

The effect of a small polyphenolic and terpenoids phytochemical constituent on curing and preventing of Covid-19 infections

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Abstract

Covid-19 spreading have caused millions of deaths worldwide and caused sever economic shrinking resulted in high levels of inflations. The on going pandemic has pushed the pharmaceutical companies to invent different vaccines to overcome the spreading of the virus and to reduce its effect on health and economy. Unfortunately, the middle and low income countries have been struggling in providing vaccines to their people due to the high expenses associated with vaccines ordering. Thus, the interest in finding a treatment and a prevention of Covid-19 from natural products has increased not in those countries only, even in high income countries. In this review we investigated the promising natural phytochemical compounds and their published mechanism of action in a prestigious peer-reviewed research journal throw different molecular docking and in *vivo* and *vitro* techniques. Its was found that the consumption of the medicinal plants containing small phenolic and terpenoids phytoconstituent like as thymoquinone, quercetin, caffeic acid, ursolic acid, ellagic acid, vanillin, and thymol have a great therapeutic effect for curing and preventing viral infections. This review has focused on the small polyphenolic and terpenoids compounds and their potential and mechanism activity against SARS-CoV-2. Our comprehensive analysis provides mechanistic insight into plant components for virus containment prevent infections and provide better solutions through natural therapeutically active ingredients.

Keywords

Covid-19, Medicinal plants, Anti-viral, Polyphenols

Introduction

The emotional alter of occasions with the later exceptional coronavirus pandemic announced by the World health organization (WHO) has incited an exponential increment of logical intrigue in coronaviruses globally (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>). As of December 2022, the widespread has resulted in hundreds of millions of infections, with tens

of millions passings around the world, which reduced by a matter of time but unfortunately still between us (Jaber 2023). Coronaviruses (CoVs) have a place to the family Coronaviridae, subfamily Coronavirinae and are expansive (genome measure 26–32 kb) wrapped, positive-sense single-stranded ribonucleic corrosive (RNA) viruses that can contaminate both creatures and people (Fig. 1). Based on their genotypic and serological characteristics, the infections are subdivided into four genera: Alpha-, Beta-,

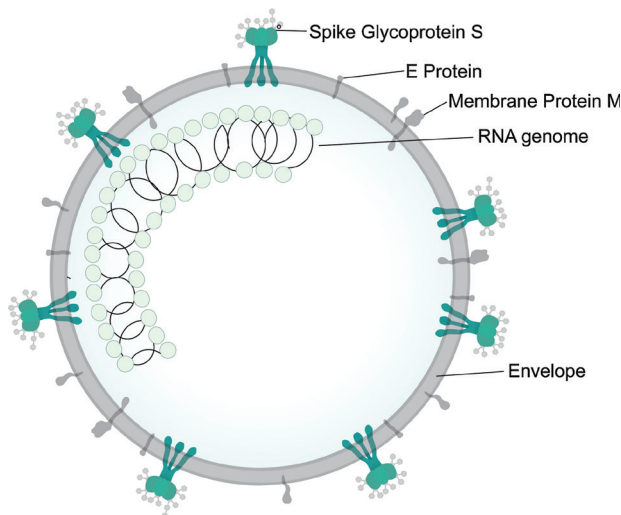


Figure 1. The common structure of a coronavirus (replicated from Wikipedia beneath CC permit 4.0). E protein = envelope protein.

Gamma-, and Delta-coronavirus (Lu et al. 2015; Chu et al. 2020; Wu et al. 2020a). At display, all distinguished CoVs that are capable of tainting people have a place to the primary two genera. These include the alpha-coronaviruses (α CoVs) HCoV-NL63 (Human CoV-NL63) and HCoV-229E and the beta-coronaviruses (β CoVs) HCoV-OC43 (Human CoV-OC43), HKU1 (Human CoV), SARS-CoV (Serious Acute Respiratory Disorder CoV), and MERS-CoV (Center Eastern Respiratory Syndrome CoV) (Lu et al. 2015). Within the past two decades there have been three scourges caused by the betaCoVs, specifically SARS in 2002–03, MERS in 2012 and COVID-19, to begin with recognized in 2019 (Yang et al. 2020b). SARS-CoV developed in 2002–03 in Southern China, causing a global danger and tainting more than 8000 individuals, with approximately 800 fatalities recorded, to a great extent in China and the encompassing regions (Pawlotsky 2014; Lu et al. 2015). MERS-CoV developed in the Middle East, spreading to a few nations to contaminate near to 2300 individuals, resulting in 845 passings as of July 2019 (WHO 2020). The new CoV widespread coming about from SARS-CoV-2, which causes COVID-19 (Chauhan 2020).

The main druggable targets of SARS-CoV-2 incorporate 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), RNA-dependent RNA polymerase, and spike (S) proteins (Wu et al. 2020b). The S proteins interact directly with a human angiotensin-converting enzyme (ACE) 2, allowing the virus to enter the cells. At present, no preventive vaccines or established antiviral therapies are available for coronaviruses (Sohrabi et al. 2020). In any case, a few manufactured compounds have appeared guarantee, counting hydroxychloroquine and chloroquine phosphate which act through a few components, counting alkalisation of the host cell phagolysosomes (Cortegiani et al. 2020). More current antiviral drugs such as lopinavir, remdesivir, and arbidol oo appear to guarantee (Khamitov et al. 2008). Other suggested treatment alternatives incorporate lopinavir/ritonavir, nucleoside analogues, neur-

aminidase inhibitors, and peptide EK1 (Yang et al. 2020a). A nitty gritty list of current and arranged clinical trials examining different drugs for the treatment of SARS-CoV-2 was given by Throb et al. (2020), with updated comes about accessible from ClinicalTrials.gov (2020) (Pang et al. 2020). In addition, traditional herbal remedies and isolated natural compounds can lead to the development of new and novel antiviral agents. Thus, usually its more efficient to design drugs based on already discovered natural compounds with known and relatively close biological and mechanistic activity. Indeed, most of the approved drugs approved between 1981–2014 are derived or designed based on the natural product (Newman and Cragg 2016; Jaber 2021). Besides, within the current outbreak of COVID-19, numerous patients show up to be turning to complementary or conventional restorative treatments, yet utilizing them almost only in conjunction with western pharmaceutical. For example, one think about recommended that nearly 92 % of 135 hospitalized patients in northeast Chonqing (China) gotten conventional Chinese pharmaceuticals in addition to western pharmaceuticals (Wan et al. 2020; Jaber and Saadh 2023). However, most researchers have stated in their conducted research about the hardness of isolating compounds in addition to the possible drug-drug interaction with synthetic drugs (Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (Zhang et al. 2020; Saadh and Jaber 2022). 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.

Thymoquinone inhibits the CoV-2

Nigella sativa can produce a wide range of bioactive compounds like thymoquinone and nigellimine that can be used in COVID-19 treatment by preventing the virus from contacting the possible host cells by changing the ionophores to improve zinc levels that enhance cells immunity (Ali et al. 2022). The main active ingredients reported in the literature have numerous biological activities such as immune regulatory, anti-inflammatory, anti-oxidant, anti-microbial, anti-tumour, analgesic, and hepatoprotective (Banerjee et al. 2009; Chaieb et al. 2011; Khader and Eckl 2014; Ahmad et al. 2019). Thymoquinone has been found to inhibit 5-lipoxygenase, leukotriene B₄, C₄, and Th₂ cytokines in the lungs that improve immunity by increasing the number of immune cells number in lung tissue (El Gazzar et al. 2006; Rana et al. 2021b). The anti-inflammatory activity of the mentioned compound is regulated by hem oxygenase 1 and human keratinocyte cells (Khader and Eckl 2014). Moreover, the molecular docking-based studies illustrated before have found nigellidine and α -hederin to be able to incorporate with SARS-CoV-2 (Xu et al. 2021). *N. sativa* extracts clearly provide better activity as it has mechanisms of action due to the presence of many bioactive compounds.

Quercetin-mediated inhibition

Quercetin (3,3',4',5,7-pentahydroxyflavone), is a flavonoid compound found in many plants consumed by humans such as apples, berries, grapes, onions, and tea, especially the green one (Ali et al. 2022). Quercetin is a poly-phenolic compound with a wide variety of biological activities including anti-oxidant, anti-inflammatory, anti-cancers, anti-viral, anti-bacterial, and immunity enhancer in addition to be used as a positive control in many biological testing for its activities (Henson et al. 2007; Nieman et al. 2007; Heinz et al. 2010; Yousuf et al. 2020). Previous studies illustrated in *vivo* and in *vitro* experiments have shown an immune-modulating activity that leads to an increase in the chemotaxis motion of neutrophils, phagocytosis, and the proliferation of immune cells that enhance the immune system (Henson et al. 2008). In addition, health workers and doctors used to recommend quercetin to improve the immune system of common people and sports professionals to reduce the risk of infections, especially with severe physical activities (Henson et al. 2007; Aucoin et al. 2020). Regarding anti-viral activity, quercetin has been reported to exert a potential and promising anti-viral activity by inhibiting viral proteases, reverse transcriptase, polymerase and binding viral capsid portions in addition to suppressing DNA gyrase (Shinozuka et al. 1988; Spedding et al. 1989; Refaat et al. 2021; Singh et al. 2021a). Regarding quercetin and SARS-CoV-2, it was found that quercetin is inhibiting the propylitic activity of 3CL protease with IC₅₀ of 4.95 μM (Colunga Biancatelli et al. 2020).

Caffeic acid effect on virus attachments

Caffeic acid is another polyphenolic compound isolated from natural source and listed as a part of phenolic acid family. Its one of the main hydroxycinnamic acid with a molecular weight of 180.16g/mol (Son and Lewis 2002; Paracatu et al. 2014). Caffeic acid can be present in a high concentration inside many medicinal plants or fruits like blueberries, kiwis, coffee, cherries, apples, oils, and tea (El-Seedi et al. 2012; Sova and Saso 2020). Caffeic acid and its derivatives have high protectives and curing abilities due to different biological activity such as, antioxidant, anti-inflammatory, anti-bacterial and anti-viral activities (Silva and Lopes 2020; Ali et al. 2021; Rana et al. 2021a). previously caffeic acid has been reported to exert a potential biological activity against different viruses such as, influenza, herpes simplex, and severe fever with thrombocytopenia syndrome viruses (Utsunomiya et al. 2014; Ogawa et al. 2018). In addition to its activity, caffeic acid and its derivatives have been used by different research companies to find a treatment for HIV, human sarcoma, polio and influenza viruses (Ali et al. 2022). Caffeic acid and its derivatives have been screened to find a novel therapeutic activity of it against SARS-CoV-2 (Ali et al. 2022). Thus, many targets have been found such as spike ectodomain (open), spike glycoprotein (closed), Nsp15 endoribonuclease, Mpro (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, khainoside C as M^{pro} modulator, khainoside B as SARS-CoV-2 fusion protein, 6-O-Caffeoylarbutin as Nsp15, khainoside C as spike (open), and vitexfolin A as spike (closed) modulator (Adem et al. 2021).

Ursolic acid inhibitory activity for M^{pro} enzyme

Ursolic acid is a pentacyclic triterpenoid compound isolated from ethanolic extracts of natural source (Kashyap et al. 2016; Hussain et al. 2017; Pironi et al. 2018; López-Hortas et al. 2018). Ursolic acid mainly isolated from *Mimusop-scaffra*, *Ilex paraguayarieni*, and *Glechoma hederacea* and was reported to exert anti-inflammatory, anti-bacterial, anti-oxidant, anti-diabetic, and anti-cancer biological activity (Pironi et al. 2018; Mlala et al. 2019; Alam et al. 2021a; Alam et al. 2021b; Singh et al. 2021b). During Covid-19, ursolic acid was tested against SARS-CoV-2 M^{pro} enzyme and was successfully active by inhibition of the mentioned enzyme (Ali et al. 2022). In addition, a molecular docking and molecular dynamic simulation study has confirmed the ability of ursolic acid and its derivatives to protease during 50 ns of MD simulation (Kumar et al. 2021). Ursolic acid show high binding affinity by forming a hydrogen bond with amino group of the Asp 108 found in PL^{pro} protease enzyme and with hydrophobic interaction on Ala 107, Pro 248, and Tyr 264 of the same enzyme (Mitra et al. 2021).

Ellagic acid effect on M^{pro} and RdRp enzymes

Ellagic acid a small polyphenolic molecule with a molecular weight of 302.197 g/mol that can be found in many types of fruits and vegetables (Malini et al. 2011; Saeed et al. 2018; Evtuyugin et al. 2020). In addition to the ellagic acid, a hydrolysable derivative ellagitannins found in many fruits such as raspberries, strawberries, pomegranate, grapes, green tea, and almond have found to be biologically active as anti-oxidant, and anti-proliferative with high health potential (García-Niño and Zazueta 2015; Derosa et al. 2016). Moreover, ellagic acid was found to obstruct tumour cells migration, and angiogenesis with potential activity to inhibit oxidative stress, and inflammation in diabetic rats (Sanati et al. 2022, Xiao et al. 2022, Núñez et al. 2023). In many studies mentioned before, the small polyphenolic molecules have a potential inhibitory activity against the main protease for SARS-CoV-2 M^{pro} enzyme with a high potential for being a treatment option for infectious diseases (Saadh and Jaber 2022, Souid et al. 2022, Ghamry et al. 2023, Jaber and Saadh 2023a). In other studies, ellagic acid was found to show a high binding with M^{pro} enzyme at the catalytic site with Cys145 (Adelusi et al. 2022). Another study performed on 14 phenolic compounds and terpenes including quercetin and ellagic acid show the ability of the

mentioned compounds to interact with RNA-dependant RNA-polymerase (RdRp) enzyme of SARS-CoV-2 on molecular docking software (Ali et al. 2022).

Vanillin inhibitory activity to M^{pro} enzyme

Vanillin is a naturally occurring compound used in different industrial sectors like food, perfumes, and pharmaceuticals industries (Ali et al. 2022). Vanillin is a small phenolic molecule that extracted from the vanilla bean and used as an intermediate molecule for other essential molecules. Its well known that vanillin has a very important biological activities due to its chemical structure such as, anti-microbial, anti-oxidant, and anti-clastogenic activity (Naz et al. 2018; Yousuf et al. 2021). The potential anti-microbial activity and anti-oxidant activity of vanillin with its small molecular structure have pushed the medicinal chemist to apply molecular docking to it for evaluation (Tai et al. 2011; Yadav et al. 2018; Yadav 2021). It was reported that vanillin and some related molecules are good starting point for the discovery of a new compound against SARA-CoV-2 virus (Law et al. 2020).

Thymol inhibitory effect on spike protein

Thymol is another small phenolic monoterpene molecule that isolated from the medicinal plant *Thymus vulgaris* and also can be found in another plants with a lower concentration. Its will known that thymol is used excessively by people due to its multi-functional role for human health as anti-viral, anti-bacterial, anti-fungal, anti-oxidant, anti-septic, anti-cancer and more. The development of nano-capsule has expanded the using of thymol in health care

and enhance its biological activity (Marchese et al. 2016; Kowalczyk et al. 2020; Turab Naqvi et al. 2020). During Covid-19 crise, thymol was one of the compound enrolled in a molecular docking study performed by Kulkarni et al and found to exert a potential binding with S1 of spike glycoprotein (Kulkarni et al. 2020). In addition, another *in silico* study was performed using 18 compounds including thymol and reported its activity against transmembrane protease serine 2 (TMPRSS2) that resulted in the cleavage of SARS-CoV-2 Spike protein (Yadav et al. 2022).

Conclusion and future prospect

In the present unfavourable of the new spreading of SARS-CoV-2 in middle and low income countries, there is an urgent need to used natural products as a therapeutic alternative to vaccines to prevent viral infections and to enhance human immunity. Due to the time-consuming process for the search of a new natural compounds with anti-Covid-19 activity its important to start with a well known compounds with their biological activity such as compounds presented in Table 1.

In this review the important phytochemical compounds with a potential anti-viral activity have been mentioned and a prove of anti-Covid-19 has been reported to put a focus on the medicinal plants that produce a high concentration of the mentioned compounds. Obviously, small polyphenolic and terpenoid compounds have a different role in anti-viral activity through, protease inhibition like M^{pro}, effect on spike proteins, virus attachment, and virus replication. Needless to say, these notable in vitro and in vivo studies Required to determine the safety and therapeutic utility of each compound. Concentrations prior to human clinical trials to be conducted. To Developing an effective COVID-19 treatment and using it in first study

Table 1. List of already known natural compounds proved to exert activity against SARS-CoV-2.

Compound	Biological activity	Activity against Covid-19	Natural source	Reference
Thymoquinone	Anti-oxidant immune-regulatory, anti-inflammatory, and anti-oxidant.	Prevent the SARS-CoV-2 entry; inhibits viral replication	Nigella sativa	(Elfiky 2021)
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	(Grochowicz et al. 1988)
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	(Ogawa et al. 2018)
Ursolic Acid	Anti-inflammatory, anti-bacterial effects, anti-oxidant, anti-cancer, and anti-diabetic	Potently block the M ^{pro} enzyme	<i>Mimusopscaffra</i> , <i>Ilex paraguarieni</i> , and <i>Glechoma hederacea</i>	(Son et al. 2020)
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 <i>Momordica charantia</i>	(Ríos et al. 2018)
Vanillin	Anti-clastogenic, anti-microbial agent, anti-oxidant	M ^{Pro} inhibition	Vanilla bean	(Yadav et al. 2018)
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.	<i>Thymus vulgaris</i> , <i>Ocimum</i> , <i>Origanum</i> , and <i>Monarda genera</i>	(Kowalczyk et al. 2020)

ecules already approved by the FDA or considered safe for drugs use the same as for the polyphenol component. It is expected that the botanical ingredients described in this report support the development of natural, effective and safe anti-SARS-CoV-2 treatment options got a connection.

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