Olive Leaves as a Potential Phytotherapy in the Treatment of COVID-19 Disease; A Mini-Review

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Beginning from December 2019, widespread COVID-19 has caused huge financial misfortunes and exceptional wellbeing emergencies across the globe. Discovering an effective and safe drug candidate for the treatment of COVID-19 and its associated symptoms became an urgent global demand, especially due to restricted information that has been discharged with respect to vaccine efficacy and safety in humans. Reviewing the recent research, olive leaves were selected as a potential co-therapy supplement for the treatment and improvement of clinical manifestations in COVID-19 patients. Olive leaves were reported to be rich in phenolic compounds such as oleuropein, hydroxytyrosol, verbascoside, apigenin-7-O-glucoside, and luteolin-7-O-glucoside and also triterpenoids such as maslinic, ursolic, and oleanolic acids that have been reported as anti-SARS-CoV-2 metabolites in recent computational and in vitro studies. In addition, olive leaf extract was previously reported in several in vivo studies for its anti-inflammatory, analgesic, antipyretic, immunomodulatory, and antithrombotic activities which are of great benefit in the control of associated inflammatory cytokine storm and disseminated intravascular coagulation in COVID-19 patients. In conclusion, the described biological activities of olive leaves alongside their biosafety, availability, and low price make them a potential candidate drug or supplement to control COVID-19 infection and are recommended for clinical investigation.

Keywords: olive leaves, phytoconstituents, antiviral, SARS-CoV-2, anti-inflammatory, anti-thrombotic

Abbreviations: SAA, serum amyloid A; HCAEC, human coronary artery endothelial cells; MMP2, matrix metalloproteinases; COPD, chronic obstructive pulmonary disease; OVA, ovalbumin; CS, cigarette smoke; ICAM-1, intercellular adhesion molecule 1; TNF-α, tumor necrosis factor alpha; MMP-9, matrix metalloproteinase 9; NO, nitric oxide; HXT, hydroxytyrosol; OA, oleanolic acid; UA, ursolic acid; MA, maslinic acid; COX, cyclooxygenase; IFN, interferon; Th2, T helper cell-2; ERK1/2, mitogen-activated protein kinases; PT, prothrombin time; PKC, protein kinase C; MARCKS, myristoylated alanine-rich C kinase substrate; FXa, coagulation factor Xa
1 INTRODUCTION

Since December 2019, the COVID-19 pandemic resulted in huge economic deterioration and exceptional uncontrolled health crisis throughout the globe. The total number of COVID-19 cases worldwide until now is about 416,614,051 cases and 5,844,097 deaths, as estimated by the WHO, on 17 February 2022 (https://covid19.who.int/). Although several vaccine candidates are now available, only few data have been released regarding the efficacy and safety of vaccines in humans, not to mention that the long-term adequacy of those vaccines still remain as an open address. Nowadays, there is a global trend toward the invention of drug leads that act against COVID-19 infection through different techniques such as in silico, in vitro, in vivo, and clinical studies of the drug candidates. However, until now, only one drug (Paxlovid®) has been approved recently, in December 2022, by the FDA for the treatment and prevention of COVID-19 infection (Parums, 2022); hence, there is a crucial requirement to develop antiviral agents capable of controlling the infection.

WHO reports revealed that COVID-19 disease is most spread in Europe (58%), Americas (23%), Southeast Asia (8%), Western Pacific (7%), Eastern Mediterranean (4%), and then Africa (1%) (© (2022). Weekly epidem, 2022). Additionally, according to the WHO, around 80% of the people in many third-world countries rely on conventional plant sources for their health issues (Ekor, 2014; Ganjhu et al., 2015). Natural products have been historically used for acute respiratory infections, and currently, different natural plant products are being investigated as antiviral agents. (Lin et al., 2014; Ganjhu et al., 2015).

The olive (Olea europaea L., family Oleaceae) is a small tree native to Asia, whose cultivation spreads to all the Mediterranean countries, Europe, Iran, and northern Africa (Cimato and Attilio, 2011; Hashmi et al., 2015; Öзcan and Matthäus, 2017). Olive trees are abundant and ethnomedically used in the countries where COVID-19 infection is widespread (Hashmi et al., 2015). Olive leaves were reported to exhibit several biological activities such as antioxidant (Benavente-Garcia et al., 2000; Soni et al., 2006), antihypertensive (Susalit et al., 2011), antihypercholesterolemic (Jemai et al., 2009), cardioprotective (Wang et al., 2008), anti-inflammatory (Khalatbary and Zarrinjoei, 2012), and anti-obesity (Santiago-Mora et al., 2011) activities.

Olive leaf extract was reported to be rich in phenolic compounds such as oleuropein, hydroxytyrosol, verbascoside, apigenin-7-O-glucoside, and luteolin-7-O-glucoside (Benavente-Garcia et al., 2000; Goldsmith et al., 2014).

2 PHYTOCHEMISTRY REVIEW

Several secondary metabolites with different chemical classification were reported and isolated from olive leaves, such as secoiridoids, flavonoids, triterpenoids, steroids, and lignans.

Oleuropein (1) has been reported from the methanolic and aqueous extracts of leaves of Olea europaea (Wichers et al., 2000; Goulas et al., 2009; Hashmi et al., 2015; Nassir et al., 2019). Oleuropein and other secoiridoids such as ligstroside (2) (Gariboldi et al., 1986; Hashmi et al., 2015), oleuricine A (3), oleuricine B (4) (Wang et al., 2009; Hashmi et al., 2015),
oleurosides (5) (Movsumov, 1994; Duquesnoy et al., 2007; Hashmi et al., 2015), secologanoside, 6′-E-p-coumaroyl-secologanoside (comselogoside) (6) (Duquesnoy et al., 2007; Hashmi et al., 2015), 6′-O-[2E]-2,6-dimethyl-8-hydroxy-2-octenoyloxy]-secologanoside (7) (Duquesnoy et al., 2007; Hashmi et al., 2015), oleoside (8) (Movsumov, 1994; Duquesnoy et al., 2007; Hashmi et al., 2015), secologanoside (9), elenolic acid methyl ester (10), hydroxytyrosol-elenolate (11) (Gariboldi et al., 1986; Hashmi et al., 2015), and 3,4-DHPEA-EDA (oleacein) (12) (Movsumov, 1994; Duquesnoy et al., 2007; Hashmi et al., 2015) were isolated from the extract of leaves of *Olea europaea*. The phenylethanoid precursors of oleuropein; hydroxytyrosol (13) and

**FIGURE 1** | Chemical structures of secoiridoids, triterpenoids, and steroids reported in *Olea europaea* leaves.

**FIGURE 2** | Chemical structures of flavonoids and phenolic compounds reported in *Olea europaea* leaves.
hydroxytyrosol acetate (14), were reported in high amount in olive leaves (Goulas et al., 2009) (Figure 1).

The ethyl acetate fraction of O. europaea leaves resulted in the isolation of different steroids and triterpenoids such as β-sitosterol (15) (Mussini et al., 1975; Hashmi et al., 2015), betulinic acid (16) (Bianchi et al., 1992; Hashmi et al., 2015), β-amyrin (17) (Mussini et al., 1975; Wang et al., 2009; Hashmi et al., 2015), erythrodiol (18) (Duquesnoy et al., 2007; Hashmi et al., 2015), uvaol (19) (Bianchi et al., 1992; Hashmi et al., 2015), ursoic acid (20) (Bianchi et al., 1992; Hashmi et al., 2015), maslinic acid (21) (Bianchi et al., 1992; Hashmi et al., 2015), oleoic acid (22) (Movsumov, 1994; Duquesnoy et al., 2007; Hashmi et al., 2015), and corosolic acid (23) (Bianchi et al., 1992; Hashmi et al., 2015) (Figure 1).

Flavonoids are also important phytochemical constituents reported to be isolated and detected in the extracts of Olea europea leaves. Different types of flavone and flavonoids such as aglycones and glycosides were reported in olive leaves such as kaempferol (24) (Özcan and Matthäus, 2017), quercetin (25) (Özcan and Matthäus, 2017), luteolin (26) (Goulas et al., 2009), diosmetin (27) (Savournin et al., 2001; Meirinhos et al., 2005; Hashmi et al., 2015), apigenin-7-O-glucoside (28) (Savournin et al., 2001; Meirinhos et al., 2005; Hashmi et al., 2015), rutin (30) (Bouaziz et al., 2005; Meirinhos et al., 2005; Hashmi et al., 2015), luteolin-4′-O-glucoside (31) (Goulas et al., 2009), luteolin-7-O-glucoside (29) (Bouaziz et al., 2005; Meirinhos et al., 2005; Goulas et al., 2009; Hashmi et al., 2015), luteolin-7,4′-O-diglucoside (33) (Savournin et al., 2001; Meirinhos et al., 2005; Hashmi et al., 2015), and quercitrin (34) (Özcan and Matthäus, 2017) (Figure 2).

Several phenolic acids were also isolated from Olea europea leaves, such as caffeic acid (35), gallic acid (36), chlorogenic acid (37), ellagic acid (38), and verbascoside (39) (Özcan and Matthäus, 2017) (Figure 2).

Other miscellaneous compounds were reported from the Olea europea leaves such as 4′-O-β-D-glucosyl-9-O-(6″-deoxyxycarrosyl) olivil (40) (Schumacher et al., 2002), 1,5-anhydroxylitol (41) (Campeol et al., 2004), and epicatechin (42) (Özcan and Matthäus, 2017) (Figure 2).

Several fatty constituents were reported in the hexane extract of Olea europea leaves, including hydrocarbons, tocopherols, triglycerides, waxes, esters, sterols, terpenic alcohols, terpenic dialcohols, and lineal (Guinda et al., 2002).

3 BIOLOGY REVIEW

3.1 Therapeutic Potential of Bioactive Compounds in the Olive Leaves Extract for the Management of COVID-19 Disease

Unlike other coronaviruses that caused several respiratory diseases, SARS-CoV-2 infection is not only a respiratory but also a systematic infection that exhibited severe immune response and resulted in multiorgan dysfunction and finally death (da Rosa Mesquita et al., 2021). The main symptoms of COVID-19 disease are fever, headache, fatigue, malaise, dry cough, and dyspnea with progression to pneumonia, diarrhea, back pain, and loss of smell and taste (da Rosa Mesquita et al., 2021; Zhou et al., 2020; Kabrah et al., 2021; Tawakul et al., 2021). The symptoms vary among patients depending on the viral load and virus strain (da Rosa Mesquita et al., 2021). The recent epidemiological studies detected certain people who are more vulnerable to COVID-19 infection, including older adults and people with serious health problems such as chronic lung disease, asthma, serious heart illness, and immunocompromised patients (C (2020). Coronavirus D, 2020; Alyami et al., 2020).

The primary reason for most of the deaths occurring in COVID-19 patients is hyper-inflammation due to the associated cytokine storm, especially IL-6, which resulted in acute respiratory distress syndrome (Cron et al., 2021; Zawawi et al., 2021). Moreover, one of the most dangerous complications of COVID-19 is the associated disseminated intravascular coagulation. Numerous reports showed that COVID-19 is related to the increased rate of thrombotic occasions (Goodman, 2020; Klok et al., 2020; Willyard, 2020). Currently, the therapies used for treatment of COVID-19 patients include different categories such as anti-SARS-CoV-2 monoclonal antibodies, antiviral products, immunomodulators, antithrombotic therapy, and supplements (H (2021a). Therapies. A, 2021a).

Several medications are prescribed for the management of hospitalized COVID-19 patients such as remdesivir, dexamethasone, tocifacitinib, baricitinib, tocilizumab, and sarilumab (H (2021b). Therapeutic, 2021b). Until now, several treatments have been prescribed for COVID-19 patients to relieve symptoms and manage complications, but no single treatment affords antiviral activity and symptomatic treatment.

The total extract of olive leaves and their compounds were reported in several studies for their antiviral, anti-inflammatory, immunomodulatory, and antithrombotic activities as described in this article. In addition, several products in the market that contain standardized olive leaf powder or extract are available for consumers, and most are standardized to 20% or 50% oleuropein. The aim of this study is to emphasize the potential benefit of the natural supplement (olive leaves) to undergo further in vivo or clinical investigations.

3.2 Antiviral (anti-SARS-CoV-2) Activity of Olive Leaf Compounds

3.2.1 In Silico and Computational Antiviral Studies

The antiviral activity of olive leaf metabolites against SARS-CoV-2 was reported in several in silico computational studies. Several viral targets were tested, such as viral proteases (Mpro/3CLpro, PLpro), TLRs, ACE2, RBD, NSP15, HSPA5 SBD, TMPRSS2, S protein, and furin (Yu et al., 2020a; Yu et al., 2020b; Derosa et al., 2020; Efiky, 2020; Hashem, 2020; Hu et al., 2020; Jena et al., 2020; Khaerunnisa et al., 2020; Sampangi-Ramaiah et al., 2020; Shawky et al., 2020; Surucu et al., 2020; Vardhan and Sahoo, 2020; Vijayan and Gourinath, 2020; Khan et al., 2021) (Table 1).
3.2.2 In Vitro Antiviral Studies
Several studies reported the antiviral activities of compounds present in olive leaves against SARS-CoV-2.

A hydroxytyrosol-rich cream (HIDROX®) showed virucidal activity against SARS-CoV-2 through structural changes in SARS-CoV-2, which is attributed to changing the molecular weight of the spike proteins and disrupting the viral genome (Takeda et al., 2021). Another study showed that the infection of Vero E6 cells by SARS-CoV-2 was decreased by luteolin with an EC50 value of 10.6 μM (CC50 = 155 μM) (Yi et al., 2004; Russo et al., 2020). In addition, kaempferol inhibited SARS-CoV-2 replication in vitro with % of inhibition equaling 88.33, 93.33, and 40.00% at a concentration of 125.00, 62.50, and 31.25 μM, respectively (Khan et al., 2021).

3.2.3 Clinical Antiviral Studies
A spray containing 3.80% hydroxytyrosol was proven for its activity as protection against SARS-CoV-2 infection in 50 volunteers, and it showed decrease in the viral load and cure in six patients within ten days (Ergoren et al., 2020).

3.3 Anti-Inflammatory, Antipyretic, and Analgesic Activities
Olive leaf extract significantly decreased the secreted protein levels of IL-6 and IL-8, and also, mRNA expression of E-selectin in serum amyloid A (SAA)–stimulated human coronary artery endothelial cells (HCAECs) and reduced matrix metalloproteinase (MMP2) levels in unstimulated cells (Burja et al., 2019) (Table 2). In addition, oleuropein was reported as a potential anti-inflammatory molecule for treating asthma and chronic obstructive pulmonary disease (COPD) when administered orally at a dose of 10–20 mg/kg in the experimental BALB/c mice model. It inhibited pulmonary inflammation and subsequent asthmatic fibrosis and alveolar emphysema in vivo of asthma induced by exposure to interleukin IL-4, ovalbumin (OVA), or cigarette smoke (CS). The mechanism of action of oleuropein was by reducing the influx of eosinophils and lymphocytes in the airway and diminishing IL-4 secretion in the lung, suppressing the infiltration of macrophages and neutrophils by blocking the induction of intercellular adhesion molecule 1 (ICAM-1), F4/80, CD68, and CD11b in airways (Kim et al., 2018).

3.4 Immunomodulatory Activity
Olive leaf extract and its phytoconstituents exhibited immunomodulatory effects by reducing the expression of pro-inflammatory mediators (IL-1β, IL-6, IL-8, TNF-α, and iNOS) that also resulted in its anti-inflammatory effects (Randon and Attard, 2007; Sánchez-Tena et al., 2013; Vezza et al., 2017; Harun et al., 2020). In an in vivo study using the mucosal explant cultures of Crohn’s disease patients and healthy volunteers, the ethanolic

![Table 1: Binding affinity (Kcal/mole) scores of olive leaf compounds against several targets in SARS-CoV-2.](http://example.com/table1.png)
The production of IL-6 (Harun et al., 2020). In addition, both uvaol and oleanolic acid significantly inhibited the production of TNF-α at a concentration of 100 μmol/L (Harun et al., 2020). Maslinic acid suppressed the chronic inflammation and exhibited antinflammatory activity comparable with that of dexamethasone through the development and sustainability of intestinal adenomatous polyps in ApcMin/+ (Sánchez-Tena et al., 2017). Oleuropein was reported to stimulate the proliferation and aggregation of lymphocytes and induce blastogenesis in vitro (Randon and Attard, 2007). Erythrodiol strongly inhibited the production of IL-6 (Harun et al., 2020). In addition, both uvaol and oleanolic acid significantly inhibited the production of TNF-α at a concentration of 100 μmol/L (Harun et al., 2020). Maslinic acid suppressed the chronic inflammation and exhibited antinflammatory activity comparable with that of dexamethasone through the development and sustainability of intestinal adenomatous polyps in ApcMin/+ (Sánchez-Tena et al., 2013).

### 3.5 Antithrombotic Activity

The ethanolic extract of olive leaves (0.1–100 μg/ml) reduced the expression of pro-inflammatory mediators such as IL-1β, IL-6, IL-8, TNF-α, and iNOS and improved the integrity of the epithelial barrier and restored the expression of ZO-1, MUC-2, and TFF-3 (Vezza et al., 2017). Oleuropein was reported to stimulate the proliferation and aggregation of lymphocytes and induce blastogenesis in vitro (Randon and Attard, 2007). Erythrodiol strongly inhibited the production of IL-6 (Harun et al., 2020). In addition, both uvaol and oleanolic acid significantly inhibited the production of TNF-α at a concentration of 100 μmol/L (Harun et al., 2020). Maslinic acid suppressed the chronic inflammation and exhibited antinflammatory activity comparable with that of dexamethasone through the development and sustainability of intestinal adenomatous polyps in ApcMin/+ (Sánchez-Tena et al., 2013).

### 3.5 Antithrombotic Activity

The ethanolic extract of olive leaves and its phytoconstituents such as hydroxytyrosol, hydroxytyrosol acetate, and maslinic acid reduced the platelet aggregation and exhibited antithrombotic activity by different mechanisms (Elzagallaai et al., 2006; Dub and Dugani, 2013; Vilaplana-Pérez et al., 2014; Kim et al., 2020). In a thromboplastin-induced thrombosis rabbit model, the pretreatment with the olive leaf ethanolic extract (100 or 200 mg/kg per day) for eight weeks modified the extrinsic coagulation pathway and drastically prolonged the prothrombin time (PT) in contrast to the control group. The extract also changed the thrombus morphology; the thrombus was filament-like in the treatment group, while it was thick in the control group and completely occluded the vein (Dub and Dugani, 2013).

Hydroxytyrosol reduced human platelet aggregation through a reduction in thromboxane B2 level, a platelet-aggregating and vasoconstrictor agent, which is the chemically stable and inactive form of thromboxane A2 (Vilaplana-Pérez et al., 2014).

Oral administration of hydroxytyrosol and hydroxytyrosol acetate for seven days in rats inhibited platelet aggregation with similar effectiveness of acetylsalicylic acid by decreasing thromboxane synthesis and increasing vascular nitric oxide (NO) production (Vilaplana-Pérez et al., 2014).

Maslinic acid was reported to regulate platelet aggregation and exhibited antithrombotic activity by different mechanisms. It inhibited protein kinase C (PKC) activation by activating the phosphorylation of myristoylated alanine-rich C kinase substrate (MARCKS), which is a phosphorylated substrate of PKC. Maslinic acid inhibited the enzymatic activity of coagulation factor Xa (FXa) and platelet aggregation induced by adenosine diphosphate (ADP) and a thromboxane A2 (TXA2) analog (Elzagallaai et al., 2006; Kim et al., 2020).
4 CONCLUSION

Olive leaves are rich in bioactive secondary metabolites. The major secoiridoid (oleuropein and its metabolite hydroxytyrosol), triterpenes (such as oleanolic, ursolic, and maslinic acids), and flavonoids (luteolin and kaempferol) exhibited in silico, in vitro, or in vivo antiviral activities against SARS-CoV-2.

Apart from the antiviral properties, these bioactive compounds significantly modulated several signaling pathways and demonstrated various activities such as anti-inflammatory, antipyretic, analgesic, immunomodulatory, and antithrombotic properties. These compounds provide a potential natural source to control the cytokine storms observed during COVID-19 infection, manage the symptoms, and protect against complications.

The potential antiviral activity of olive leaves and their other described benefits such as biosafety, availability, and low cost, along with the absence of an effective treatment for COVID-19 infection, makes olive leaves a potential natural remedy for the treatment and control of COVID-19. Clinical studies should be conducted with this plant and its metabolites to prove its efficacy in the treatment of COVID-19 infection.

AUTHOR CONTRIBUTIONS

All the authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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