*Citrus* spp.	
Pectolinarin	Pectolinarin	*Linaria vulgaris, Cirsium* spp.	
		Linaria spp.	
Gingerols	6-Gingerol	*Zingiber officinale*	
Flavonoid	Dihydromyricetin	*Vitis vinifera*	NSP1
	Dihydroquercetin	*Madhuca longifolia*	
	Tricetin	*Camellia sinensis*	
Alkaloid	10-methylcephaeline	*Alangium salviifolium*	
	Pseudolycorine	*Narcissus tazetta*	

Table 3. Continued.

Classification	Phytochemicals	Source	Target of action in SARS- CoV-2
Berbamine	Berbamine	*Berbaris amurensis*	ACE2/E protein channel
Alkaloids	Berberine	*Berberis petiolaris*, *Berberis vulgaris*	Late stage
Alkaloid	Capharanthine	*Stephania* spp.	Fusion entry/S-ACE interaction
Alkaloids	Emetine	*Psychotria ipecacuanha*	Replication translation
Alkaloid	Hernandezine	*Thalictrum podocarpum*	Fusion entry
Alkaloid	Neferine	*Nelumbo nucifera*	Fusion, entry
Alkaloid.	Tetrandrine	*Stephania tetrandra*	Entry, TPC2 inhibition
Flavonoid	Baicalein	*Scutellaria baicalensis, Scutellaria lateriflora*	M^{pro}, entry, NSP15
Catechols	Brazilin	*Paubrasilia echinate, Caesalpinia sappan*	Binding/entry, TMPRSS2
Flavonoid	Catechin	*Camellia sinensis*	Viral inactivation
Anthocyanin	Chrysanthemin	*Olea europaea, Vaccinium* spp.	M^{pro}, PL^{pro}
Catechin	Epigallocatechin-3-gallate	*Camellia sinensis*	M^{pro}, Attachment/binding, NSP15, viral inactivation
Flavonols	Isorhamnetin	*Hippophae rhamnoides, Opuntia ficus-indica*	S-ACE binding
Flavonoid	Naringenin	*Citrus* spp. *Lycopersicum esculentum*	TPC2, M^{pro}
-	Panduratin A	*Baesenbergia pandurate*	Pre-entry
Flavonoids	Rutin	*Fagopyrum esculentum, Rheum* spp.	PL^{pro}
Flavonoids	Theaflavin 3,3'-di-O-gallate	*Camellia sinensis*	M^{pro}, Viral inactivation, binding/entry/TMPRSS2
Terpenoid	Andrographolide	*Andrographis paniculate*	Late stage/M^{pro}
Prenol lipids	Cryptotanshinone	*Salvia miltiorrhiza*	PL^{pro}
Curcuminoids	Curcumin	*Curcuma longa*	Binding/entry, TMPRSS2
Diterpenoids	Dihydrotanshinone I	*Salvia miltiorrhiza*	PL^{pro}
Polyphenol	Ellagic acid	*Rubus fruticosus, Fragaria ananassa*	RBD-ACE2
Bianthrone	Hypericin	*Hypericum perforatum*	M^{pro}, PL^{pro}
Lignan	Nordihydroguaiaretic acid	*Larrea tridentata*	PL^{pro}, NSP3
Saponin	Platycodin D	*Platycodon grandiflorum*	Entry, ACE2/TMPRSS2
Stilbenoid	Pterostilbene	*Vaccinium* spp. *Pterocarpus marsupium*	Post-entry
Ellagitannin	Punicalagin	*Punica granatum, Terminalia catappa*	RBD-ACE-2
Phytoalexin	Resveratrol	*Vitis vinifera, Ampelopsis cantoniensis*	Post-entry
Polyphenol	Tannic acid	*Caesalpinia spinosa, Rhus semialata*	M^{pro}, TMPRSS2
Lipophilic phenanthrene	Tanshinone I	*Salvia miltiorrhiza*	PL^{pro}
Lipophilic phenanthrene	Tanshinone II	*Salvia miltiorrhiza*	PL^{pro}

trum of essential oils is due to their unique chemical composition and act synergistically in nature [19]. These are widely used in aromatherapy and cosmetics in day-to-day life. Since the novel coronavirus is taking a toll globally, researchers worldwide have experimented with various intervention strategies to overcome the situation. Monoterpenes, sesquiterpenes, and aromatic propanoids present in essential oils are known to disrupt the phospholipid bilayer membrane of human coronaviruses [56].

Moreover, being lipophilic, essential oils tend to disintegrate the viral membranes by nonspecific insertion into the envelope lipid bilayer and further altering the fluidity of the membrane [56].

4.3.1 *In-Silico* Studies Using Bio-Essential Oils against SARS-CoV-2

A recent *in-silico* study has been published on screening essential oil components that exhibit antiviral activity against SARS-CoV-2. The research involves the screening of 171 different components from medicinal plants against the M^{pro} (PDB: 5R7Z, 5R80, 5R81, 5R82, 5R83, 5R84, 6LU7, 6M03, and 6Y84), Nsp15/NendoU (PDB: 6VWW, 6W01, and 6W02), ADP-ribose-1″-phosphatase (SARS-CoV-2 ADRP), and RdRp (PDB: 6M71) and found that the sesquiterpene hydrocarbons, including (E)-β-farnesene, (E, E)-α-farnesene, (E, E)-farnesol, and (E)-nerolidol showed excellent binding to M^{pro} with a lowest binding energy of DSnorm = –115.4 kJ/mol, –115.0 kJ/mol, –112.4 kJ/mol, and –110.7 kJ/mol, respectively [20]. The (E, E)-farnesol showed high exothermic docking to SARS ADRPP with a DSnorm of –121.4 kJ/mol, and the rest were found to be weak targets to interact with the essential oils. It is also proposed that the binding sites of these essential oil components, individually, are not at the spike-ACE2 interface and are unlikely to prevent SARS-CoV-2 internalization into the host [20]. Thus, individual essential oil components cannot be used as effective chemotherapeutic agents against SARS-CoV-2 at entry-level. These components and the mixture of other components in essential oils have a synergistic effect in inhibiting the virus [20].

In contrast, Thuy *et al*. [54] suggested using garlic essential oil as a therapeutic strategy for COVID-19. GC-MS analysis was performed on the garlic essential oil. The results revealed the presence of allyl sulfide, allyl disulfide, allyl trisulfide, allyl (*E*)-1-propenyl disulfide, allyl methyl trisulfide, allyl (*Z*)-1-propenyl disulfide, carvone, diacetone alcohol, diallyl tetrasulfide, 1,2-dithiole, methyl allyl disulfide, 1-propenyl methyl disulfide, trisulfide (2-propenyl propyl), trisulfide ((1*E*)-1-propenyl 2-propenyl), trisulfide ((1*Z*)-1-propenyl 2-propenyl), 2-vinyl-4*H*-1,3-dithiine, 3-vinyl-1,2-dithiacyclohex-4-ene, and cyclic octatomic sulfur. Among these, allyl disulfide, allyl trisulfide, allyl methyl trisulfide, diallyl tetrasulfide, and trisulfide (2-propenyl propyl) are the major components of garlic essential oil and show good binding with human ACE2 and SARS-CoV-2 M^{pro} (PDB 6LU7) protein with binding energy values of –14.06, –14.01, –12.84, –12.76, and –12.5 kcal/mol, in *in-silico* docking studies [54]. The biological functions of these components were reported to be directly proportional to their sulfur content. The organosulfur compounds present in the essential oils are shown to interact and block the ACE2 receptor externally. For instance, garlic essential oil has a 95.63% sulfur content and is recommended for use as an antiviral compound against SARS-CoV-2 [54].

In-silico docking and density-functional theory (DFT) studies have been performed on various essential oils against the RBD domain of the SARS-CoV-2 S protein. The *In-silico* study also reported that Carvacrol, cinnamaldehyde, cinnamyl acetate, geraniol, L-4 terpineol, and anethole (star anise) strongly bind to the RBD of the viral S protein, with a binding affinity of –5.2, –5.0, –5.2, –5.0, –5.1 and –5.2 kcal/mol respectively [55]. These compounds showed one or more hydrogen-bonding interactions with residues Arg454, Lys458, Ser459, Ser469, Glu471, Leu492 and Tyr505. The DFT molecular descriptor scores showed the highly electronegative cinnamaldehyde, followed by other components, including carvacrol, cinnamyl acetate, anethole, thymol, pulegone, and menthol, can be used in targeting the viral spike protein [55]. Another essential oil from an antimicrobial plant, *Ammoides verticillata* (Desf.) Briq was studied using an *in-silico* approach [57]. The essential oil of *A. verticillata* contains isothymol, thymol, limonene, p-cymene, and c-terpinene. Isothymol has been reported to show good binding and inhibition of ACE2 receptor, with a binding score of –5.7853 kcal/mol and hydrogen interaction at THR445 amino acids of 6VW1 target active site. Additionally, the ADME analysis showed that the compound followed Lipinski's, Veber's, Egan's, Ghose's and Muegge's rules, has a 1.96 SA value indicating ease of synthesis, could cross the blood-brain barrier and is easily absorbed by the intestines [57]. It is also reported that the Isothymol is an inhibitor of CYP450A2, CYP4502C9, CYP4502C19, and the substrate of CYP450A2, CYP4593A4, CYP4502C19, CYP4502D6 Thus indicating that the Isothymol could be used as a potential drug molecule [57,58].

4.3.2 *In-Vitro* Studies Using Bio-Essential Oils against SARS-CoV-2

Similarly, another study investigated the ACE2 inhibitory effects of ten different essential oils and found that geranium oil from *Pelargonium graveolens* and lemon essential oil from *Citrus limon* effectively inhibited ACE2 in epithelial cells initially by docking studies [59]. A GC-MS study was performed on both oils to reveal the components responsible for this activity. The major components (60%) were citronellol (27.1%), geraniol (21.4%), neryl acetate (10.5%), α-pinene, α-myrcene, limonene, linalool, phenylethyl alcohol, isopulegol, menthone, citronellal, isomenthone, α-terpineol, nerol, neral, citronellyl formate,

aristoene, germacrene D, δ-cadinen, guaiol, eudesmol, and α-bisabolol. Limonene was the major component (73%), and the other components included α-pinene, sabinene, β-pinene, β-myrcene, p-cymene, γ-terpinene, neral, and geranial [59].

The experiment was set up on HT29 cells (a colon adenocarcinoma cell line) by testing them against these essential oils in MTT assay with the essential oil concentration of (25–200 μg/mL) for 48 h. It was found that the geranium oil, was not cytotoxic up to a concentration of 200 μg/mL but lemon oil showed cytotoxicity at IC_{50} 57.93 μg/mL and hence 50 μg/mL of Geranium oil and 25 μg/mL of Lemon oil showed excellent ACE2 inhibitory effect. Following that, the ELISA assay is done, and significant downregulation of ACE 2 was recorded in HT29 cells from 17.68 ng/mL (control) to 1.43 ng/mL and 4.34 ng/mL for geranium and lemon essential oil [59].

The results were further confirmed by assessing ACE2 protein expression in the immunoblotting assay. The results showed significant downregulation of ACE2, in accordance with the ELISA results. qPCR analysis revealed that the lemon and geranium oils successfully reduced the ACE2 and S protein primer transmembrane serine protease 2 (TMPRSS2) [60] mRNA levels in HT29 cells. Moreover, the overall cytotoxicity of these essential oil components was tested to ensure human usage safety [56]. This study infers that lemon and geranium essential oils can be potential therapeutic agents for COVID-19. Docking and dynamics simulation study done on dithymoquinone (DTQ) from Nigella sativum showed efficient binding to M^{pro} with a binding energy of –8.56 kcal/mol [61]. This was experimentally verified in *in-vitro* studies using SARS-CoV-2 (SAID: EPI_ISL_430820) infected Vero E6 cells where the dosage of the compound required to decrease the viral cytopathic effect (CPE) by 50% in the cells (IC_{50}) is calculated to be 23.15 [62].

Although there are many studies on the antimicrobial properties of essential oils, they remain an underutilized resource. Asian countries are abundant in medicinal plants, and Ayurvedic medicine has been in practice for many decades. The compounds available naturally can be more potent, readily available, economical, and less toxic than the synthetic drugs used in western medicine. They can also induce a positive synergistic effect when combined with other therapeutics. *Melissa officinalis* essential oil is an excellent example in this case. It is reported to show increased efficiency and synergistic effect when combined with the oseltamivir drug in treating against avian influenza A virus and is prescribed in western medicine [56]. Thus, a comprehensive approach is required to develop therapeutic strategies to safeguard human health.

5. Future Directions

Research on drug development for treating COVID-19 is increasing. However, conventional antiviral drugs do not specifically treat this condition. Although drug repurposing is an attractive strategy to discover the hidden potential of several drugs. Thus, an alternative approach that employs phyto-drugs must be considered to explore the potential of herbs and other phytocompounds.

Ethnomedicine and plant-based medicines have been widely used in many countries since ancient times. The organic extracts and essential oils from medicinal plants can cure various conditions ranging from common fever to deadly viral diseases, with almost no side effects. Essential oils have great potential for managing diseases, mainly because of their rich antimicrobial components. Many natural antiviral components derived from Indian medicinal herbs remain unexplored in the context of SARS-CoV-2 [48,63]. Moreover, plants such as *Gymnema sylvestre* R. Br. (Asclepiadaceae), *Pergularia daemia* (Forsskal), Chiov. (Asclepiadaceae), *Sphaeranthus indicus* L. (Asteraceae), *Cassia alata* L. (Caesalpiniaceae), *Evolvulus alsinoides* L. (Convolvulaceae), *Clitori aternatea* L. (Fabaceae), *Indigofera tinctoria* L. (Euphorbiaceae), *Abutilon indicum* G. Don. (Malvaceae), *Vitextri folia* L. (Verbenaceae), *Clerodendrum inerme* (L.) Gaertn (Verbenaceae), and *Leucas aspera* Spr. (Lamiaceae), are abundant in India and show potential antiviral effects [57]. In addition, a list of Indian plants showing antiviral properties against various viruses has been discussed in detail by Dhawan *et al*. [41]. These compounds can be screened to evaluate their antiviral activity against SARS-CoV-2. Many such compounds have already been explored and computationally studied to inhibit SARS-CoV-2. Although many phytoconstituents have been discovered to target viral proteins, more *in-vitro* and *in vivo* studies are required to evaluate these *in-silico* results to standardize the treatment for COVID-19.

6. Conclusions

Scientists worldwide are trying to identify drug molecules that can be used to treat COVID-19. Many previously known broad-spectrum antivirals have been tested on a trial-and-error basis as the first line of treatment. Even though several vaccines are being administered, efficacy against the rapidly developing variants of SARS-CoV-2 is under evaluation. So far, no straight drug has been reported to show potential antiviral activity against SARS-CoV-2. Identifying new candidates or synthesizing potential components is a tedious and time-consuming process that may not help in handling the current pandemic situation. Accordingly, drug repurposing is a good alternative because FDA-approved safe drugs could be developed without much delay at this hour of crisis. However, it lacks specificity in treating the infection, and most of the drugs tested so far have not been effective against SARS-CoV-2. Phytocompounds, including essential oil components, have long been known for their activities against various microbes; however, this approach is still underexplored.

Recently, the use of Phyto-drugs against microbial infections has gained popularity, and studies have been conducted on phytochemicals against SARS-CoV-2 showing promising potential. Although, many of these drug-like compounds are only evaluated through computational procedures, further *in-vitro* and *in vivo* studies are required to standardize inhibitory potential/drug action. Based on this review, we collectively conclude that Flavonoids, Terpenes, Phenols, and certain Organo-sulphurs could be a potential target to explore for therapeutics against $3CL^{pro}$, M^{pro}, RBD targets of SARS-CoV-2, as reported by the *in-silico* studies. However, *in-silico* studies have also identified that the binding sites of individual essential oil components does not completely prevent SARS-CoV-2 internalisation into the host but shows a synergic effect when combined with other components in the source. Thus, plant phytochemicals can serve as the best alternative medicine to treat SARS-CoV-2 infection, but further investigation is necessary. More insights into alternative medicines that employ ethnobotany and phytochemistry are required to identify potential drugs for the treatment of COVID-19.

Author Contributions

VR and TM conceived and designed the study; SAK, VD, PD, KNR and RS consulted literature and collected data; TM wrote the manuscript, reviewed and edited; PV, PA and PR reviewed and edited the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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