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Biomedicine & Pharmacotherapy 147 (2022) 112658

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Natural products can be used in therapeutic management of COVID-19: Probable mechanistic insights

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ARTICLE INFO

Keywords:
SARS-CoV-2
Phytoconstituent
COVID-19 therapy
Natural anti-viral products
Polyphenols
Alkaloids

ABSTRACT

The unexpected emergence of the new Coronavirus disease (COVID-19) has affected more than three hundred million individuals and resulted in more than five million deaths worldwide. The ongoing pandemic has underscored the urgent need for effective preventive and therapeutic measures to develop anti-viral therapy. The natural compounds possess various pharmaceutical properties and are reported as effective anti-virals. The interest to develop an anti-viral drug against the novel severe acute respiratory syndrome Coronavirus (SARS-CoV-2) from natural compounds has increased globally. Here, we investigated the anti-viral potential of selected promising natural products. Sources of data for this paper are current literature published in the context of therapeutic uses of phytoconstituents and their mechanism of action published in various reputed peer-reviewed journals. An extensive literature survey was done and data were critically analyzed to get deeper insights into the mechanism of action of a few important phytoconstituents. The consumption of natural products such as thymoquinone, quercetin, caffeic acid, ursolic acid, ellagic acid, vanillin, thymol, and rosmarinic acid could improve our immune response and thus possesses excellent therapeutic potential. This review focuses on the anti-viral functions of various phytoconstituent and alkaloids and their potential therapeutic implications against SARS-CoV-2. Our comprehensive analysis provides mechanistic insights into phytoconstituents to restrain viral infection and provide a better solution through natural, therapeutically active agents.

1. Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging strain of coronavirus (CoV), has affected millions of people worldwide. The coronavirus infection has rapidly spread all over, affecting 210 countries and territories across the globe. According to the surveillance statistics reported by the World corona tracker, by January 19, 2022, the pandemic has caused more than 336 million number of confirmed infection cases, with 5.5 million worldwide deaths (https://www.worldometers.info/coronavirus). COVID-19 has marked the history with the third life-threatening coronavirus epidemic in the human population during the 21st century [1–5]. This emerging health crisis calls for the urgent development of specific therapeutics against COVID-19 to potentially reduce the burden of this emerging pandemic [6]. Chinese scientists released the sequence of the SARS-CoV-2 genome to understand viral physiology and develop new diagnostic tools, treatment options and anti-viral vaccines [7,8].

A total of six different human infecting coronavirus strains, SARS-CoV, MERS-CoV, H-CoV-229E, H-CoV-OC43, H-CoV-NL63, H-CoV-HKU1, have been reported at present [9]. Except for SARS-CoV and

Abbreviations: ACE2, Angiotensin-Converting Enzyme 2; COVID-19, Coronavirus Disease; Nsp15, Endoribonuclease; E Protein, Envelop Protein; Mpro, Main Protease; SARS-CoV-2, Novel Severe Acute Respiratory Syndrome Coronavirus; Nsps, Non-Structural Proteins; N Protein, Nucleocapsid protein; pp, Polyprotein; RBD, Receptor-binding domain; S Protein, Spike protein.

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https://doi.org/10.1016/j.biopha.2022.112658
Received 3 December 2021; Received in revised form 18 January 2022; Accepted 18 January 2022
Available online 20 January 2022

MERS-CoV strains responsible for the respiratory infections in China during 2002–2003 and in the Middle East in 2012, respectively. The other four strains are common and cause the common cold in healthy individuals. The novel coronavirus, including six other species in the coronavirus genus of the coronavirus family, distributed broadly among birds, humans and other mammals, have been reported [10–13]. The genome length of coronaviruses ranged from ~27 kb to ~31 kb, establishing the genome of coronaviruses as the largest found in any RNA viruses (Fig. 1).

The SARS-CoV-2 is an enveloped, positive sense-RNA β-coronavirus with around 30 kb genome [14]. The complex genome of SARS-CoV-2 encodes for several non-structural proteins (Nsps) and structural proteins [15]. A major part of the genome consisting of replicase ORF1ab encompassing Nsps, encodes for pp1a and pp1ab, the two overlapping polyproteins (pp) of SARS-CoV-2 [16]. The main protease (M^{pro}), ~306 amino acids long of the virus, is encoded by these polypeptides pp1a and pp1ab [17]. The M^{pro} of the virus cleaves the polypeptides at multiple conserved sites resulting in 16 functional viral Nsps. These digested Nsps perform various viral enzymatic activities and are involved primarily in the replication process [15,16,18]. An important SARS-CoV-2 protein, Nsp15, is a crucial endoribonuclease required for viral intervention during an innate immune response [15]. Considering the importance of M^{pro} and Nsp15 in viral replication and survival, these viral proteins could be attractive drug targets to develop effective COVID-19 therapy (Fig. 2).

Other than Nsps, the coronavirus genome comprises several genes encoding for the structural protein such as including the S (spike) gene, E gene (viral envelope protein), and N (nucleocapsid protein) gene. The spike protein of the virus plays an important role in the viral entry into the human cells by attaching to the human angiotensin-converting enzyme 2 (ACE2) receptor through which the virus fuses with the target membrane [19]. The affinity for the human ACE-2 was found much more in the novel strain of coronavirus SARS-CoV-2, as compared to the SARS-CoV strain, indicating the SARS-CoV-2 fusion mechanism as a novel and attractive target for coronavirus inhibition. The S1 submit of spike protein binds the ACE2 receptor, whereas the S2 subunit forms the fusion core, bringing viral and host cell membranes closer for effective fusion following infection [20]. Therefore, the S2 submit of spike protein is considered a potential target for viral fusion inhibition [21,22].

This global calamity has posed a difficult time throughout the world, impeding the normal lifestyle. It has become urgent to develop a new vaccine or drugs against this deadly infectious disease at the earliest [23–25]. The scientific community worldwide has reported various preliminary studies on the pathophysiology of COVID-19 patients and provided some clues to treat this pandemic [26]. Unfortunately, currently, no FDA-approved drugs are available and the development of new therapeutic moieties and vaccines remains a costly and time-consuming affair with high failure chances, too [27,28]. Considering this pervasive situation, it is essential to apply different strategies to tackle the present scenario. The plants with medicinal properties have provided an excellent and widespread therapeutic alternative since ancient times against various infectious diseases owing to their safer, cheaper, and less toxicity profile [29–33]. Phytoconstituents are important compounds for drug discovery against various human diseases [34–36]. Recent studies have suggested the potential of polyphenols, alkaloids to combat COVID-19 with their chemical properties are listed in Table 1.

Phytoconstituents like polyphenols, flavonoids, and alkaloids are found in ample amounts plants and are abundant in a broad range of human diet [37–42]. The best-characterized complex class, all the structurally diverse members, comprise a central oxygenated heterocycle, a three-ring structure with two aromatic center [43,44]. Presently, these phytoconstituents are of great interest for their antioxidative, anti-inflammatory, anti-pathogenic, cardioprotective, and anti-carcinogenic properties [45–49]. These polyphenolic compounds, alkaloids, comprise multiple essential characteristics against viral diseases like immune system alteration [50], suppression of viral replication [51], and decrease in viral uptake by host target membrane [52]. Moreover, studies have suggested the anti-viral activity of phytoconstituents against rabies virus, HIV, chandipura virus, Japanese Encephalitis Virus, Enterovirus, Influenza A/H1N1, other influenza viruses, and SARS-CoV-2 [30,53–55]. Phytoconstituents show beneficial impact on COVID-19 therapy are listed in Table 2, and their sites of action are illustrated in Fig. 3.

This review summarizes the therapeutic properties of essential phytoconstituents, polyphenols, alkaloids, like thymoquinone, quercetin, caffeic acid, ursolic acid, etc., and further discusses their therapeutic potential in COVID-19.

2. Thymoquinone inhibits the CoV-2 entry and replication

Nigella sativa consists of a wide range of bioactive constituents such

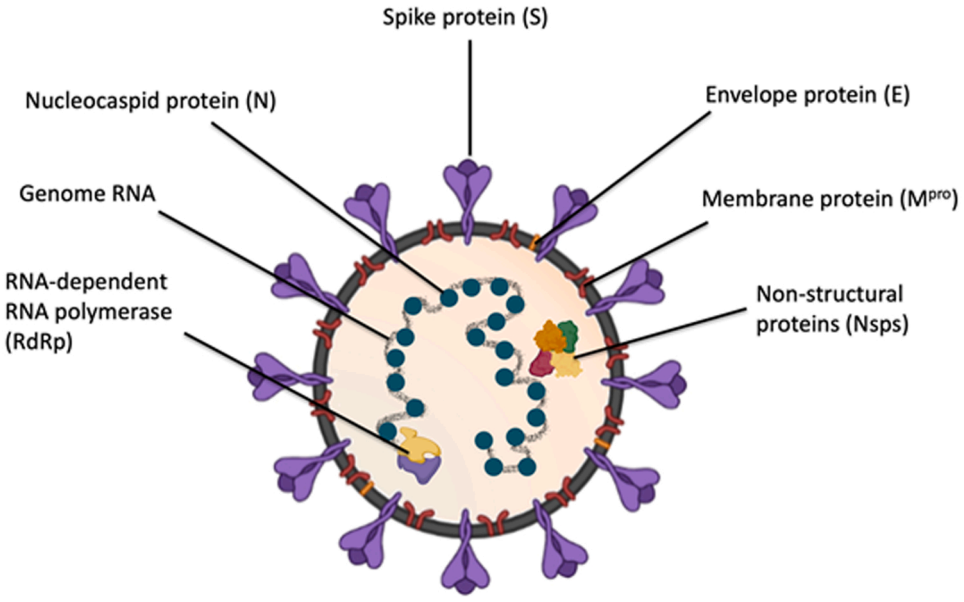


Fig. 1. Structural representation of SARS-CoV-2.

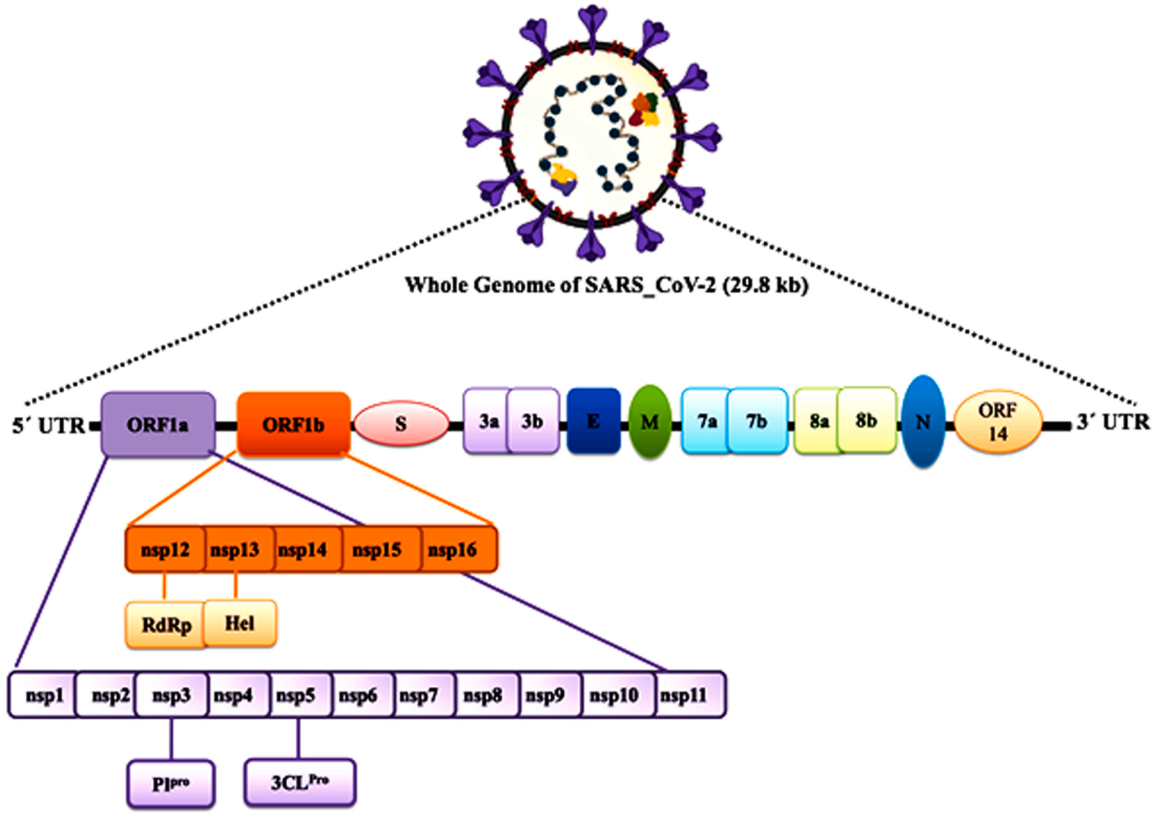


Fig. 2. Schematic diagram of the SARS-CoV-2 genome organization and the different proteins encoded by various genes.

as thymoquinone and nigellimine offer a range of beneficial spectra for the COVID-19 treatment by blocking the virus introduction to host pneumocytes; by furnishing ionophores to improve zinc consumption, thus enhancing the host immune response to coronavirus-2, and further suppressing the viral replication. Thymoquinone (2-Isopropyl-5-methyl-1, 4-benzoquinone) is the main active ingredient of *Nigella sativa.* El primarily extracted by Dakhakhny and subsequently found to exhibit numerous therapeutic properties as immune-regulatory, anti-inflammatory, anti-oxidant, antimicrobial, antitumor, analgesic, anti-Alzheimer, and hepatoprotective [98–101]. Thymoquinone-mediated inhibition of 5-lipoxygenase, leukotriene B4, C4, and Th2 cytokines in bronchoalveolar lavage fluid was reported with a remarkable increase in immune cell numbers in lung tissue [102,103]. The anti-inflammatory activities of thymoquinone are regulated by the higher production of hem oxygenase 1 (HO-1) in HaCaT (human keratinocyte) cells [101]. Furthermore, the anti-oxidant properties of thymoquinone are linked with the redox activities of quinone structure and unrestricted competence of thymoquinone to cross substantial barriers to cellular niche [26, 104].

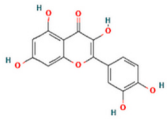
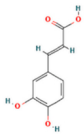
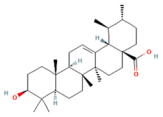
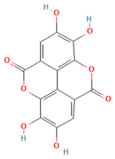
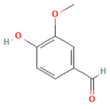
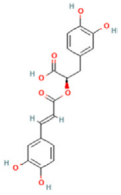
Nigella sativa extract and thymoquinone were highly effective in avian influenza virus (H9N2 AIV) infection model [105]. Intriguingly, *Nigella sativa* extract treatment of the cells before infection with coronavirus reduces the division and survival of the virus inside the cell [106]. Additionally, thymoquinone regulates nitric oxide (NO), reactive oxygen species (ROS), and transforming growth factor β1 (TGF-β1) production and protects the multiple organ dysfunction syndromes (MODS) [56,58,107–109].

A molecular docking-based study has identified nigellidine and α-hederin among the compounds against SARS-CoV-2 [110]. *N. sativa* extract decelerates COVID-19 infection and might provide better results [26]. The beneficial effects of thymoquinone could be enhanced by using a zinc supplement because zinc during any pathogenic virus or bacterial infection may improve innate and adaptive immunity. The effectiveness of the zinc salt supplement in combination with thymoquinone could also be augmented as it functions as an ionophore to allow Zn^{2+} to enter pneumocytes, the target cell for SARS-CoV-2 [57]. Bioactive compounds of *N. sativa* seed, especially thymoquinone, α-hederin, and nigellidine, could be alternative and promising herbal drugs to combat COVID-19 infection [56]. Thymoquinone and other active ingredients of *N. sativa* seed could influence the immune response and thus protect from COVID-19 [26].

3. Quercetin mediated inhibition of 3CL protease activity, and viral entry

Quercetin (3,3′,4′5,7-pentahydroxyflavone), classified as a flavonoid, is found in many plants and foods consumed by humans such as apples, berries, grape, onions, green tea, and Ginkgo biloba. A polyphenolic compound, quercetin, presents a variety of physiological benefits, including anti-oxidant, anti-inflammatory, anti-cancerous, anti-viral, anti-bacterial, and immunomodulatory [49,111–115]. Studies including in vitro system and in vivo animal model have shown the immune-modulating effects of quercetin, such as an increase in the chemotaxis motion of neutrophil cells, phagocytosis, lytic activity and proliferation of different immune cells. Additionally, the cytokines expressing genes are regulated by quercetin [111]. The quercetin treatment to cell cultures inhibited influenza strains and preventing H5N1 viral entry [116]. Health workers and doctors recommend using quercetin to improve healthy immune function. The use of quercetin supplements in the common people and sports professionals has been reported. It is proven that severe physical activities are responsible for a short-term decline in the immune, which enhances the risk of infection [66,111]. Furthermore, the use of quercetin has been reported in viral infection owing to its potential anti-viral effects in inhibiting viral proteases, reverse transcriptase, polymerases, reverse transcriptase, binding viral capsid proteins, and suppressing DNA gyrase [117–124].

Table 1
Phytoconstituents from natural sources with their chemical properties.

S. N.	Compound	Structure	Chemical Formula	Molecular Mass
1	Thymoquinone		$C_{10}H_{12}O_2$	164.201 g/mol
2	Quercetin		$C_{15}H_{10}O_7$	302.236 g/mol
3	Caffeic Acid		$C_9H_8O_4$	180.16 g/mol
4	Ursolic acid		$C_{30}H_{48}O_3$	456.71 g/mol
5	Ellagic acid		$C_{14}H_6O_8$	302.197 g/mol
6	Vanillin		$C_8H_8O_3$	152.15 g/mol
7	Thymol		$C_{10}H_{14}O$	150.22 g/mol
8	Rosmarinic Acid		$C_{18}H_{16}O_8$	360.31 g/mol

The anti-viral activities of quercetin have been well established. In cultured cells, the administration of quercetin inhibits the growth of various respiratory viruses [121,125]. Quercetin significantly restrained the cytomegalovirus replication inoculated HeLa cells with an IC_{50} (half inhibitory concentration) of 0.8 μM [126]. The treatment of quercetin inhibits replication of dengue virus type 2 in Vero cells with an IC50 of 35.7 μg/mL, resulting in a 67%reduction of dengue virus RNA [127].

The anti-viral effects of quercetin were studied on various associates of the Corona viridae family [128]. Quercetin binds and inhibits the proteolytic activity of the 3CL protease of SARS-CoV-2 with an IC_{50} of 4.95 μM [129]. The hydroxyl group of quercetin regulates the inhibition of 3CL protease. Mutational modeling analysis of Q189A identified the Gln189 as an essential position on 3CL protease responsible for the quercetin binding. Additionally, treatment of Vero E6 cells with quercetin interrupts viral entry with an EC_{50} (half-effective concentration) of 83.4 μM and with low CC_{50} (cytotoxicity) of 3.32 mM [128].

4. Caffeic acid regulates the CoV-2 attachment to the host cell

Caffeic acid (3,4-dihydroxycinnamic acid) is a polyphenol, belongs to the phenolic acid family. It is one of the potent and abundantly found in nature hydroxycinnamic acids [69]. The chemical formulation of caffeic acid is [(E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid] with a molecular mass of 180.16 g/mol[130–132]. Caffeic acid is the main hydroxycinnamic acid abundantly present in blueberries, kiwis, coffee, cherries, apples, oils, and tea [70–72]. Besides the mentioned foodstuffs, caffeic acid is also found in propolis, a mixture used in medicine [133]. In the last few years, several studies reported the biological properties of caffeic acid, caffeic acid derivatives (CAFDs), and the Caffeic Acid Phenethyl Ester (CAPE) that have shown various immune-modulatory properties such as; anti-oxidant, anti-inflammatory, anti-bacterial and anti-viral effects [134–141]. Caffeic acid derivatives have a high potential for treating and preventing various human disorders [142–144]. Caffeic acid with advantageous biological properties, accompanied by acceptable safety characteristics, makes them suitable candidates for clinical studies [143]. The role of caffeic acid as a potential anti-viral agent has been reported against the influenza virus, herpes simplex virus, and severe fever with thrombocytopenia syndrome (SFTS) virus [75,145]. Furthermore, caffeic acid, CAPE, CAFDs as a potential anti-viral agent for the treatment of a number of viruses such as HCV, HIV, human sarcoma, polio, and influenza A viruses. The scientific basic and antiviral mechanisms of CA, CAPE, and CAFDs might be same and/or

Table 2
A list of different phytoconstituents shows anti-viral activity against SARS-CoV-2.

Compound	Biological Role	Activity against Covid-19	Natural source	Ref.
Thymoquinone	Anti-oxidant immune-regulatory, anti-inflammatory, and anti-oxidant benefits	Prevent the SARS-CoV-2 entry; inhibits viral replication	*Nigella sativa*	[26, 56–61]
Quercetin	Anti-oxidant, anti-inflammatory, anti-cancerous, anti-viral, anti-bacterial, and immunomodulatory	Inhibition of 3CL protease activity and viral entry inside the host cell	Apples, Honey, Raspberries, Onions, Red Grapes, Cherries, Citrus Fruits, And Green Leafy Vegetables	[49, 62–68]
Caffeic Acid	Anti-oxidant, anti-inflammatory, anti-bacterial and anti-viral	Inhibit the virus attachment to the host cell; Binds 3CL protease inhibits the viral replication	Blueberries, Kiwis, Coffee, Cherries, Apples, Oils, And Tea	[69–75]
Ursolic Acid	Anti-inflammatory, anti-bacterial effects, anti-oxidant, anti-cancer, and anti-diabetic,	Potently block the M^{pro}enzyme	*Mimusopscaffra, Ilex paraguarieni,*and *Glechoma hederacea*	[76–80]
Ellagic Acid	Anti-oxidant and anti-proliferative, Inhibit fibrosis, oxidative stress, and inflammation in the diabetic liver	Inhibits the M^{pro} and RdRp; Prevent viral attachment and internalization to the host cell	Raspberries, Strawberries, Pomegranate, Persimmon, Grapes, Black Currants, Plumes, Mango, Guava, Walnuts, Almonds, Longan seeds, Green Tea, and *Momordica charantia*	[81–85]
Vanillin	Anti-clastogenic, anti-microbial agent, anti-oxidant	M^{Pro} inhibition	Vanilla bean	[86–90]
Thymol	Anti-oxidant, local anesthetic, anti-carcinogenesis, anti-nociceptive, cicatrizing, antiseptic, as well as a potential as a growth enhancer and immunomodulator	Inhibit the viral spike protein; prevent the SARS-CoV-2 entry, potent disinfectants.	Thymus vulgaris, Ocimum, Origanum, Monarda genera, members of Verbenaceae, Scrophulariaceae, Ranunculaceae, and Apiaceae families	[91–93]
Rosmarinic Acid	Antispasmodic, analgesic, anti-rheumatic, diuretic, and antiepileptic agent food flavoring agent,	Inhibition of viral entry, replication	Rosemary, Perilla, Sage, Mint, and Basil.	[94–97]

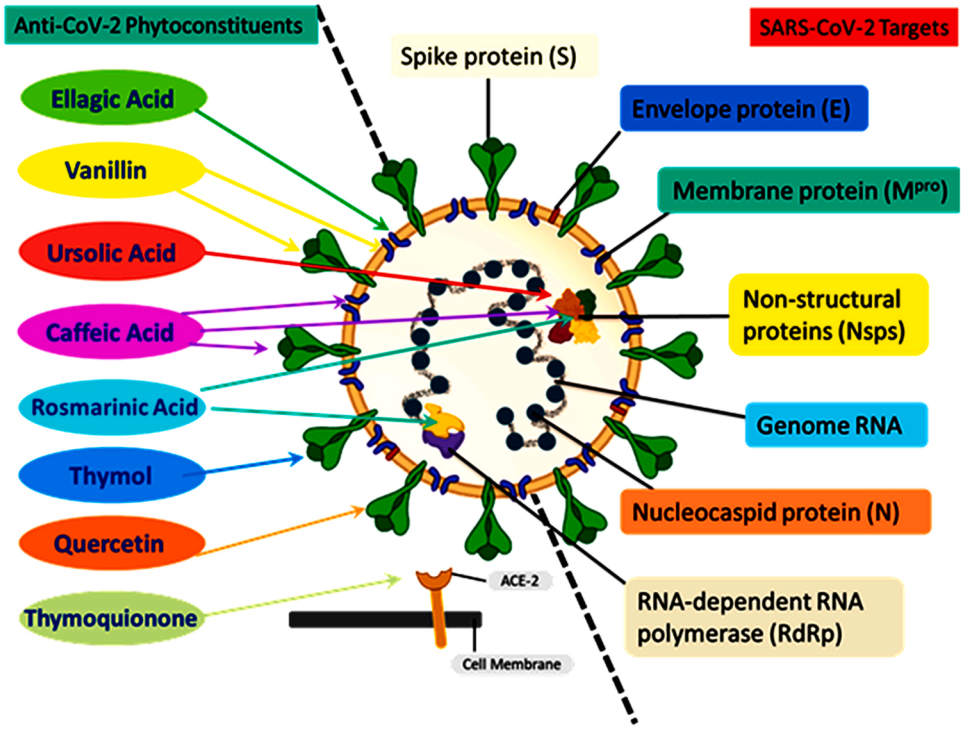


Fig. 3. Schematic representation of SARS-CoV-2 structure showing the viral genome and important viral proteins (S protein, N protein, E protein, M^{pro} protein, Nsps, and RdRp,). Natural phytochemicals showed therapeutic potential against the SARS-CoV-2 via binding to these proteins followed by inhibiting their functions. The phytochemicals such as thymoquinone interact with ACE-2 receptors to block the entry; thymol interacts with S protein; quercetin interacts with 3CL protease; vanillin interacts with both the 3CL protease and S1 proteins; rosmarinic acid interacts with NSP-15; ursolic acid interacts with NSP15 and M proteins; ellagic acid interacts with M proteins and caffeic acid, and its derivatives interact with M proteins, NSP-15, and spike protein.

different depending on the type of the virus.

Anti-viral activity of caffeic acid has previously been reported against the human sarcoma, polio, and influenza A viruses [73,146]. CAPE has anti-viral activity against HIV and hepatitis C virus [141,147]. A library consisting of CAFDs was screened to identify the novel therapeutic natural compounds as an anti-COVID19 agent. The important drug targets of SARS-CoV-2, such as spike ectodomain (open), spike glycoprotein (closed), Nsp15 endoribonuclease, M^{pro} (6LU7), and S2 subunit (6LXT), have been subjected to the study. The analysis has identified several CAFDs as modulators of SARS-CoV-2 drug targets, in particular, khainaoside C as M^{pro} modulator, khainaoside B as SARS-CoV-2 fusion protein, 6-O-Caffeoylarbutin as Nsp15, khainaoside C as spike (open), and vitexfolin A as spike (closed) modulator [22]. The effect of ethanolic extracts of Sambucus formosana (elderberry) stems from a variant HCoVNL63 of the human coronavirus was studied. A very high efficacy was reported (EC50 of 1.17 ± 0.75 μg/mL). Subsequent analysis of the phenolic constituents of the extracts identified caffeic acid as the most potent compound (EC_{50} of 3.54 ± 0.77 μM; or $\sim 0.64 \pm 0.14$ μg/mL) in anti-viral assays [148]. Caffeic acid has also been found to inhibit the virus attachment to the host cell [149]. Caffeic acid, CAPE, galangin, and chrysin have a high potential to suppress the viral 3CL protease enzyme and prevent viral replication [150].

The host cell surface heat shock protein A5 (HSPA5) during viral infection is upregulated and subjected to be recognized by the SARS-CoV-2 spike protein. Molecular docking and molecular dynamics simulations studies were performed to observe the binding potential of natural compounds to HSPA5 substrate-binding domain β (SBDβ). The results showed high to a moderate binding affinity for several phytoestrogens, including caffeic acid, CAPE, and thymoquinone, to the HSPA5 SBDβ and indicated the potential of these compounds as anti-COVID-19 agents [61]. In addition, docking studies revealed that CAPE showed the highest affinity to both 3CL-protease and S1 spike protein [121]. Furthermore, hydrogen bond formation between the catalytic site residue Lys50 of M^{pro} and caffeic acid was reported. Caffeic acid forms hydrogen bonds with the catalytic site residues of both E and N protein with a docking score of −6.1 kcal/mol and −7.4 kcal/mol [151,152].

5. Ursolic acid, a potent inhibitor of viral M^{pro} enzyme

Ursolic acid (3-β-hydroxy-urs-12-en-28-oic acid) is a naturally occurring pentacyclic triterpenoid of isoprenoid units [76–78]. Ursolic acid is highly soluble in alcoholic NaOH and glacial acetic acid and low soluble in an aqueous medium [153,154]. The biosynthesis of ursolic acid occurs by folding and cycling squalene from a dammarenyl cation, making the third ursolic acid ring expand and generate an additional ring [76,155]. Ursolic acid, majorly extracted from medicinal plants *Mimusopscaffra*, *Ilex paraguarieni,* and *Glechoma hederacea*, show anti-inflammatory, anti-bacterial, anti-oxidant, anti-cancer, and anti-diabetic potential. Still, its bioavailability and solubility limit its clinical application [76,79,80,156–159].

Ursolic acid has been reported to effective anti-viral response against the SARS-CoV-2. The studies have reported that ursolic acid modulates the M^{pro} activity of SARS-CoV-2, which is required to process replicase-transcriptase machinery for viral replication and particle assembly. Ursolic acid, including other natural metabolites, was reported as a potential inhibitor against M^{pro} [160]. Furthermore, in a study using molecular docking and molecular dynamic simulations, three ligands bound to protease during 50 ns of MD simulations [161]. To review the ethnobotanical knowledge of medicinal plants traditionally used to treat different viral diseases by the Ethiopian people, Tegen et al. [162] suggested those plants consisting of active anti-viral components, including ursolic acid, are promising to treat COVID-19. The bioactive constituents of herbal origin, ursolic acid, with a few more compounds, bind and potentially block the M^{pro} enzyme of SARS-CoV-2. The ursolic acid showed the highest docking score (−8.7 kcal/mol) with the M^{pro} followed by other compounds tested, suggesting the potential binding and inhibitory effects of ursolic acid [163]. Ursolic acid showed a high binding affinity (−9.7 kcal/mol) for papain-like protease PL^{pro} of SARS-CoV-2 and forms hydrogen bonding at amino acid residues Asp108 and attaches at Ala107, Pro248 and Tyr264 with alkyl, π-alkyl interaction [164].

6. Ellagic acid mediated binding of viral M^{pro} and RdRp enzymes

Ellagic acid (2,3,7,8-tetrahydroxy[1]-benzopyranol [5,4,3-cde] benzopyran-5,10-dione), discovered by Braconnotin 1831 and found in numerous fruits and vegetables, is a naturally occurring polyphenolic compound [81,165]. Ellagic acid with a molecular weight of 302.197 g mol^{-1} and a melting point of 350 °C is a highly thermostable molecule [166]. The structural feature of ellagic acid represents four lipophilic domains that form hydrogen-bond sides, four phenolic groups that function as electron acceptors, and two lactones that denote the hydrophilic domain [167,168]. Ellagic acid is found in the forms of hydrolyzable tannins called ellagitannins in many fruits, in particular raspberries, strawberries, pomegranate, persimmon, grapes, black currants, plums, mango, guava, walnuts, almonds, longan seeds and green tea [82–84]. The anti-oxidant and anti-proliferative biological activities of ellagic acid have encouraged research towards the potential health benefits of the compound [169,170]. Ellagic acid can obstruct tumor cell migration, extracellular matrix invasion and angiogenesis, important for infiltrative tumor behavior and metastatic function [171–174]. Additionally, ellagic acid enhances the tumor susceptibility to radio- and chemo-therapies [175]. Ellagic acid extracted from *Momordica charantia*was reported to inhibit fibrosis, oxidative stress, and inflammation in the diabetic rat liver. It performs a favorable function in improving several health conditions [85,176,177].

In several studies, small molecule inhibitors have targeted the main protease (Mpro) of SARS-CoV-2 to develop a promising treatment option for the infectious disease COVID-19 [32,178,179]. Ellagic acid has shown remarkable binding with the catalytic site of the M^{pro} enzyme with noteworthy interaction with the prime catalytic site residue Cys145 [180], thereby representing their potential to act as drug candidates for COVID-19 therapeutic. Shaldam et al. [181] studied the binding affinity of 14 selected phenolics and terpenes against the M^{pro} and RNA-dependent RNA polymerase (RdRp) enzymes of the SARS-CoV-2 virus using molecular docking. They reported that the ellagic acid, quercetin, with two more compounds, interacts most with the SARS-CoV-2 target enzymes. Another molecular docking analysis has shown that ellagic acid, gallic acid, geraniin, kaempferitrin, kaempferol, and quercetin with significant binding affinity for a receptor-binding domain (RBD) and (GRP78) of SARS-CoV-2 [182]. Furthermore, the constituents of *Moringa oliefera* consisting of ellagic acid were investigated for the interactions against two crucial proteins of SARS-CoV-2 using quantum chemical, molecular docking and dynamic methods. The analysis has shown that the ellagic acid possesses the highest binding affinities of −7.1 kcal mol^{-1} against nsp9 and −6.9 kcal mol^{-1} against nsp10 [183].

7. Potential beneficial effects of vanillin as an inhibitor of CoV-2M^{pro} inhibitor

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is a naturally occurring organic compound, commonly used as a flavoring and aromatic agent in various foods, perfumes, and pharmaceuticals. The vanillin consists of aldehyde, ether, and hydroxyl with a molecular formula of $C_8H_8O_3$. Primarily extracted from the vanilla bean, it is generally used as an intermediate chemical molecule to produce crucial pharmaceutical formulations and other agents. Vanillin is of interest because of its medicinal uses as an anticlastogenic, antimicrobial agent and its biogenetic relationship to the phenylpropanoid pathway and other molecules of physiological significance, notably salicylate [41,184]. Following the expression of the HCHL (4-hydroxycinnamoyl-CoA hydratase/lyase) enzyme of the Pseudomonas, efforts have been made to establish a direct capacity for vanillin production into plants by deviation of the phenylpropanoid pathway [86,87]. The therapeutic potential of vanillin and its main metabolites as an anti-oxidant and antimicrobial for treating inflammatory diseases and their actions on redox status using molecular docking evaluation have been reported [88–90,185–187]. Law et al. [188] subjected vanillin derived 20-compounds together with monolaurin and tetrodotoxin as test sets and evaluated their potential as SARS-CoV-2 inhibitors.

8. Thymol as a spike protein inhibitor

Thymol (2-isopropyl-5-methylphenol) is the phenolic monoterpene in thyme species and the main constituent of thyme essential oils. Other than the medicinal plant thyme (Thymus vulgaris), thymol is also extracted from plants such as Ocimum, Origanum, Monarda genera, and other plants, for instance, the members of Verbenaceae, Scrophulariaceae, Ranunculaceae, and Apiaceae families. Thymol has been used in traditional medicine as an expectorant, and antiseptic agent, primarily as a treatment option for the upper respiratory system, coughs, headaches, and diarrhea. The current search of medicinal plant compounds as a therapeutic option for various human diseases has involved thymol. Recent reports have suggested the multi-functional role of thymol as an anti-viral, anti-bacterial, antibiofilm, antifungal, anti-inflammatory, antileishmanial, and anti-cancer agent. The novel development of nano-capsules comprised of the thymol compounds expanded their medicinal use [93]. Several studies have shown additional biological properties of thymol, in particular anti-oxidant, local anesthetic, anti-carcinogenesis, anti-nociceptive, cicatrizing, antiseptic, as well as a potential as a growth enhancer, and immunomodulator [91,92,189,190].

Kulkarni et al. [191] have docked the major components of several essential oils against the S1 receptor binding domain of the spike glycoprotein. The group has observed several phytochemicals, including thymol, are effective anti-viral agents that inhibit the viral spike protein [191]. An *in-silico* study was performed by selecting eighteen well-reported anti-viral phytochemicals to find out whether they can prevent SARS-CoV-2 infection. The structure of a host protein, TMPRSS2 (transmembrane protease serine 2), was predicted, which cleaves the spike protein of SARS-CoV-2, thereby aiding the viral internalization. Subsequently, the catalytic domain of TMPRSS2 was docked against the eighteen selected phytochemicals. Following it, the target-inhibitor complex's stability was analyzed using molecular dynamic simulation, which indicated thymol as a better inhibitor due to their stable binding with TMPRSS2, inducing subtle modification in the spatial arrangement of the catalytic triad residues [192].

Using an *in silico* approach, it was suggested that unique phytocompounds thymol could physically bind SARSCoV-2 spike glycoproteins (6VXX and 6VYB), SARS-CoV-2 B.1.351 South Africa variant of spike glycoprotein (7NXA), and ACE2 to prevent the SARS-CoV-2 binding to the host ACE2, TMPRSS2 and neutrapilin-1 receptors [193]. Qazi et al. [194] recently elucidated the epigenetic mechanism of SARS-CoV-2 and its impact on the environment. Thus, inactivating it from the surfaces when sprayed and are not harmful to the biological environment.

9. Rosmarinic acid-meditated inhibition of CoV-2 entry and replication

Rosmarinic acid (3,4-dihydroxyphenyllactic acid) is a polyphenol molecule commonly found in many culinary herbs, such as rosemary, perilla, sage, mint, and basil. It is found to be slightly soluble in an aqueous medium whereas very well in most organic solvents. This phytoconstituent comprises several compelling biological and pharmacological properties, particularly anti-oxidant, anti-inflammatory, antiviral, anti-bacterial, hepatoprotective, and anti-nociceptive. The rosmarinic acid functions as a defense molecule in the plants, whereas the rosmarinic acid-containing medicinal plants, herbs and spices have beneficial and health-promoting effects and rheumatic, diuretic, and antiepileptic agents. Additionally, rosmarinic acid has remarkable carcinogenesis progression [195]. The L-phenylalanine and L-tyrosine, the primary amino acids, together with several eight enzymes and other

co-factors, are required for rosmarinic acid biosynthesis [94–96].

Tegen et al. [162] reviewed the ethnobotanical knowledge of medicinal plants used as a treatment option for various viral infections since ancient times. They predicted the use of phyto-compounds as COVID-19 therapeutics. Medicinal plants containing rosmarinic acid, ursolic acid, and some others are a few promising compounds for treating COVID-19. In another report, natural compounds, including rosmarinic acid and a few other compounds, have been displayed the potential to enhance the expression of ACE-2. They could exasperate SARS-CoV-2 infection by degrading the host receptors aiding viral endocytosis [97].

Furthermore, a molecular docking study has analyzed the binding affinities of various phytocompounds with the Nsp15 protein. It represented rosmarinic acid, ursolic acid interacting successfully with Nsp15 viral protein suggesting their potential role in inhibiting the SARS-CoV-2 replication [196]. The RdRp of SARS CoV-2 has been subjected to molecular docking analysis with compounds from *Plectranthusamboinicus* consisting of rosmarinic acid. The interaction profiling of rosmarinic acid with the target protein SARS-CoV-2 linked RdRp has been reported for further consideration [197].

10. Conclusion and future prospects

In present unfavorable conditions of COVID-19 across the world, there is an urgent need to develop antiviral drugs or therapeutic alternatives. The identification and development of novel drugs are time-consuming, and further validation and clinical trials of such novel drugs/targets are mandatory to check the efficacy and effectiveness. Additionally, the absence of COVID-19 specific treatment and drugs encourages the scientific community across the globe to look for other options to successfully combat the current disease scenario.

In this view, the medically important plants containing specific phytoconstituents could provide a wide scope as therapeutic against COVID-19. The medically critical phytochemicals that naturally possess a wide range of therapeutic beneficial and dynamic resources of chemical constituents show anti-viral characteristics [198,199]. Numerous docking simulations studies have recommended using these compounds to improve COVID-19 therapy. The phytoconstituents reviewed in this article include thymoquinone, quercetin, caffeic acid, ellagic acid, ursolic acid, thymol, vanillin, rosmarinic acid. These phytoconstituents represent a promising option for treating infections of coronavirus disease by targeting viral protein and inhibiting viral replication or endocytosis. However, the dosage of these compounds at higher concentrations may be toxic beyond a certain level.

It is needless to mention that remarkable in vitro and in vivo studies are required to determine each compound's safe and therapeutic concentration before the clinical trials in humans to be carried out. To develop effective COVID-19 therapy, initial studies involve those molecules that have already been FDA-approved or considered safe for drug use, as in the case of polyphenolic constituents. It is anticipated that the phytoconstituents discussed in this report will aid the development of an effective and safe anti-SARS-CoV-2 treatment option from naturally procured compounds.

Funding

This work is support and funded through the Indian Council of Medical Research (Grant No. BMI/11(39)/2020).

CRediT authorship contribution statement

Sabeeha Ali: Conceptualization, Writing – original draft, Data curation, Investigation, Methodology. **Manzar Alam:** Conceptualization, Writing – original draft, Methodology. **Fatima Khatoon:** Writing – original draft. **Urooj Fatima:** Writing – original draft. **Abdelbaset Mohamed Elasbali**: Data curation, Investigation, Methodology, Project administration. **Mohd Adnan:** Data curation, Investigation, Methodology. **Asimul Islam:** Data curation, Investigation, Methodology. **Md. Imtaiyaz Hassan:** Conceptualization, Writing – original draft, Investigation, Supervision. **Mejdi Snoussi:** Data curation, Investigation, Writing – review & editing. **Vincenzo De Feo:** Conceptualization, Writing – original draft, Investigation, Supervision, Project administration.

Conflict of interest statement

All authors declare that they have no conflict of interest.

Data Availability

The information that supports the findings of this study is available in this article.

Acknowledgments

AME extends his appreciation to the Deanship of Scientific Research at Jouf University for funding his work through Research Grant Number (DSR-2021-01-0365). MA expresses thanks to the Indian Council of Medical Research for financial support (Grant No. 45/6/2020-DDI/BMS). MIH, SA and MA sincerely thank the Department of Science and Technology, Government of India, for the FIST support (FIST program No. SR/FST/LSII/2020/782).

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