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Review Article

Therapeutic Potential of Olive's Bioactive Compounds in COVID-19 Disease Management

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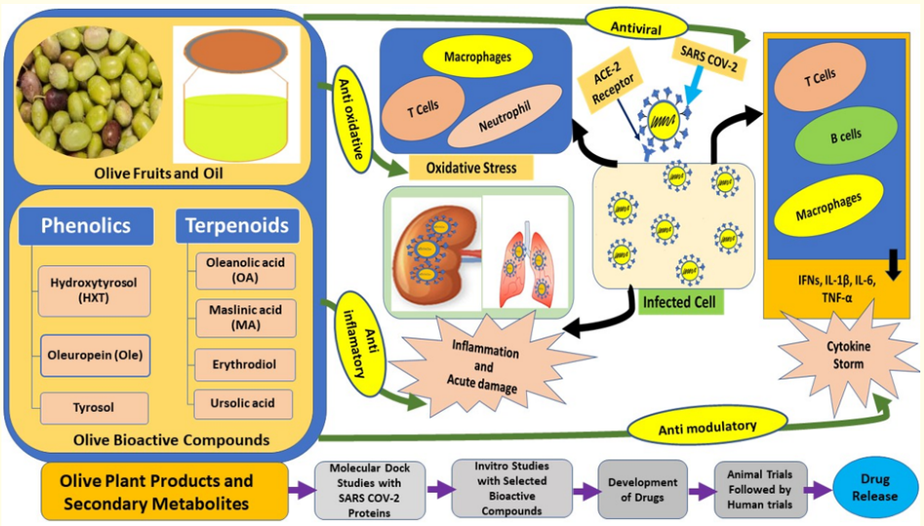
Graphical Abstract



Abstract

Currently, the world is continuously discovering effective treatment strategies for controlling the Coronavirus disease - 2019 (COVID-19). Many researchers have focused on designing drugs that can affect the replication or protease activity of coronavirus. The clinical testing and regulatory approvals for these drugs will take time. However, currently, there's an urgent requirement for treatment strategies that are safe, effective, and can be implemented through readily available products in the market. Many plant-derived products rich in secondary metabolites have potential health benefits and antimicrobial properties. The olive plant products (olive oil and leaf extracts) are rich in secondary metabolites, for instance, phenols (oleuropein and hydroxytyrosol) and terpenoids (oleanolic, maslinic, and ursolic acid). These compounds were used as an effective anti-viral agent in the past. The phenolics affect the virus attachment and replication. Whereas the terpenoids mainly affect the membrane fluidity of the virus. In recent molecular dock studies, it was found that these compounds effectively bound to Mpro and 3CLpro protease sites of COVID-19 virus (SARS-CoV-2) and were hypothesized to affect the replication of the virus. Apart from anti-viral properties, these bioactive compounds function as anti-inflammatory, anti-modulatory, anti-thrombotic, and anti-oxidative agents. Olive oil has been widely used for cooking all over the world. The consumption of olive oil is safe and is believed to increase immunity against various infectious microbes. Hence olive products can be explored in control of COVID-19 disease. This review summarizes and discusses the numerous properties of phenolic and terpenoid compounds found in olives in the context of COVID-19.

Keywords: COVID-19; Olive Oil; Phenols; Terpenes; Plant Secondary Metabolites

Abbreviations

ADMET: Absorption, Distribution, Metabolism, and Excretion; ASA: Acetylsalicylic Acid; AP-1: Activator Protein 1; ADP: Adenosine Diphosphate; ACE-2: Angiotensin-converting Enzyme-2; APC: Antigen-presenting Cell; AA: Arachidonic Acid; AZT: Azidothymidine; AGEs: Advanced Glycation; BRV: Bovine Rotavirus; CVD: Cardiovascular Disease; COVID-19: Coronavirus Disease 2019; CRP: C-reactive Protein; CD: Crohn's Disease; COX: Cyclooxygenase; ET-1: Endothelin 1; EVOO: Extra Virgin Olive Oil; FAV: Fowl Adenovirus; cGMP: Current Good Manufacturing Practices; HBV: Hepatitis B Virus; HDL: High-density Lipid; HMGB1: High Mobility Group Box 1; HIVRT: Human Immune Deficiency Virus Reverse Transcriptase; HOCl: Hypochlorous Acid; HXT: Hydroxytyrosol; HXT-AC: Hydroxytyrosol Acetate; IFN-γ: Interferon- γ; IRF-1: Interferon regulatory factor-1; IL: Interleukins; LDH: Lactate Dehydrogenase; LPS: Lipopolysaccharide; LOX: Lipoxygenase; LDL: Low-density Lipid; MA: Maslinic Acid; MMP-9: Matrix metalloproteinase 9; MERS CoV: Middle Eastern Respiratory Syndrome Coronavirus; MUFA: Monounsaturated Fatty Acids; MARCKS: Myristoylated Alanine-rich C Kinase Substrate; NHC: National Health Commission; NDV: New Castle Disease Virus; NO: Nitric Oxide; iNOS: Nitric Oxide Synthase; NF: Nuclear Factor; NF-kB: Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; OA: Oleanolic Acid; Ole: Oleuropein; PBMC: Peripheral Blood Mononuclear Cells; PAF: Platelet-activating Factor; PRP: Platelet-rich Plasma; PDB: Protein Data Bank; PKC: Protein Kinase C; ROS: Reactive Oxygen Species; RBD: Receptor Binding Domain; RNA: Ribonucleic Acid; RdRp: RNA Dependent RNA Polymerase; SFAED: Saturated Fatty Acid-enriched Diet; SARS CoV: Severe Acute Respiratory Syndrome Coronavirus; STAT-1α: Signal Transducer, and Transcription-1α; SOD: Superoxide Dismutase; TPA: 12-O-tetradecanoylphorbol-13- acetate; TI: Therapeutic Index; TF: Transcription Factor; TGF: Transforming Growth Factor; TNF α: Tumor Necrosis Factor-α; TMPRSS-2: Type 2 Transmembrane Protease Serine; US: United States; UA: Ursolic Acid; VEGF: Vascular Endothelial Growth Factor; VOO: Virgin Olive Oil

Introduction

The coronaviruses (CoVs) are enveloped RNA (ribonucleic acid) viruses, and their genome size varies from 26 - 32 kb [1]. Based on the serological and genetic characteristics, these viruses are grouped into six genera's (Alpha (α), Beta (β), Gamma (γ), and Delta (δ)). The coronaviruses can infect mammals and are known to cause respiratory diseases. However, all the CoVs which have infected humans were reported from α (Human(H) coronavirus-229E and HCoV-NL63,) and β (HCoV -OC43, HCoV-KU1, Severe Acute Respiratory Syndrome Coronavirus (SARS CoV), and Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV)) genera's only. The CoVs belong to β genera have caused a severe epidemic (SARS and MERS in 2002 - 2003 and 2012, respectively).

The analysis of history indicates that human beings were affected and influenced by many viral diseases. Until now, billions of people have died worldwide due to various viral infections. The current Coronavirus disease 2019 (COVID-19) pandemic had caused substantial morbidity and mortality all over the globe. The COVID-19 is a lower respiratory tract disease characterized by flu-like symptoms, usually after 5 - 6 days of virus infection. The various symptoms of the disease include pharyngitis, cough, pyrexia, myalgia, and loss of taste/smell was also observed in some cases. These symptoms are very similar to the SARS and MERS diseases. Aged people and people with poor immunity were found more vulnerable to the disease [2]. According to National Health Commission (NHC) China, the infected patients are the potential sources of transmission of the virus. The disease symptoms are not visible in some individuals (asymptomatic individuals); however, they also act as a source of infection. The disease gets transmitted from an infected person to others via aerosols generated through the respiration process and due to close contact [3].

Effective treatment or therapies are indispensable to save the world from the COVID-19 pandemic and stabilizing the global economy. So far, an approved drug is not available for COVID-19. Hence an effective anti-viral agent is required to control the infection. In many developing countries, ~80% of people depend on traditional plants for their medicinal needs [4]. With the advancement of technological resources, various plant products were explored as natural anti-viral drugs. The primary and secondary metabolites of plants are known to impart multiple health benefits; some are anti-viral and known to boost immunity against various infectious diseases. In the current scenario of the COVID-19 pandemic, a diet rich in these plant products is essential to increase immunity against the virus.

The olive oil and table olives used in the human diet are rich sources of phenolics, terpenoids, phytosterols, monounsaturated fatty acids (MUFA) (oleic acid) micronutrients. The various health benefits of olive phenols and terpenes have been scientifically illustrated. Olive oil is known to exert health benefits by interacting with the body's genetic, physiologic, and metabolic functions. Many ancient Greek doctors and Hippocrates mentioned olive plants and their products (virgin olive oil (VOO)) as a potent pharmacological agent and have been used for treating ~60 health conditions. Many pieces of evidence highlighted the beneficial aspects of olive products in controlling various viral, cardiovascular disease (CVD), and inflammatory diseases [5]. This manuscript summarizes the therapeutic potential of bioactive components of olives such as phenolics and terpenoids to control COVID-19.

SARS-CoV-2 infection and immune response

The spike (S) protein is a characteristic feature of all SARS coronaviruses. The variable receptor-binding domain (RBD) of the

antigen region recognizes the receptors and determines the infectivity of the virus. Angiotensin-converting enzyme-2 (ACE-2) is a transmembrane protein receptor specific to SARS-COV-2 present in various organs such as lungs, heart, gastrointestinal tract, and kidney cells. The virus enters primarily into these organs through this receptor. Once the virus binds to ACE-2 receptors, the type 2 transmembrane protease serine (TMPRSS-2) activates the S protein of the virus [6]. The SARS-CoV-2 infection and entry into the host cell are very similar to influenza and human metapneumovirus. The virus entry triggers the inflammation in the lower respiratory tract and immune response in the host. The cells which have both ACE-2 and TMPRSS-2 are most susceptible to virus infection. The cytokines and chemical factors are produced in higher quantity during severe infection of COVID-19. The antigen-presenting cell (APC) is an immune cell (dendritic, B cell, and macrophages) that triggers the immune responses. APC processes and presents the virus/antigen to T helper (Th1/$CD4^+$ T) cells, releases proteins (cytokines) to activate Th1 cells. The Th1 cells activate $CD8^+$-T-killer (Tk) cells and trigger B-cells to produce specific antibodies. The immune cells release many inflammatory cytokines, which leads to the formation of cytokine storms. The cytokines storms mainly include interleukins (IL)-1, 6, interferon- γ (IFN-γ) and tumor necrosis factor-α (TNF α). The TNF-α production triggers the various signaling events within cells, leading to necrosis or cell death to control the infection.

TNF-α and IL1β involve the induction of vascular permeability, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). The iNOS enzyme produces nitric oxide (NO), and this gaseous free radicle plays a crucial role in secondary inflammation and apoptosis. Patients develop wet lung and multiple organ failure [7]. Generally, viral infections are associated with inflammation and associated with coagulation disorders or thrombotic complications. Evidence suggests that inflammation and coagulation are related. Inflammation impacts the various phases (initiation and propagation) of blood coagulation [8]. Blood coagulation is regulated by circulating coagulation inhibitors (antithrombin and heparin cofactor II). Xu., *et al*. [9], in their immunological study with various blood samples of SARS-CoV-2 patients, found that the virus was involved in activation of pathogenic T cells and induction of multiple cytokines such as IFN-γ, IL-1, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The GM-CSF further stimulates monocytes, $CD14^{+,}$ and $CD16^+$ cells to secrete inflammatory cytokines such as IL-6. Because of this process, the inflammatory cascade continues, and the built-up immune solid response damages the body's essential organs. Li., *et al*. [10] found that the systemic cytokine storm caused by the COVID-19 virus and microcirculation dysfunction responsible for sepsis and multiple organ dysfunction. Therefore, anti-viral agents that immediately control the spread of viral particles and stabilize the immunity developed after exposure to the pathogen are essential to treat COVID-19.

Status of various treatment strategies for control of COVID-19

Current research in drug development against SARS-COV-2

Scientists are screening various existing anti-viral drugs to test the efficacy against COVID-19. All over the world, ~140 clinical trials are ongoing in which 23 are being carried out only in the United States (US), and the remaining are carried out by other countries (China, France, Canada, Spain, Russia, Germany, and Italy). The various groups of drugs and their mode of action are listed in table 1.

Current research in vaccine development against SARS-CoV-2

Prevention is always better than cure; vaccines are the cost-effective options in preventing various viral infections. Globally scientists are working out to discover the vaccines for COVID-19. However, this task remains challenging due to the highly variable RBD found in the S protein region of the virus. The vaccines developed against this virus will be ineffective due to faster virus mutation rates [24]. The new drugs developed should follow the current Good Manufacturing Practices (cGMP) and need to go for safety and toxicity assays in animals and humans. The development of vaccines will not happen overnight, requiring an enormous amount of time and money. Few examples of vaccines that are in phase II of clinical trials are shown in table 2.

Natural products as an alternative therapeutic agent for control of SARS-CoV-2

In traditional medicine, natural products and their derivatives or extracts were used to treat various infections, including viruses. The herbal nutraceuticals market is growing at a very rapid rate due to its accessible acceptability. Many plant products were identified as potential anti-viral agents [25]. Some of the plant's extracts found effective against SARS-CoV are *Lycoris radiate*, *Artemisia annua*, *Purrosia lingua*, *Lindera* a*ggregate*, *Isatis indigotica*. The anti-viral properties of these plant extracts are related to various kinds of secondary metabolites.

Plant secondary metabolites and their role in the control of various viral infections

The plant produces various kinds of secondary metabolites, which are organic compounds. These are not required for the primary growth of plants; however, they play a crucial role in defense mechanisms. Secondary metabolites are grouped into phenolics, terpenes, and nitrogen-containing substances. Many plant phenols and polyphenols possess anti-viral properties and have shown inhibitory activity against SARS-CoV-2 [26].

Drug Type	Drug Name	Tested viruses	Mode of Action	References
Antimalarial drugs	Chloroquine (CQ) and hydroxychloroquine (HCQ)	SARS-CoV-2, SARS, Human immunodeficiency virus (HIV), MERS	Increasing intracellular pH of lysosomes, interfering with glycosylation of viral receptor	[11]
Membrane fusion inhibitors	Arbidol (Umifenovir)	SARS-CoV-2	Membrane fusion inhibitor	[12]
Protease inhibitors	Anti-HIV drugs (Ritonavir, Lopinavir, Emtricitabine and Darunavir)	SARS-CoV-2, HIV	Protease inhibitor	[13]
	Cobicistat in combination with Darunavir	SARS-CoV-2	Cytochrome P450 inhibitor	[14]
	ivermectin	SARS-CoV-2, HIV	Inhibit integrase protein nuclear import (IN) and HIV-1 replication	[15]
	Camostat mesylate (FOY 305)	SARS-CoV-2	Targets TMPRSS2 protease and prevent viral entry	[16]
Replication inhibitors	Remdesivir (anti-HIV drug)	SARS-CoV-2, HIV	Adenine analogue	[17]
	Ribavirin	SARS-CoV-2, Respiratory syncytial virus (RSV), Hepatitis C virus (HCV)	Guanine analogue	[18]
	Favipiravir	SARS-CoV-2, influenza, yellow fever	Guanine analogue	[19]
Anti-inflammatory	methylprednisolone (DEPO-Medrol)	SARS-CoV-2	Prevent cytokine response in pneumonia	[20]
Cytokine inhibitors	Tocilizumab	SARS-CoV-2	Antibody targets IL-6 receptor	[21]
JAK1/JAK2 inhibitors	Ruxolitinib	SARS-CoV-2	Inhibitors of JAK1 and JAK2	[22]
Other therapies	Convalescent plasma	SARS-CoV, MERS -CoV		[23]

Table 1: Drugs under clinical trials for control of SARS-CoV-2.

Phase	Name	Type	Location	Trial No.
I/II	ChAdOx1	Non-replicating viral vector	UK	NCT04324606
II	Ad5-nCoV	Non-replicating viral vector	China	NCT04341389
I/II	Sinovac vaccine	Inactivated	China	NCT04352608
I/II	BNT162	RNA	Germany	NCT04380701
I/II	WIBP vaccine	Inactivated	USA	ChiC-TR2000031809
I/II	BNT162	RNA	Canada	NCT04368728
I/II	Sinovac vaccine	Inactivated	USA	NCT04383574
I/II	AV -COVID-19	Other	China	NCT04386252

Table 2: Vaccines in phase II of clinical trials for SARS-CoV-2 (WHO DRAFT landscape of COVID-19).

Secondary metabolites of olives

The olives are consumed either as table olives or olive oil for many years. These products are a rich source of various secondary metabolites such as phenolics, terpenes. These bioactive compounds present in the olive plant and its different products (oil, fruit, and leaf) have pharmacological significance and are being researched widely. Olive oil has been categorized into refined, lampante, pomace, and virgin olive oil based on the production methodology. Virgin olive oil is produced only by mechanical means without any chemical intervention. Olive pomace oil is extracted from the residue of the fruit press. The chemical refining of any virgin oil produces refined oil, and it doesn't have color, flavor and low in fatty acids and bioactive compounds. This olive pomace and refined oil have fewer health benefits due to the lower concentration of bioactive compounds. The chemical composition of olive oil

determines the health benefits. The main chemical components found in olive oil are classified into major and minor. The oleic acid, a monounsaturated fatty acid (MUFA), is a significant component and the other minor component includes phenols and terpenoids, etc., [27]. The primary-secondary metabolites such as phenolics and terpenes found in olives are discussed briefly.

Main phenolic compounds of olives

Phenolic compounds contain a single aromatic ring structure, whereas; polyphenols have one or more ring structures with an attached hydroxyl group [28]. The phenolic compounds of VOO are classified as lignans, phenolic acids, phenolic alcohols, secoiridoids, flavonoids, and hydroxy-isocromans. Among these, phenolic acids were found in the least quantity, and secoiridoids were found in the most significant amount. Oleuropein (Ole), hydroxytyrosol (HXT), and tyrosol are the significant phenolics found in olives.

The oleuropein is a secoiridoids phenol; the uniqueness of secoiridoids is that it is only found in plants belongs to the Oleaceae family. Chemically, oleuropein is an ester of phenyl ethyl alcohol (tyrosol and hydroxytyrosol) and an oleanolic acid glycoside. Oleuropein is a major phenolic compound found in Olive plants, its concentration is ~14% in fruits and 60-90 mg. g^{-1} in leaves on a dry matter basis. HXT is phenolic phytochemicals and is found in the form of an oleanolic acid ester of oleuropein, and its concentration varies with the type of oil and fruit. In Extra virgin olive oil (EVOO) the HXT concentration is 14.32 ± 3.01 $mg.kg^{-1}$ and in refined virgin olive oil it is ~1.74 ± 0.84 $mg.kg^{-1}$. The Green black olives, Spanish green olives, and Greek kalamata olives contain HXT concentrations of 100 - 340 $mg.kg^{-1}$, 170 - 510 $mg.kg^{-1}$ and 250 - 760 $mg.kg^{-1,}$ respectively.

Main terpenoid compounds of olives

Triterpenes are chemically composed of terpene/isoprene units. These compounds are generally found in fruit, fruit peel, leaves, and stem of olive plants. Oleanolic acid (OA), maslinic acid (MA), uvaol, and erythrodiol are the major triterpenes found in olive oil. The EVOO from different cultivars was found to contain triterpenes in the range of 40 -185 $mg.kg^{-1,}$ and the various oil varies from 8.90-112.36 $mg.kg^{-1}$ [29].

Pharmacological applications of phenolics and terpenoids of olives

Phenolics and terpenoids of olives as anti-viral agents

Plant secondary metabolites are known for their anti-viral activity. These compounds are known to affect the virus life cycle (entry, multiplication, assembly, and discharge) and virus-host interaction [4]. The main phenolic and terpenoids compounds of olives and their anti-viral properties are reviewed here.

Phenolics of olives as anti-viral agents

The hydroxyl group from phenol molecules dissociates and produces phenolate ions with a negative charge. The hydroxyl groups found on phenols also interact electro statistically or make hydrogen bonding or ion bonding with positively charged amino groups of the protein. The incubation study of phenolic compounds such as tannins with a protein molecule is shown to disturb the 3D structure of the protein or its activity [30]. Sometimes the polyphenols bind to the viral capsid (envelope) and prevent the virus particles attach to the host cells.

Oleuropein is a potential anti-viral phenolic compound. In US patent (US6117844A), the oral, parenteral administration of oleuropein either in crude extract or in the pure form is found effective against viruses such as bovine rhinovirus or hepatitis virus, herpes mononucleosis, feline leukaemia virus, canine parvovirus, and rotavirus. In another report, it has been mentioned that the human orthopneumovirus (RSV) and para-influenza type 3 virus can be effectively controlled by oleuropein. In one of the anecdotal reports, it has been mentioned that the olive leaf extracts containing oleuropein were found to inhibit Human immune deficiency virus reverse transcriptase (HIVRT) by increasing the activity of (-)-2'-Deoxy-3'-thiacytidine (3TC), which is a selective inhibitor of HIV replication. The phenolic extract from the olive leaf was found to inhibit the infection and replication of HIV-1, salmonid rhabdovirus, hemorrhagic septicemia virus (VHSV). In another study, the olive leaf extract containing oleuropein was reported to affect cell to cell transmission of HIV-1 at a half-maximal effective concentration (EC50) of 0.2 µg/ml by affecting HIV-1 gp41 (surface glycoprotein subunit) part of the virus [31].

Guiqin Zhao., *et al*. [32] studied oleuropein anti-viral properties on Hepatitis B virus (HBV) in HepG2 2.2.15 cell lines. At 23.2 µg/ml concentration (inhibitory concentration 50 (IC50) value) of oleuropein, the secretion of hepatitis B surface antigen (HBsAg) in HepG2 2.2.15 cell line was stopped entirely. The intraperitoneal administration of 80 $mg.kg^{-1}$ of oleuropein twice daily into duckling infected with duck hepatitis B virus (DHBV) showed reduced viral load. The mechanism of suppression of HBsAg gene expression was not appropriately understood. However, it was hypothesized that Ole might directly affect the transcription machinery of the HBsAg gene.

Hydroxytyrosol (HXT) was known to inhibit influenza-A virus sub types H5N1, H1N1, H9N2, and H3N2. Kentaro Yamada., *et al*. [33] studied the anti-viral effects of HXT using influenza-A virus, Bovine rotavirus (BRV), New Castle Disease Virus (NDV), and fowl adenovirus (FAV). In many studies, HXT was found ineffective against non-enveloped and effective against enveloped viruses. HXT was found to affect the surface structure of enveloped viruses. In a study, the electron microscopic pictures revealed that the HXT-treated H9N2 virus lacked surface spikes and was disintegrated. The other results, such as inhibition of transcription and translation, were also observed. These results indicate the anti-viral properties of HXT.

Lee-Huang., *et al*. [31] demonstrated the combined anti-viral effects of HXT and Ole. These compounds were found to affect the entry and integration of the virus into the host. Guiqin Zhao., *et al*. [32] investigated the anti-HIV properties of Ole and HXT. In molecular simulation studies, Ole and HXT were found to attack the HIV-gp41 fusion complex of the virus. They also found that these compounds affect the cell's cell transmission of HIV and p24 antigen production.

Terpenoids of olives as anti-viral agents

The lipophilic terpenoids are found in many plant oils. These lipophilic compounds interact non-specifically with the virus's lipid bilayer and affect the membrane fluidity and cause lysis. The triterpenoids found in olive oil, such as Oleanolic acid (OA) and Ursolic acid (UA), were found effective against HIV and hepatitis virus [34]. The terpenoids and their derivatives inhibit HIV-1 protease, resulting in the production of non-infectious virions, which block the life cycle of HIV and improves the patient's health. It was observed that when HIV-infected peripheral blood mononuclear cells (PBMC) are incubated with different doses of OA, the replication of the virus gets significantly reduced as compared to the azidothymidine (AZT) drug. The study found that OA eliminates HIV infection in H9 cell lineage with a therapeutic index (TI) of 12.8.

The inhibitory activities of OA and UA were tested against HCV and HBV, which causes hepatocellular carcinoma in humans [35]. OA inhibits HCV-RNA replication by suppressing the NS5B RNA-dependent RNA polymerase (RdRp). When incubated with HBV infected protein-transactivated cell lineages, UA had decreased the secretion of matrix metalloproteinase-3, and treated cells were found more sensitive to transforming growth factor (TGF) induced apoptosis. Because of these properties, UA is one of the potential candidates for developing a new class of anti-viral compounds for HBV.

OA-treated peritoneal macrophages were found to produce IL-12 cytokine required to activate T helper cell 1(CD4+Th1) to eliminate intracellular pathogens [36]. The anti-viral activities of OA and UA were dependent on the type of virus and host cell and exhibited a high level of selectivity and sensitivity. Both OA and UA have a similar mechanism of action and act mainly on the multiplication of virus particles.

Phenolics and terpenoids of olives as anti-inflammatory agents

Inflammation is a defensive process that protects the body from harmful infectious agents and allergens associated with a cellular cascade. The pathological infections and several diseases such as arthritis, cancer, and neurodegenerative disorders generate chronic inflammations [37]. The anti-inflammatory properties of phenolics and terpenoids found in olives are reviewed.

Phenolics of olives as anti-inflammatory agents

The phenolic compounds found in VOO were found to have prominent anti-inflammatory properties. The consumption of heated VOO rich in phenolics was reported to reduce the postprandial inflammatory responses. The VOO or mix of rapeseed or sunflower oil supplemented with olive phenolic compounds was found to reduce the postprandial inflammations. The phenolics enriched olive oil to reduce the stimulation of lipopolysaccharide (LPS), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and plasma concentration compared to sunflower oil and demonstrated the inflammatory effects. Various studies reported the effectiveness of VOO phenolics in modulating inflammatory mediators such as 6-keto-PG F1a and thromboxane B2 obtained in response to arachidonic acid. They were also found effective against C-reactive protein (CRP) and IL-6 inflammatory agents. The phenolics of olive were found to attenuate the expression of IL-8 and modulate the acute inflammatory responses in epithelial cells of the intestine [38]. In *in-vitro* studies with monocyte cell lines, the oleuropein was found to inhibit the expression of matrix metalloproteinase 9 (MMP-9), induced by tumor necrosis factor-alpha (TNF α). The monocytes and their secretary molecules are essential for the development of inflammatory disorders. A significant reduction of cytokine-induced MMPs and inflammatory responses were observed after 30 minutes of oleuropein administration. This was also associated with reduced atherosclerosis in arteries.

Impellizzeri., *et al*. [39] observed that the administration of oleuropein into a mouse challenged with carrageenan-induced inflammatory disease triggered a significant reduction of TNF, IL-1β, and NO. Visioli., *et al*. [40] shown an increased level of immune-competent cells in macrophages treated with oleuropein. In the study, oleuropein was found to induce nitric oxide (NO) synthase enzyme to produce NO in macrophages treated with LPS. The oleuropein was also known to inhibit the other inflammatory agents such as leukotriene B4 production and lipoxygenase activity.

The anti-inflammatory mechanism of oleocanthal of olive was found very similar to the anti-inflammatory drug ibuprofen. Oleocanthal was found to inhibit inflammatory enzymes such as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) in *in-vitro* studies. The oleocanthal was found more efficient than ibuprofen at the same concentration. The oleocanthal was found to attenuate inflammatory intermediates like inducible iNOS, which are common illnesses.

HXT of olive oil exhibited inhibitory activity against inflammation in an animal model. HXT had reduced the expression of pro-inflammatory cytokines like IL-1β and TNF α in inflammatory disorders*. In vitro* conditions, HXT was found to attenuate the inflammatory mediators such as COX-2, iNOS, and TNF α in LPS-challenged human monocytic THP-1 cells [41]. The HXT has the property of inhibiting LOX (lipoxygenase) and COX (cyclooxygenase) enzymes of arachidonic acid (AA) and found to reduce the oxidative damages of inflammations [42].

LPS stimulated J774 murine macrophage cell lines shown an increased mRNA level of NO synthase and cyclooxygenase 2, and ROS generation. The HXT Treatment was found to blocks the stimulation of NF-κB, interferon regulatory factor-1 (IRF-1), signal transducer, and transcription-1α (STAT-1α). HXT treated cells shown reduced expression of COX-2 and iNOS. Because of these properties, HXT can be considered a potent natural compound for the regulation of inflammation.

Terpenoids of olives as anti-inflammatory agents

Terpenoids including UA, OA, MA, and Uvaol have been examined and reflected effectively against inflammation [43]. On the exposure of allergens, OA was found to downregulate the infiltration of eosinophil, inflammation of the allergic airway, IL-5, IL-13, and IL-17 production. It was found to reduce the degranulation of mast cells, phospholipase A2 type-IIA (sPLA2-IIA), T helper cell-2 (Th2) type cytokines, capillary permeability, and type I allergic reactions. OA has inhibited the relinquishment of high mobility group box 1 (HMGB1) and HMGB1-mediated adhesion and movement of the monocytic cell line THP-1. In addition to this, it has been found to suppress the expression of the HMGB1 receptor, thereby prevents the down regulation of HMGB1-dependent tumor necrosis factor (TNF) and nuclear factor (NF). It was also found to lower the acetic acid-driven hyper-permeability, and carboxymethyl cellulose prompted leukocyte movement and stimulation of TNF and NF [44].

The *In-vitro/In-vivo* inflammatory models were used for assessing the activity of UA against inflammation. When arthritic balb/c mice treated with UA leads to suppressing pro-inflammatory cytokines like IL-2, Interferon (IFN) and TNF from Th-2 cell. The UA treatment was also reported to inactivate the pro-inflammatory enzyme sPLA2 and hide E-selectin by preventing the translocation of NF-k into the nucleus [45]. It was also found to suppress the advanced glycation (AGEs) end products and other molecules like COX-2 and iNOS, responsible for inflammation.

Banno., *et al*. [46] first assessed the inhibitory activity of MA against inflammation in a potent tumor promoter, 12-O-tetradecanoylphorbol-13- acetate (TPA). MA was known to regulate inflammation by inhibiting the binding of transcription factor (TF) NF-κB to the promoter sequence of COX-2 and iNOS [47]. NF-κB is a stress-controlled TF, which regulates inflammatory reactions. In addition to this, MA can down-regulate the stimulation of activator protein 1 (AP-1). This leads to the prevention of NF-κB phosphorylation, nuclear translocation, and DNA-binding action by suppressing the receptor of NF-κB expression.

Marquez-Martin., *et al*. [48] and Allouche., *et al*. [49] have reported the anti-inflammatory effects of triterpenes of olive oil. Asthma produces the inflammatory reactions of eosinophils, which are responsible for the pathological process of allergic diseases. Uvaol inhibits the infiltration of eosinophils, and the concentrations of IL-5 as inhibitory activity against inflammation as IL-5 have a key role in the infiltration of eosinophils and inflammation due to allergic reactions. The inflammatory responses in an asthma model can be regulated by inhibiting the phosphorylation of mitogen-activated protein kinases (ERK1/2), which controls the inflammation and mucus formation in the airways. Uvaol could reduce the growth of myofibroblasts by down regulating the phosphorylation of ERK1/2 and decrease the perivascular fibrosis [50].

Uvaol in human mononuclear cells facilitates the down regulation of cytokine IL-1β secretion, which is required to express adhesion molecule in eosinophils. The UA was found to prevent the production of antigen-stimulated IL-5 [51] considerably. Uvaol attenuates allergic inflammatory reactions by eosinophils, secretion of mucus, and alveolar collapse that appears to involve the decrease in the concentration of IL-5. Therefore, uvaol signifies a new molecule to regulate allergic reactions with several pharmacological properties.

Phenolics and terpenoids of olives as Anti-modulatory agents

Immunomodulator are molecules having the capability to control both innate and adaptive immune systems. Numerous bioactive compounds obtained from medicinal plants and their oils can be explored to modulate immune function.

Phenolics of olives as anti-modulatory agents

Teresa Vezza., *et al*. [52] assessed the olive leaf extract's inhibitory activity against inflammation and their immunomodulatory effects. The inhibitory activity against inflammation of olive leaf extract (0.5-25 mg/kg) containing oleuropein was tested in DSS and DNBS colitis mice models. The immune-modulatory effects were studied invivo using the extract (0.1-100 μg/mL) in mucosal organ cultures of both healthy individuals and patients with Crohn's disease (CD). In both the conditions, the extract was found to restore the expression of MUC-2, TFF-3, and ZO-1 to improve the barrier integrity of the epithelial line and down-regulate the expression of pro-inflammatory intermediates (iNOS, IL-1β, and TNF-α). The formation of pro-inflammatory intermediates (IL-6, IL-8, IL-1β, and TNF-α) was reduced in mucosal samples collected from the intestine of CD patients. They concluded that oleuropein's anti-inflammatory activities were linked to its immune-modulatory properties and ability to restore the barrier integrity of intestinal epithelial lines. Additionally, it also controls the cellular movement involved in inflammatory reactions.

Terpenoids of olives as anti-modulatory agents

The pentacyclic triterpenes (OA and UA) were assessed for their impact on T-cell multiplication. UA and OA were found to regulate T-cell multiplication with IC50 values down more than 50 μg/mL and 3.01 μg/mL, respectively. The chemical structures of OA and UA are varying at ring E in the methyl group position, which has imparted the different functionality. OA stimulates macrophages to produce additional TNF-α and NO [53], whereas UA showed suppression effects. Compared to OA, UA had shown significant inhibitory activity on T-cell multiplication.

The pentacyclic triterpenes are classified as acid and alcohol-based on carboxyl moiety and methyl at the C-17 location. UA's inhibitory activities against T-cell multiplication revealed that the six E rings containing UA were found more effective. The inhibitory properties of pentacyclic triterpene were due to the presence of the methyl group on the E ring. The pentacyclic triterpenes of olive oil, including OA, MA, uvaol, and erythrodiol, have been tested for their immunomodulatory activity on human mononuclear cells for cytokine production. Erythrodiol showed resilient activity in down-regulating the production of IL-6. OA and uvaol have considerably repressed the production of TNF-α at the highest concentration (100 μmol/L) while erythritol at the same attention did not show any effect [50].

MA-supplemented food has repressed tumor development in the small intestines of the ApcMin/+ mouse model by controlling the genes involved in modulatory pathways. The ApcMin/+ is a mouse model having point mutation (multiple intestinal neoplasias) in the APC gene. MA was found to inhibit prolonged inflammation, which is responsible for enlarging adenomatous tumors formed in the intestine of ApcMin/+ [54]. The MA fraction anti-modulatory activity was comparable with dexamethasone, but the effect was dependent on the specific compounds and cytokine.

Phenolics and terpenoids of olives as anti-thrombotic agents

Thrombosis is forming blood clots (thrombus) inside a blood vessel, which prevents blood circulation. It is a critical event in vascular disorders responsible for worldwide morbidity and mortality [55]. The secondary metabolites of olive plants were reported to have anti-thrombotic effects.

Phenolics of olive oil as anti-thrombotic agents

Thrombosis involves the cascades of adhesion, aggregation, and secretion by platelet activation, ultimately leading to death [56]. Coagulation and fibrinolysis are the two processes of thrombosis. The phenolics such as HXT, oleuropein, aglycone, and luteolin were reported as potent platelet aggregation inhibitors in several studies [57]. Consumption of virgin olive oil containing phenolic compounds (400 mg/kg) by hyper cholesterol patients showed inhibition of various procoagulant factors (VII and CH) due to reduced platelet aggregation.

Jose., *et al*. [58] evaluated the inhibitory effect of hydroxytyrosol acetate (HXT-AC) on thrombosis and compared the results with HXT and acetylsalicylic acid (ASA). The study's objective was to measure the invitro anti-aggregating activity of HXT-AC against

platelets present in human blood. Both HXT and HXT-AC inhibited platelets' aggregation, induced by arachidonic acid, adenosine diphosphate (ADP), and collagen in platelet-rich plasma (PRP) whole blood. HXT-AC and ASA both significantly impacted whole blood compared to PRP when these were used with collagen or ADP as an inducer. HXT-AC and ASA both showed a significant effect on PRP þ leucocytes compared to PRP alone. All three compounds can reduce the production of leucocyte 6-keto-prostaglandin F1a (6-keto-PF1a) and platelet thromboxane B2. The inhibition ratio (which is an indirect index of the balanced prostanoid) of thromboxane/6-keto-PGF1a was ten ·8 (SE 1), 1·0 (SE 0·1) and 3·3 (SE 0·2) for HXT-AC, HXT, and ASA respectively.

Terpenoids of olives as anti-thrombotic agents

Aggregation of platelets is one of the crucial steps in the blood-clotting process [59], whereas MUFA reduces platelet aggregation. Platelet-activating factor (PAF) is a resilient inflammatory lipid mediator required for platelet aggregation and necessary for stimulating and binding leukocytes to the endothelial cells. The polar lipid fraction of olive oil terpenoids is PAF antagonists as compared to other seed oils.

The derivatives of the olive terpenoids were found to reduce the reactivity of human platelets. Brzosko., *et al*. [60] evaluated the impact of virgin olive oil on thrombosis invivo and found that thrombotic occlusion is delayed in the aortic loop. They also observed a reduction in the fibrinogen concentration with more minor platelet wall interactions. Another study by Cruz., *et al*. [61] used saturated fatty acid-enriched diet (SFAED) containing 15% olive oil and showed a reduction in platelet activation and vascular thrombogenicity in rabbits.

The regulation of platelet aggregation by MA and the molecular mechanism was determined. The platelet aggregation was instigated by two means: enactment of protein kinase C (PKC) and by increment in cytosolic Ca^{2+}. The impacts of MA on PKC enactment were studied by analyzing the phosphorylation level of myristoylated alanine-rich C kinase substrate (MARCKS), a phosphorylation substrate of PKC in human platelets indicated that MA treatment restrained PKC [62].

Ca^{2+} and PKC induce the granule emission and stimulation of glycoprotein PAC-1 (GPIIb/IIIa) that act as a receptor of platelet conglomeration. MA suppresses platelet conglomeration via down-regulating the activation of PKC and Ca^{2+} ions. Thereby, MA down-regulates the platelet conglomeration by diminishing the outflows of P-selectin and PAC-1 in platelets. The regulation of vasomotion from the controlled formation of nitric oxide and endothelin 1 (ET-1) empowers sufficient support of vascular homeostasis [63]. The effect of MA on nitric oxide (NO) and ET-1 were further studied to understand the MA mediated anti-aggregation.

Phenolics and terpenoids of olives as anti-oxidative agents

Oxidizing agents are low-molecular-weight compounds, severely damaging the cell walls/membranes, leading to cell death. The secondary metabolites from olive oil showed anti-oxidative properties in humans [64]. The anti-oxidative properties of phenolics and terpenoids found in olives are discussed in this section.

Phenolics of olives as anti-oxidative agents

Oleuropein was found to inhibit the oxidation of low-density lipoproteins (LDL) mediated by copper sulphate [65]. Visioli., *et al*. [65] demonstrated the scavenging action of oleuropein using hypochlorous acid (HOCl). HOCl is mainly produced at the site of inflammation by neutrophil myeloperoxidase and can create potential harm to the proteins. In their investigation, Coni., *et al*. [66] found that feeding rabbits with olive oil rich in oleuropein were found to expand obstruction of LDL oxidation and lower free, esterified, and total cholesterol in plasma. Puerta., *et al*. [67] reported the nitric oxide (NO) scavenging capacity of oleuropein, and it was found to increase the iNOS expression in the cell. Visioli., *et al*. [68] reported that ingestion of oleuropein into the human body was found to decrease the secretion of 8-iso-PGF2α in a dose-dependent manner.

The HXT of olive oil is a powerful natural anti-oxidant and two times more potent than coenzyme Q10 [69]. The HXT has a structural affinity for certain groups of compounds containing amino groups. The simple structure of HXT makes it easy to assimilate by the human body. European Food and Safety Authority in 2012 approved HXT as a cardiovascular system protector which avoids the oxidation of low-density lipid (LDL) cholesterol by its free radicals and prevents atherosclerosis and normal high-density lipid (HDL) in blood [70]. The consumption of HXT regulates the concentration of glutathione and delivers anti-oxidant enzymes to lipid tissue. This compound was found to control the intracellular redox state and protect the cell from oxidative damage.

Terpenoids of olives as anti-oxidative agents

MA is known to suppress inducible iNOS and COX-2 at the transcription and translational level [71]. MA is known to inhibit LPS mediated NO production. The inhibition of NO formation by OA and

MA was described in murine RAW 264.7 cells. MA decreases the generation of reactive oxygen species (ROS) in breast malignancy cells [49]. Triterpenes can protect cells against H_2O_2 initiated DNA damage in various leukemic 96 and human breast malignancy cell lines. Triterpenes decrease ROS, NO levels and reduce vascular endothelial growth factor (VEGF) [72].

OA reduces the H_2O_2 or MMP+ mediated cell death and secretes lactate dehydrogenase (LDH), which reduces the oxidative pressure in PC12 cells. It spares glutathione (GSH), raising the action of catalase and superoxide dismutase (SOD), which reduces the secretion of TNF-α and IL-6. The reduction of ROS and proteins related to oxidative stress is another anti-oxidative effect of OA [73].

Control of SARS-CoV-2 using phenolics and terpenoids of olives

COVID-19 pandemic spread can be controlled by using certain disinfectants. Various chemical disinfectants are used to destroy the presence of virus particles. Few studies showed that these chemical disinfectants have side effects and not economical for large-scale disinfection. To overcome the challenges, scientists are looking for alternative options using natural compounds that are safe, effective, and economical [74]. The triterpenoids of *Olea europaea* L can destroy the infectious agents. The triterpenoids found in olive gum oil were used for fumigation [75]. Oleanane triterpenes, the derivative of oleanolic acid, was reported to inhibit the coronavirus; hence, these derivatives can prepare disinfectants. Scientists are continuously researching various natural biomolecules to find effective ones against SARS-CoV-2 using multiple tools such as molecular dock, computer simulation, silicon absorption, distribution, metabolism, and excretion (ADMET). The molecular dock studies are conducted to study the interaction between ligand and target molecules.

In a simulation study, binding affinities of ligand to the target molecule and conformational changes were analyzed [76]. The chymotrypsin-like protease ($3CL^{pro}$) and principal protease (Mpro/6LU7) parts of COVID-19 are essential for replicating the virus, and these two are primary targets for many potential drugs. These proteases have been organized and deposited in a protein data bank (PDB) and are open to the public for research [77]. Khaerunnisa Siti., *et al*. [78] performed molecular docking studies with oleuropein of olive oil and Mpro of the virus. They have used Autodock 4.2, Biovia Discovery Studio 4.5 with the Lamarckian Genetic Algorithm, and Pymol version 1.7.4.5 Edu. They have analyzed the likelihood of docking oleuropein with Mpro (6LU7). The study found that oleuropein with the 6LU7 amino acids through hydrogen bonds (Glu166, His163, Leu141, and Tyr54) showed the binding energy of -7.83 kcal/mol for Mpro.

Similarly, the oleanolic acid found in *Olea europaea* was analyzed for its inhibitory activity on proteases of SARS-CoV-2 by molecular docking [79]. Two proteases, 6LU7 and 6Y2E of SARS-CoV-2, were used for this investigation. PyMOL and Biovia Discovery Studio 20.1.0 visualized the protein-ligand and structure interactions. The results suggest that oleanolic acid has -7.8 and -8.0 binding affinities (kcal/mol) for 6LU7 and 6Y2E proteases. These affinity results indicate that oleanolic acid effectively binds with viral proteases and is predicted to inhibit virus replication. In another study, Vardhan and Sahoo [80] used maslinic acid as a ligand against RBD of SARS-CoV-2, S protein. The maslinic acid shown-9.3 binding affinity (Kcal/mole) for RBD and was mainly interacting with three different sites of S protein and predicted to affect the binding of S protein with ACE2 receptor of the target it could inhibit the access of SARS-CoV-2 into the host cell. They have additionally tested the interaction of maslinic acid with the ACE2 receptor. In the interaction study, maslinic acid had shown -10.2 binding affinity (Kcal/mole) for ACE2. In addition to this, they have tested the OA and UA of olive oil against the 3CLpro protease of SARS-CoV-2. The protease $3CL^{pro}$ is indispensable for the translation and replication of a virus. They found that OA and UA both have a binding affinity of -8.9 for $3CL^{pro}$ protease. Therefore, oleuropein, oleanolic acid, maslinic acid, and ursolic acid were found to prevent COVID-19. However, further exploration is essential to examine the therapeutic use of the olive bioactive compound to control COVID-19.

Conclusion

The olive plant and its products are rich sources of various plant secondary metabolites. The oleuropein, hydroxytyrosol, oleanolic acid, and maslinic acid from olives have been used as an effective anti-viral agent for treating many other diseases. In molecular docking investigation, it was discovered that the oleuropein, oleanolic acid, and maslinic acid had shown the highest affinity to Mpro and $3CL^{pro}$ parts of SARS-CoV-2, which are essentially required for virus reproduction and found encouraging future drugs against COVID-19. Apart from anti-viral properties, these bioactive compounds interfere and modulate various signaling pathways and possess multiple properties such as anti-inflammatory, anti-modulatory, anti-thrombotic and anti-oxidant properties. These compounds were known to control the cytokine storms observed during various viral infections and other diseases. The virgin ol-

ive oil produced from olive fruit by the mechanical press is a rich source of all the bioactive compounds. Hence, olive oil should be a part of our daily diet to harness the potential health benefits and boost immunity against COVID-19. The olive oil can also be applied all over the body as a preventive measure to avoid the virus infection. The oleanane, a triterpenoid extracted from the olive plant, was reported as a safe and effective fumigant and was used to prevent the spread of infectious biological agents. Hence, the olive oil/ the olive plant or leaf extracts can be used to prepare hand sanitizers and body lotions/soaps to control the COVID-19. With all this proven scientific evidence of anti-viral, potential health benefits, and general safety, these compounds can be considered for future pharmaceutical developments against SARS-CoV-2 or other viral diseases. Considering the current situation and absence of any effective therapy or vaccine for novel corona virus, clinical studies should be conducted with these compounds to prove the efficacy and provide affordable and risk-free treatment to COVID-19.

Conflicts of Interest

All the authors declare that there is no conflict of interest.

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