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# The Role of Olive Tree Polyphenols in the Prevention of COVID-19: A Scoping Review, part 1

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**Abstract**

The global COVID-19 outbreak, started in December 2019, resulted in severe financial losses and extraordinary health crises. Finding a potent and secure medication candidate to treat SARS-CoV-2 infection and its symptoms is still an urgent global need. After reviewing previous studies, olive leaves, being rich in polyphenolic compounds (a large class of bioactive substances naturally found in plants), were proposed as a viable co-therapy supplement to treat and improve clinical symptoms in COVID-19 patients. It has long been known that olive tree polyphenols—such as oleuropein, hydroxytyrosol, verbascoside, as well as triterpenoids like maslinic, ursolic, and oleanolic acids—have anti-inflammatory and multitarget antiviral effects on several virus families, and they could be one of the reasons of the beneficial effects of the Mediterranean diet against COVID-19. Thus, olive tree polyphenols were tested in silico and in vitro for preventing SARS-CoV-2 infection, claiming that they have beneficial effects. Nevertheless, there is still a small number of research studies on this topic. The aim of this scoping review is to provide more information and offer an opinion on the feasibility of using olive tree polyphenols as a springboard for the creation of innovative natural remedies against this viral illness, ultimately planning future relevant studies. ***Clin Ter 2023; 174 Suppl. 2 (6):142-148 doi: 10.7417/CT.2023.2480***

**Key words:** *SARS-CoV2, COVID-19 pandemic, polyphenols, antiviral, olive tree*

## Introduction

The COVID-19 pandemic started in December 2019, and it caused both economical and sanitary crisis worldwide. As of August 2022, the World Health Organization estimates that there have been almost 600 million COVID-19 cases and more than 6 million fatalities globally (1). The development of therapeutic leads that combat COVID-19 infection using various methods—including in silico, in vitro, in vivo, and clinical trials—is now a global trend. However, FDA has only recently authorized just a few medicines for treating and preventing COVID-19 (2). As a result, it is imperative to create antiviral drugs that can manage the infection.

SARS-CoV-2 infect the respiratory tract, causing also a systemic infection, which displays a significant immune response, leading to multiorgan dysfunction. This is in contrast to different coronaviruses, which cause only respiratory illnesses (3). Indeed, the primary symptoms of COVID-19 disease are fever, headache, pneumonia, and loss of smell and taste (4,5). Symptoms differ from patient to patient, based on viral load and virus strain (5).

Hyper-inflammation, brought on by the related cytokine storm, particularly IL-6, leads to acute respiratory distress syndrome, the main cause of mortality in COVID-19 patients (6,7). Furthermore, COVID-19 causes disseminated intravascular coagulation, a hazardous side effect; indeed, numerous studies revealed a connection between COVID-19 and an increase in thrombotic events (8,9). At the moment, COVID-19 patients are being treated with a variety of medications, including anti-SARS-CoV-2 monoclonal antibodies, antivirals, immunomodulators, and antithrombotic drugs. These drugs are able to manage the symptoms of COVID-19, but no treatment is able to effectively cure the disease (7,8).

Plant-based natural products have been proposed for treatment of SARS-CoV-2 infection. Indeed, natural products have historically been proposed for treatment of respiratory diseases, and a variety of natural molecules derived from

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plants are now studied for their antiviral properties (10). One of the most common natural products used in the nutraceutical industry for treating many diseases are olives (*Olea europaea L.*, family Oleaceae). The olive tree originated in Asia, but it is now cultivated across the Mediterranean region, in Iran, and in Northern Africa. In the nations where COVID-19 infection is endemic, olive trees are common and are utilized medically as antiviral drugs (11), so olive leaves and their extract could be used as a phytotherapy for COVID-19 treatment (12). Indeed, they contain polyphenolic components such as oleuropein, hydroxytyrosol (HT), verbascoside, apigenin-7-O-glucoside, which have several biological activities, including antioxidant, antihypertensive, anti-hypercholesterol activity (11–16).

Polyphenols are one of the biggest and most investigated family of bioactive substances found in many plants. They are formed as secondary metabolites and have anti-cancer radiation, anti-pathogen, and anti-oxidative stress properties (17). According to their structural definition, polyphenols are compounds that have one or more phenolic rings with hydroxyl groups. Polyphenols can be divided into flavonoids (which include stilbenes or lignans), phenolic acids, polyphenolic amides, and other (such as anthocyanins, flavones, flavonols, flavonones, flavonols, and flavan-3-ols) (18). Evidence has demonstrated polyphenols have several beneficial properties, among which anti-inflammatory, antioxidant and antiviral effects (19–24). Numerous studies have specifically shown that polyphenols are effective against a variety of pathogens, such as the herpes simplex virus (19,20), influenza virus (21), and other viruses causing infections of the respiratory tract (22,23). In this context, resveratrol was extensively studied because of it can (i) disregulate viral replication by reducing the expression of immediate-early virus proteins; (ii) inhibit the NFkB signaling cascade; and (iii) activate the AMPK/Sirt1 pathway (20). Moreover, elenolic acid, a metabolite of olive polyphenols, acts as an antiviral in the form of calcium enolate, inhibiting reverse transcriptases (25,26).

Polyphenols were proposed for the treatment of COVID-19 mainly because of their antiviral and immunomodulatory activities (12,27). The goal of this scoping review is to highlight some encouraging data about olive tree polyphenols' possible anti-COVID19 action, which might spur research into the creation of new approaches to fight the SARS-CoV-2 pandemic.

## Materials and Methods

### *Literature Scoping Review and Inclusion Criteria*

The scoping review section followed PRISMA guidelines for scoping reviews (28). Our search included original and review articles focusing on SARS-CoV-2 and the effects of olive polyphenols, HT, oleuropein, oleochantal, oleanolic acid, and olive leaf.

The articles employed had to be written in English and published in the period 2019-2022. Congress abstracts, manuscripts not written in English and studies not relevant to the topic of the present manuscript were excluded. Articles previously published by the MAGI laboratories or by any of the authors of this paper were not considered for this scoping review.

### *Literature Search*

PubMed database was searched to retrieve articles published from 2019 to 2022 that satisfied the inclusion criteria. The search keywords were: (olive polyphenols OR hydroxytyrosol OR oleuropein OR oleochantal OR oleanolic acid OR olive leaf) AND (SARS-CoV-2 OR COVID-19 OR long COVID OR post COVID). In addition, the reference lists of the papers found were scanned manually to find further relevant papers.

### *Study Selection*

All the resulting articles were assessed independently for eligibility by authors who evaluated titles and abstracts according to the above inclusion criteria. Once a paper was found eligible, its references were screened to find new papers.

## Results

47 papers published from 2019 to 2022 were found, based on the literature review search criteria. Only 44 pertained to the topic of the current review and were read completely. Another 10 papers were included after reading the references of the articles. Finally, 28 studies, considered to be the most relevant, were discussed in the manuscript.

The following sections will highlight the main findings of the included articles. Indeed, several studies have been published on the antiviral, anti-inflammatory, immunomodulatory, and antithrombotic effects of olive leaf extract, both in its entirety and considering only its components. Moreover, possible advantages of additional in vivo studies or clinical trials studying the effects of olive leaf-based natural supplements will be discussed.

### *In Silico Antiviral Studies*

Several in silico investigations suggest the efficacy of olive leaf metabolites against SARS-CoV-2. Many viral proteases, the spike protein, and the ACE-2 receptor were studied for their binding affinity against olive leaf polyphenols, among which: oleuropein, HT, oleanolic acid, maslinic acid, ursolic acid, rutin, luteolin, luteolin-7-O-glucoside, quercetin, kaempferol, verbascoside, caffeic acid, gallic acid, ellagic acid, epicatechin (29–35). Many of these studies revealed high binding affinity of polyphenols to viral proteins.

The study by Thangavel et al. (36) found potential secoiridoids that can block SARS-CoV-2 entrance, replication, and related hyperinflammatory reactions thanks to molecular docking and molecular dynamics-assisted virtual search of OliveNetTM directory. OliveNetTM is an ongoing database of phytochemicals derived from various olive tree components (Oleaceae). The Mediterranean and Arabian diets are inextricably linked to olive oil and to the phenolic-rich olive fruits that are recognized for their health advantages. The

study also evaluated 78 secoiridoids, showing that two main secoiroids, Nüzhenide oleoside and Demethyloleuropein have an inhibitory effect on the spike protein and SARS-CoV-2 main protease $M^{pro}$. Moreover, Nüzhenide oleoside and other secoiroids identified by molecular docking showed an anti-inflammatory potential, because of an inhibitory effect to IL1R, IL6R, and TNFR1 (36).

Another study by Alhadrami et al. (37) investigated the inhibitory potential of betulinic acid and its anti-SARS-CoV-2 effect acting on its main protease. Betulinic acid and three other triterpene congeners present in olive leaves (ursolic acid, maslinic acid, and betulin), inhibit $M^{pro}$ (37).

A study by Vijayan et al. (38) examined the role of thymopentin and oleuropein, phenolic compounds found in olive tree leaves, as potent inhibitors for SARS-CoV-2. They screened a natural product database for compounds against the viral protein NSP15, and found that thymopentin and oleuropein from olive tree bind to NSP15 forming a stable complex with high binding energy (38).

Gosh et al. (39) screened natural compounds from olives as possible inhibitors of protein tyrosine kinase (PTK). PTK has a role in both cancer progression and coronavirus infection. Indeed, overexpression of PTK enhances viral infectivity, and the use of tyrosine kinase inhibitors reduces the infection length. They virtually screened 161 natural compounds from olives and employed multilinear regression QSAR-based model and docking. The QSAR-based virtual screening successfully identified several possible inhibitors, and the best-docked ones were further investigated, revealing the high potential of many natural molecules derived from olives in PTK inhibition.

### *In Vitro Antiviral Studies*

A small number of in vitro research examined the direct effects of polyphenols from olive tree extract on coronaviruses, in addition to the general mechanisms of action outlined against different viruses. HT found in olive leaves is demonstrated to have antiviral activity against SARS-CoV-2. Indeed, HT targets the spike proteins the viral genome (40). In a different investigation, luteolin had similar results, reducing SARS-CoV-2 infection in vitro (41,42). Furthermore, kaempferol prevented SARS-CoV-2 multiplication in culture with high percentage of inhibition (43).

A study by Takeda et al. (40) examined the SARS-CoV-2-inactivating activity of HT-rich aqueous olive pulp extract (HIDROX®) in vitro. They have demonstrated that the HIDROX® solution has anti-SARS-CoV-2 effects that are time- and concentration-dependent, and higher than pure HT. Moreover, they analyzed the mechanism of action of HIDROX® and HT, demonstrating that both structurally change SARS-CoV-2, altering the spike protein. As a result, the cream containing HIDROX® can be used topically as a hand lotion to combat viruses, helping to make SARS-CoV-2 prevention strategies more effective.

### *Clinical Antiviral Studies*

Bezmialem Vakif University conducted a clinical study (44) investigating the possible effects of effects of drinking Olive Leaf Tea (OLT) in influencing the immune response and COVID-19. The study enrolled 249 workers, 168 of which were OLT drinkers. The results showed higher values of NK cells, NKT cells, total NK cells, and serum IFN-γand IL-2 levels in OLT drinkers as compared to the non-drinkers. Thus, they proved that OLT drinkers have an altered immune defense mechanisms. Moreover, specific COVID-19 IgG levels were found in 60% of OLT drinkers and in 38% of OLT non-drinkers, although both groups reported no history of COVID-19. The authors concluded that drinking OLT could help in fighting COVID-19 by increasing the innate immune response (44).

Another clinical trial study at Fayoum University Hospital in Egypt (45) will enroll RT-PCR confirmed-COVID-19 adult patients showing mild to moderate disease, excluding patients with multi-organ failure, ventilator support, and chronic diseases. Patients will receive, along with standard care, capsules containing oleuropein from olive leaves or placebo up to 10 days. The controlled outcomes include symptom alleviation, virus clearance, improvement of blood biomarkers and reduction of mortality (45).

The Spanish Hospital of Jean will begin a clinical trial to test a dietary supplement made of olive polyphenols and flavonoids for preventing the progression of COVID-19. They will recruit COVID-19 positive patients over 60 years old, and they will evaluate how many patients will progress from mild to severe symptoms. They will measure several parameters, among which cytokines, ferritin, D-Dimer, antioxidant markers, and thrombogenicity (46).

### *Role of the Mediterranean Diet in COVID Prevention*

Obesity, type 2 diabetes, and hypertension are all common COVID-19 risk factors. They are all related to nutrition, thus implying that healthy diets may reduce COVID-19-related outcomes and SARS-CoV-2 infection.

Green at al. (47) studied the association between Mediterranean diet adherence and COVID-19, based on the influence of nutrition on immune function. Moreover, the Mediterranean diet reduces the risk to develop several chronic diseases that are comorbidities in COVID-19 patients. In this regard, they also investigated the relationship between regional adherence to a Mediterranean diet and COVID-19 cases and fatalities. They found that, in 17 areas of Spain, adherence to the Mediterranean diet was negatively linked with both COVID-19, and that the association persisted after adjusting for well-being characteristics. They also saw a negative correlation between COVID-19-related fatalities and adherence to the Mediterranean diet across 23 nations. The Mediterranean diet's anti-inflammatory effects, which are probably caused by the diet's high content of polyphenols from olive oil, could be the biological explanation for their findings.

Ferro et al. (48) showed how to assess the potential benefits of a Mediterranean diet in reducing the risk of coronavirus illness. Moreover, they also evaluated the possible anti-COVID-19 action of many vitamins, minerals, fatty acids, and phytochemicals found in olive tree leaves extracts. They examined how the Mediterranean diet is beneficial for the immune system and inflammation, showing that it may protect against SARS-CoV-2.

Perez-Araluce et al. (49) presented the first epidemiological research that has linked a dietary pattern to COVID-

19. Their findings suggest that greater adherence to the Mediterranean diet may be linked to a reduced chance of developing COVID-19 in the future. They discovered that people following the Mediterranean diet have a risk reduction of more than 60%. Despite the promising results, one of the major limitations of this study is the lack of data on the exposure to the virus that each individual may have had, also depending on how strictly they adhered to other non-pharmacological preventative measures.

Finally, Kim et al. (50) examined the effects of plant-based and pescatarian diets on COVID-19 severity. They recruited people from six countries and had them complete a survey on dietary information and COVID-19 outcomes. The results showed that vegetarian or pescatarian diets were linked to a decreased risk of moderate-to-severe COVID-19 in six different nations. These eating habits could be taken into account as potential COVID-19 protection.

### *Reviews on Polyphenols for COVID19 Treatment*

Santos et al. (51)'s research examined the anti-inflammatory effect of a polyphenols-based diet in COVID-19 elderly and obese patients. Moreover, they examined the pathophysiology, clinical consequences, and disease indicators linked to senescence in COVID-19 patients. They showed that it is necessary to reach a better understanding of SARS-CoV-2 infection to treat or prevent severe COVID-19. Furthermore, they suggested that high levels of polyphenols could have a protective impact on COVID-19-related outcomes.

In a review by Giovinazzo et al. (52), the authors investigated the existing literature on the potential efficacy of polyphenols in the battle against SARS-CoV-2 infection. Even though this year has seen significant advancements in anti-inflammatory medicines, no effective cytokine blockers for COVID are presently being used in clinical settings. Accordingly, they showed that bioactive phytochemicals like polyphenols may prove to be effective adjuvants for reducing SARS-CoV-2 infection. Such nutrients, which share anti-inflammatory and antioxidant qualities with traditional anti-inflammatory medications, may aid in lowering inflammation in COVID-19 patients.

Majumder et al. (53) focused on the Mediterranean diet and on olive oil intake. Olive oil has anti-inflammatory and cardioprotective properties because it contains a variety of bioactive polyphenolic components, including oleanolic acid, oleuropein, oleocanthal, and HT. They also investigated the ongoing in silico research on the action of olive oil phytochemicals in inhibiting SARS-CoV-2 virus.

A review by da Silva et al. (54) aimed to summarize the most recent data from well-known potent flavonoid and non-flavonoid polyphenols derived from plant extracts—including catechin, quercetin, and kaempferol—that inhibit coronavirus strains in vitro or in silico. This research showed that the creation of novel coronavirus therapies, treatments/medicines, or formulations may benefit from the study of molecules outside of the established treatments.

A study by Paraiso et al. (55) reviewed the impact of polyphenols on COVID-19 therapeutic targets and offered insights into the potential use of polyphenols in the creation of all-natural treatments for this viral illness.

A mini-review by Abdelgawad et al. (12) showed that many in silico and in vitro studies have identified polyphenolic compounds found in olive tree leaves extract, such as oleuropein and HT, as anti-SARS-CoV-2 molecules. Additionally, they highlighted the anti-inflammatory, analgesic, immunomodulatory, and antithrombotic properties of olive leaf extract in a number of in vivo studies. These properties could be extremely helpful in the management of the COVID-19-associated inflammatory cytokine storm and disseminated intravascular coagulation.

Finally, a recent study by Annunziata et al. (56) studied the possibility that polyphenols may have additional anti-coronaviruses action to that already seen in vitro. They also shed some light on studies that have been published in the literature, which supported the idea that the primary general mechanisms of action behind the positive impact of polyphenols against coronaviruses are the decrease in viral titer and the suppression of nucleocapsid protein expression. Table 1 summarizes the main findings of the most relevant presented studies.

## Conclusion

Olive tree polyphenols are bioactive molecules known for their antiviral activity against SARS-CoV-2 in silico, in vitro, and in vivo. These bioactive substances alter many signaling pathways and display a wide range of actions—including anti-inflammatory, antipyretic, immunomodulatory, and antithrombotic capabilities—in addition to their antiviral effects. Olive tree polyphenols offer a potentially safe natural source to treat the signs and symptoms of COVID-19 infection, including cytokine storms, and guard against negative outcomes. In this scoping review, we showed how polyphenols found in olive tree may help against COVID19 spread. Moreover, we shed some light on how the Mediterranean diet, which is notoriously rich in olives and olive oil, can help in the prevention of coronavirus infection. Finally, we presented how the work done in bioinformatics may reveal the mechanism of action of natural molecules, among which olive tree polyphenols.

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### *Conflicts of interest statement*

Authors declare no conflict of interest.

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*Table 1. Review articles, in silico, in vitro, in vivo studies and clinical trials studying the effects and the mechanism of action of polyphenols from olive leaves for COVID-19 treatment.*

| Article Type | Reference | Aim of the Study |
|---|---|---|
| Review articles | (56) | They reviewed the antiviral action against coronaviruses of polyphenols from different sources, focusing on SARS-COV-2. |
| | (12) | They reviewed the beneficial activities demonstrated in in vivo studies of polyphenolic compounds found in olive tree leaves. These properties could be helpful in the management of COVID-19-associated cytokine storm and disseminated intravascular coagulation. |
| | (55) | They evaluated the impact of polyphenols on COVID-19 therapeutic targets and offered insights into the potential use of polyphenols in the creation of all-natural treatments. |
| | (54) | They reported the most recent data from well-known potent flavonoid and non-flavonoid polyphenols derived from plant extracts that inhibit coronavirus strains in vitro. |
| | (53) | They investigated the Mediterranean diet, the intake of olive oil, and the ongoing in silico research on olive oil's phytochemicals, which may be able to inhibit SARS-CoV-2 virus. |
| | (52) | They reviewed the existing literature on the potential efficacy of polyphenols against SARS-COV-2 infection. |
| In silico experimental articles | (36) | They found that secoiridoids may inhibit SARS-CoV-2. |
| | (37) | They looked for the inhibitory potential of betulinic acid and its activity against the main protease of SARS-CoV-2. |
| | (38) | They examined the role of thymopentin and oleuropein, which are phenolic compounds found in olive tree leaves, as potent inhibitors of SARS-CoV-2. |
| | (39) | They screened a library of 161 natural molecules from olive as inhibitors of tyrosine kinase, which is overexpressed in virus host cells. |
| In vitro experimental articles | (40) | They tested olive leaf hydroxytyrosol for its virucidal activity against SARS-CoV-2. |
| | (41–43) | They studied the effect of luteolin and kaempferol in preventing SARS-CoV-2 multiplication. |
| | (40) | They examined the anti-SARS-CoV-2 potential of hydroxytyrosol HT-rich aqueous olive pulp extract in vitro. |
| Epidemiological studies | (51) | They examined the anti-inflammatory effect of a polyphenol-based diet in COVID-19 elderly and obese patients. They also examined the pathophysiology, clinical consequences, and disease indicators linked to senescence in COVID-19 patients. |
| | (47) | They investigated the relationship between following the Mediterranean diet and COVID-19 cases and fatalities in a group of people from 17 areas of Spain. |
| | (49) | They presented the first epidemiological research that has linked a dietary pattern to COVID-19 severity in various subgroups patients. |
| Clinical trials | (50) | They examined the effects of plant-based and pescatarian diets against COVID-19 severity surveying small populations from six countries. |
| | (44) | They investigated the immunomodulatory and preventive effects of olive leaf tea against COVID-19 infection among 249 workers. |
| | (45) | They will conduct a clinical trial in which confirmed COVID-19 adult patients will be enrolled. Patients will be randomly assigned to receive, along with standard care, standardized olive leaves capsules or placebo, up to 10 days. |
| | (46) | They will investigate the effect of a dietary supplement containing olive polyphenols and flavonoids in preventing the progression of COVID-19. |

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