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

Chandrashekharaiah P. S[1], Santosh Kodgire[1], Vishal Paul[1], Dishant Desai[1], Shivbachan Kushwaha[1], Debanjan Sanyal[1]*, Santanu Dasgupta[2]

[1] Reliance Industries Ltd., Jamnagar Gujarat
[2] Reliance Industries Ltd., Navi, Mumbai

*Corresponding author

ABSTRACT

In this present time the world is continuously discovering effective treatment strategies for controlling the Coronavirus disease - 2019 (COVID-19). Many researchers have focused on designing drugs which can affect replication or protease activity of coronavirus. The clinical testing and regulatory approvals for these drugs will take time. However, currently there is an urgent requirement of treatment strategies which are safe, effective and can be implemented through readily available products in market. Many plant derived products rich in secondary metabolites having potential health benefits and antimicrobial properties. The olive plant leaf extracts and olive oil are rich sources of secondary metabolites such as phenols (oleuropein and hydroxytyrosol) and terpenoids (oleanolic, maslinic and ursolic acid). These compounds have been used as an effective antiviral agents in the past. The phenolics affect the virus attachment and replication. Whereas, the terpenoids mainly affects the membrane fluidity of the virus. In the recent molecular docking studies, it was found that, these compounds effectively bound to Mpro and $3CL^{pro}$ protease sites of SARS-CoV-2 and were predicted to affect the replication of the SARS-CoV-2. Apart from antiviral properties, these bioactive compounds possess various other pharmacological properties such as anti-inflammatory, anti-modulatory, anti-thrombotic and anti-oxidative. The olive oil is consumed as a source of dietary fat and is the secret behind the good health in Mediterranean people. The consumption of olive oil is safe and is believed to increase the immunity against various infectious microbes. Hence olive products can be explored in management of COVID-19. In this review the various properties of phenolic and terpenoid compounds found in olives were discussed in the context of COVID-19.

Keywords: COVID-19, Olive oil, Phenols, Terpenes, Plant secondary metabolites.

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1. Introduction

The coronaviruses (CoVs) are large enveloped viruses, contain positive (+) sense single strand ribonucleic acid (ssRNA) as genetic material and the genome size varies from 26-32 kb [1]. The coronaviruses belong to the family Coronaviridae, sub family Coronavirinae and are grouped into Alpha (α), Beta (β), Gamma (γ), and Delta (δ) genera based on their serological and genetic characteristics [2-3]. The coronaviruses have the capability to infect mammals and known to cause respiratory diseases. However, all the CoVs which have infected humans were reported from α (Human CoV-NL63, Human CoV-229E) and β (Human CoV-OC43, Human KU1, Severe Acute Respiratory Syndrome (SARS) CoV and Middle Eastern Respiratory Syndrome (MERS) CoV genera's only [3]. The COVs belongs to β genera have caused severe epidemic in the past (SARS and MERS in the year 2002-2003 and 2012 respectively).

The analysis of history indicates that, human beings were affected and influenced by many viral diseases. Till now billions of people have died worldwide due to various viral infections and now the SARS-CoV-2 causing COVID-19 had caused substantial morbidity and mortality all over the globe. The COVID-19 is a lower respiratory tract disease and it is characterized by flu-like symptoms which occurs usually after 5–6 days of virus infection. The various symptoms include sore throat, cough, fever, muscle or body aches and even loss of taste or smell was also observed in some cases. These symptoms are very similar to the SARS and MERS diseases [4]. Aged people and people with poor immunity were found more vulnerable to the disease [5]. According to National Health Commission (China), the infected individuals are the main sources of transmission. The disease symptoms are not visible in some individuals (asymptomatic individuals) however, they act as potential source of SARS-CoV-2 infection. The disease gets transmitted through respiratory droplets, close contact with the infected person and exposures to the aerosols generated by the infected individuals because of these reasons the COVID19 disease is spreading rapidly and is responsible for death of millions of people across the globe [6].

The effective treatment or therapies against SARS-CoV-2 are very much essential to save the world from COVID-19 pandemic and to stabilize the global economy. However, there is no approved treatment is available for COVID-19 so far, hence there is a crucial requirement to develop antiviral agents which are effective to control the infections. According to WHO ~80 % of the people in many developing countries depends on conventional plant sources for various health needs [7-8]. With the advancement of technological resources various natural plant products have been explored as antiviral agents [7, 9-10]. The plant primary and

secondary metabolites are known to impart various health benefits, some are antiviral and known to boost the immunity against the various infectious diseases [11-12]. The diet rich with these products are very important at the current scenario to boost the immunity against these viruses.

Olive plants and its products such as table olives and olive oil used in human diet are rich sources of monounsaturated fatty acids (MUFA) (oleic acid), phenolics, terpenoids, phytosterols and micronutrients. The positive effects of olive biophenols and terpenes on human health have been scientifically demonstrated [13-14]. Traditionally olive oil was used in diet due to its protective and beneficial properties [15]. Olive oil protects human health by changing epigenetic, metabolic and physiologic mechanisms [15]. In the history many ancient Greek doctors and Hippocrates mentioned olive plants and its products (virgin olive oil (VOO)) as a potent pharmacological agent and they have been used for treating ~60 health conditions [15]. Many evidences highlighted the beneficial aspects of olive products in controlling various viral, cardiovascular disease (CVD) and inflammatory diseases [16]. This manuscript summarizes the potential activities of various bioactive components of olives such as phenolics and terpenoids in relation to the management of COVID-19 disease.

2. SARS-CoV-2 infection and immune response

The presence of spike (S) protein is a characteristic feature of all SARS related coronaviruses. The variable receptor binding domain (RBD) found on S protein of SARSCoV-2 recognizes and binds to the receptor angiotensin converting enzyme-2 (ACE-2). ACE-2 is a transmembrane protein present in lungs, heart, gastrointestinal tract and kidney, there by facilitates the virus entry in to target cells [17]. Once the virus binds to the ACE-2 receptors in the type II pneumocytes in the lungs, the type 2 transmembrane protease (TMPRSS-2) complex cleaves ACE-2 and activates the S protein of the virus [18-19]. The mechanism of infection and viral entry observed with SARS-CoV-2 is similar to the infection process observed in influenza and human metapneumovirus. The cells which have both ACE-2 and TMPRSS-2 are mostly susceptible to virus infection [20]. The SARS-CoV-2 entry and infection in to the cell triggers the host immune response and cascade of inflammation in the lower respiratory tract [21].

The patients with severe SARS-CoV-2 infection show an elevated level of inflammatory cytokines and chemical factors [22-23]. The inflammatory responses are triggered by antigen presenting cells (APC). The APC performs two functions, firstly it presents the virus, to $CD4^+$ T-helper (Th1) cells and secondly releases interleukin (IL)-12 to further stimulate Th1 cells. The stimulated Th1 cells activate $CD8^+$-T-killer (Tk) cells that will target and attack

any cells containing foreign antigen and triggers B-cells to produce the specific antibodies against the antigen. Hence, to fight with the antigens immune cells releases many inflammatory cytokines which leads to the formation of cytokine storms. The cytokines storms mainly include, tumor necrosis factor-α (TNF α), interleukins (IL)-1, 6 and interferon-γ (IFN-γ). The pain, redness and swelling are the signs of inflammation. The TNF-α production triggers the various signalling events within cells, leading to necrosis or cell death as a mechanism to control the spread of infection. TNF-α and IL1β are involved in a wide range of events, including vascular permeability, inflammatory cells, induction of inducible nitric oxide synthase (iNOS) and cyclooxigenase-2 (COX-2) [24-25]. The iNOs is one of the three distinct enzymes that produces nitric oxide (NO), a free radical gas molecule which is known to have a crucial role in the development of the secondary inflammatory response and cell apoptosis [26]. Because of these reasons patients susceptible to acute respiratory distress syndrome (ADR) and multiple organ failure [23, 27]. Generally, the viral infections are not only associated with inflammation but also associated with coagulation disorders or thrombotic complications. Evidences suggest that inflammation and coagulations are related. Inflammation impacts the initiation, propagation and inhibitory phases of blood coagulation [28]. Blood coagulation is regulated by circulating coagulation inhibitors (antithrombin and heparin cofactor II). Xu et al. (2020), in their immunological study with various blood samples of SARS-CoV-2 patients, found that SARS-CoV-2 virus immediately activates pathogenic T cells and induces various cytokines such as, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, IL-6, and IFN-γ [29]. GM-CSF further activates $CD14^+$ cells, $CD16^+$ cells and monocytes, resulting in further release of inflammatory cytokines such as IL-6. This process continues to strengthen the inflammatory cascade and intense immune response cause damages to the vital organs. Li et al. (2020), in their study found that SARS-CoV-2 systemic cytokine storm and the microcirculation dysfunctions together leads to viral sepsis and multiple organ failures [30]. Therefore, effective antiviral agents and therapies which controls innate immune response and stabilizes the adaptive immune response are important for effective treatment of COVID-19.

3. Current treatment status for COVID-19

3.1. Current research in drug development

The treatment for COVID-19 is in early stage, currently doctors are trying to test the existing antiviral drugs against COVID-19. All these testing's are under clinical trials to prove the effectiveness and safety. There are ~140 clinical trials are ongoing in various parts of the world in which 23 are being carried out in the United States (US) and remaining are carried

out by other countries (China, France, Canada, Spain, Russia, Germany and Italy) The promising drugs used against SARS-CoV-2 virus are classified based on their mode of action. The various groups of drugs and their mode of action are listed in table 1 and table 2

Table 1. Drugs under clinical trials

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	[31-33]
Membrane fusion inhibitors	Arbidol (Umifenovir)	SARS-CoV-2	Membrane fusion inhibitor	[34-36]
Protease inhibitors	Anti-HIV drugs (Ritonavir, Lopinavir, Emtricitabine and Darunavir)	SARS-CoV-2, HIV	Protease inhibitor	[37-40]
	Cobicistat in combination with Darunavir	SARS-CoV-2	Cytochrome P450 inhibitor	[41-42]
	ivermectin	SARS-CoV-2, HIV	Inhibit integrase protein nuclear import (IN) and HIV-1 replication	[43-44]
	Camostat mesylate (FOY 305)	SARS-CoV-2	Targets TMPRSS2 protease and prevent viral entry	[45-46]
Replication inhibitors	Remdesivir (anti-HIV drug)	SARS-CoV-2, HIV	Adenine analogue	[47-49]
	Ribavirin	SARS-CoV-2, Respiratory syncytial virus (RSV), Hepatitis C virus (HCV)	Guanine analogue	[50-51]
	Favipiravir	SARS-CoV-2, Influenza, yellow fever	Guanine analogue	[49, 52]
Anti-inflammatory	methylprednisolone (DEPO-Medrol)	SARS-CoV-2	Prevent cytokine response in pneumonia	[53-54]
Cytokine inhibitors	Tocilizumab	SARS-CoV-2	Antibody targets IL-6 receptor	[55]
JAK1/JAK 2 inhibitors	Ruxolitinib	SARS-CoV-2	Inhibitors of JAK1 and JAK2	[56]
Other therapies	Convalescent plasma	SARS-CoV, MERS - CoV		[57-58]

3.2. Current research in vaccine development

Prevention is always better than cure hence, vaccines are the cost-effective options in preventing the viral infection than treating the disease [59-60]. As of 21st May2020, there is

no proper vaccine for treatment of COVID-19. Globally scientists are working to discover vaccines against this virus. The receptor binding domain (RBD) of S protein is highly variable region because of this reason the development of vaccine against SARS-CoV-2 is highly challenging [61]. Moreover, the mutation rates of RNA viruses are higher than DNA viruses with high genetic diversity [62]. Also, the new drugs used which needs to be tested for safety using toxicity assay in animals and should follow the current Good Manufacturing Practices (cGMP). Some examples of vaccines in phase II of clinical trials are given in table 2.

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

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	ChiCTR2000031809
I/II	BNT162	RNA	Canada	NCT04368728
I/II	Sinovac vaccine	Inactivated	USA	NCT04383574
I/II	AV-COVID-19	Other	China	NCT04386252

4. Natural products as an alternative therapeutic agents for control of SARS-CoV-2

Natural products and their derivatives are used in traditional medicine to treat numerous diseases comprising viral infections [7]. The scope of herbal medicines in the context of nutraceuticals market is vast [63] and the acceptability as well as research on plant- based drugs is growing. Many plant products were identified as antiviral agents [64-65]. Some of the natural extracts prepared from various plants were found effective against SARS-CoV Ex., *Lycoris radiate*, *Artemisia annua*, *Purrosia lingua*, *Lindera aggregate*, *Isatis indigotica*. The antiviral properties of these plant extracts are related to various kinds of secondary metabolites.

4.1. Role of secondary metabolites in human health and control of SARS-CoV-2

Secondary metabolites are organic compounds produced by organisms which are not directly involved in the normal growth, development, or reproduction of the organism. The plant produces various kinds of secondary metabolites which are not essential for their growth but required for defence mechanisms. These are grouped in to phenolics, terpenes and nitrogen containing substances. Many plant phenols and poly phenols were found to possess antiviral properties and have shown inhibitory activity against SARS-CoV-2 [66]. Intake of various

bioactive lipids may involve in enhancing the immunity and helps in recovery from various coronavirus diseases [67].

4.2. Secondary metabolites of olives

The olive tree (*Olea europaea*) is a rich source of all types of secondary metabolites. The olives are consumed either as table olives or olive oil [68]. The phenolics, terpenes and other bioactive components [14, 69] present in olive oil, fruit and leaf have pharmacological significance and are being researched widely [70] to explored as functional foods [71]. Based on the production methodology, olive oil has been categorized into virgin olive oil, olive pomace oil, lampante olive oil, or refined olive oil. Virgin means the oil was produced by only mechanical means without any chemical intervention. The term virgin oil includes extra Virgin Olive Oil (EVOO), Virgin olive oil (VOO), Ordinary virgin and Lampante virgin olive oil products. VOO are the main source of dietary fat in Mediterranean people and the main reason for their superior health [72-73].

Olive pomace oil is extracted from the residue that remains after the fruit is pressed. Refined olive oil is the olive oil obtained from any grade of virgin olive oil by chemical refining methods. The refining process removes colour, odour, flavour, and low in free fatty acids and bioactive compounds. These olive pomace and refined oil have less health benefits due to less concentration of bioactive compounds. Health protective effect of olive oil is based on its chemical composition [74]. The chemical composition of olive oil is divided into two components: major and minor. The major component of olive oil is oleic acid, which is a monounsaturated fatty acid (MUFA) [75]. Minor components of olive oil constitute nearly 2 % of the weight of olive oil [75] which includes terpenoids, phenols and many other minor compounds [75]. The main secondary metabolites of bioactive importance to our present discussion are discussed briefly.

4.2.1. Main phenolic compounds of olives

Phenolic compounds contain single aromatic ring structure whereas, polyphenols contain one or more ring structures with attached hydroxyl group [76]. The phenolic compounds of VOO are classified as phenolic alcohols, phenolic acids, secoiridoids, flavonoids, hydroxy-isocromans and lignans. Among these, phenolic acids were found in least quantity and secoiridoids were found in largest quantity [77]. The major phenolic compounds found in olive plants are oleuropein (Ole), hydroxytyrosol (HXT) and tyrosol [13].

The oleuropein is a secoiridoids phenol, secoiridoids usually bound to glycosides and produced by secondary metabolism of terpenes. The uniqueness of secoiridoids is that it only found in plants belongs to Oleaceae family. Oleuropein is chemically an ester of phenyl ethyl

alcohol (hydroxytyrosol and tyrosol), elenolic acid glycoside [78-79]. Oleuropein is a major phenolic compound found in Olive plants, its concentration is ~14 % [80] in fruits and 60-90 mg/g in leaves on dry matter basis [80-81].

HXT is phenolic phytochemical and found in the form of elenolic acid ester oleuropein. The concentration of HXT in EVOO and table olives is affected by various factors such as the geographical locations of cultivation, plant variety, time of collection and the processing conditions [82-83]. In EVOO the HXT concentration is 14.32 ± 3.01 mg/kg, where in refined virgin olive oil its concentration is reduced to 1.74 ± 0.84 mg/kg [84]. The concentration of HXT is, 170–510 mg/kg in Spanish green olives, 100–340 mg/kg in Greek black olives and 250–760 mg/kg in Greek kalamata olives [85].

4.2.2. Main terpenoid compounds of olives

Triterpenes are chemically composed of terpene/isoprene units [86]. These compounds are generally found in stem, bark, leaves and fruit peel of olive plants. Based on chemical structure triterpenes are classified in to pentacyclic derivatives like ursane, lupane, and oleanane which possess various pharmacological properties [87]. Triterpene concentration in olive oil ranges from 8.90-112.36 mg/kg, mainly includes oleanolic acid (OA), maslinic acid (MA), uvaol and erythrodiol [88]. Oleanolic and maslinic acids are the main triterpene acids present in VOO [89]. Total triterpene acid content of EVOO obtained from fruits of different olive cultivars was found in the range of 40 -185 mg/kg.

5. Pharmacological applications of phenolics and terpenoids of olives

5.1. Phenolics and terpenoids of olives as antiviral agents

Plant secondary metabolites are known for their antiviral activity. These compounds known to affect the virus life cycle including virus-host interaction, entry, multiplication, assembly and discharge [7, 90]. The antiviral properties of main phenolic and terpenoids compounds of olive leaf extracts and olive oil are reviewed here.

5.1.1. Phenolics of olives as antiviral agents

The hydroxyl group from phenol molecules dissociates and produces phenolate ion 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 protein. The incubation study of phenolic compounds such as tannins with a protein molecule shown to disturb 3D structure of protein or its activity [91]. Sometimes the polyphenols bind to the viral capsid (envelope) and prevents the virus particles attachment to the host cells. Most of the natural phenolic compounds were reported as antiviral agents and were known to affect the viral entry and infection [92].

Oleuropein is a potential antiviral phenolic compound. In US patent (US6117844A) it has been claimed that the oral parenteral administration of oleuropein either in crude extract or in pure form exhibited profound antiviral activity against various viruses such as hepatitis virus, bovine rhinovirus, herpes mononucleosis, canine parvovirus, feline leukaemia virus and rotavirus [93]. In another report it has been mentioned that the human orthoneumovirus (RSV) and para-influenza type 3 virus can be effectively controlled by using oleuropein [94]. In one of the anecdotal reports it has been mentioned that, the leaf extracts of olive containing mainly the oleuropein was 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 [95]. The leaf extracts rich in phenols were found to inhibit a salmonid rhabdovirus, haemorrhagic septicaemia virus (VHSV) and HIV-1 infection and replication [96]. The olive leaf extract containing oleuropein at half maximal effective concentration (EC50) of 0.2 µg/ml, was reported to affect transmission of HIV-1 from one cell to other. Oleuropein was mainly targeting the HIV-1 gp41 (surface glycoprotein subunit) part of virus there by affects the entry of HIV into normal cells. [97].

Guiqin Zhao et al. (2009), demonstrated the anti-viral activity of oleuropein in vitro on Hepatitis B virus (HBV) in HepG2 2.2.15 cell lines [98]. Oleuropein was found to block the secretion of hepatitis B surface antigen (HBsAg) effectively in HepG2 2.2.15 cell lines at inhibitory concentration 50 (IC50) value of 23.2 µg/ml. Invivo studies using duck hepatitis B virus (DHBV) and duckling shown that, the intraperitoneal administration of 80 mg/kg, of oleuropein twice daily had reduced the viral load. The mechanism of how Ole suppresses the HBsAg gene expression in HepG2 2.2.15 cells was not yet clear. However, it was hypothesized that Ole may directly travel into the cell and alter the transcriptional machinery of HBsAg gene [99].

Hydroxytyrosol (HXT) was known to inhibit influenza-A virus sub types H5N1, H1N1, H9N2 and H3N2. Kentaro Yamada et al. (2009), studied the antiviral effects of HXT using influenza-A virus, New castle Disease Virus (NDV), Bovine rotavirus (BRV) and fowl adenovirus (FAV) [100]. HXT was effective against the enveloped viruses and found ineffective against non-enveloped viruses. Under electron microscope, the HXT-treated H9N2 virus was found lacking surface spikes and structure was affected. These results suggest that HXT mainly targets the structure of viral envelope. The other results such as inhibition of mRNA synthesis and lack of viral nucleo-protein were also observed in the H9N2 virus treated with HXT indicating the antiviral property of HXT.

Lee-Huang et al. (2007), demonstrated the antiviral effects of HXT and Ole in combination [97]. These compounds were found to affect the entry and integration of the virus in to the host. Guiqin Zhao et al. (2009), also investigated anti-HIV properties of Ole and HXT [98]. Molecular docking simulations indicate that Ole and HXT interact with the conserved hydrophobic pocket on the surface of the central trimeric coiled-coil of HIV-gp41 fusion complex. They found that these compounds found to affect the cell to cell transmission, antigen p24 production of HIV-1

5.1.2. Terpenoids of olives as antiviral agents

The lipophilic terpenoids found in many plant oils. The lipophilic compounds non-specifically interact with lipid double layer of the viral envelope, which affects the membrane fluidity and cause membrane lysis [92]. The triterpenoids found in olive oil such as Oleanolic acid (OA) and its isomer Ursolic acid (UA) have shown antiviral activity against HIV and hepatitis virus [101]. These terpenoids with its derivatives were capable of inhibiting HIV-1 protease [102-103]. The inhibition of protease enzyme produces immature and non-infectious virions which blocks the life cycle of HIV and improve the patient's health [104]. It was observed that, when HIV-infected peripheral blood mononuclear cells (PBMC) incubated with different doses of OA, the replication of virus gets significantly reduced as compared to the azidothymidine (AZT) drug. OA has ability to eliminate the HIV infection with therapeutic index (TI) ratio of 12.8 in H9 cell lineage [105].

The antiviral ability of OA and UA were tested against HBV and HCV. These viruses are responsible for the development of hepatocellular carcinoma and having high mortality rate in humans [106-107]. OA has ability to suppress the viral NS5B RNA dependent RNA polymerase (RdRp) enzyme, required for HCV-RNA replication [101]. UA, when incubated with HBV infected protein-transactivated cell lineages, it has decreased the secretion of matrix metalloproteinase-3. UA treated cells were found more sensitive to transforming growth factor (TGF) mediated apoptosis [108]. Because of these properties UA is one of the potential candidates for the developing new class of antiviral compounds, as they block the pathological effects of HBV in cell lineages.

OA containing fraction triggered IL-12 production in treated peritoneal macrophages [109], which is an important cytokine that is responsible for activating the (CD4+Th1) T helper cell 1 population for eliminating intracellular pathogens [110]. The antiviral activity of OA and UA were depending on virus type and host cell and exhibits high levels of selectivity and sensitivity. Both OA and UA have similar mechanism of action and act mainly on multiplication of virus particles.

5.2. Phenolics and terpenoids of olives as anti-inflammatory agents

Inflammation is a kind of protective mechanism of the body against deleterious agents such as allergens, damaged cells, and pathogens, which involve an organized fluid and cellular cascades [111-112]. Various diseases such as cancer, arthritis, neurodegenerative and many pathological infections generate chronic inflammations [113]. The anti-inflammatory properties of phenolics and terpenoids found in olives are reviewed.

5.2.1. 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 [114]. The VOO or mix of rapeseed or sunflower oil supplemented with olive phenolic compounds reduced the postprandial inflammations. The phenolics enriched olive oil was found to reduce the activation of lipopolysaccharide (LPS), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), plasma concentration compared to other vegetable oils such as 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 [115-117] inflammatory agents. Muto et al. (2015), studied the phenolics of olive on Caco-2 cells exposed to the inflammatory effects of LPS [118]. They found that olive oil phenolic extract attenuate IL-8 expression and modulate the acute inflammatory responses in epithelial cells of intestine. In invitro studies with monocyte cell lines, the oleuropein was found to inhibit the tumor necrosis factor alpha (TNF α) induced matrix metalloproteinase 9 (MMP-9) The monocytes and their secretary molecules play a significant role in developing inflammatory diseases [119]. The 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 [119].

Impellizzeri et al. (2011), reported that administration of oleuropein in a mouse model with carrageenan-induced pleurisy, caused a significant reduction of TNF-, IL-1β and NO [120]. Visioli et al. (2002), have shown that the oleuropein increases the production of nitric oxide (NO) in macrophages treated with LPS through nitric oxide synthase enzyme induction, there by increases the functional activity of immune competent cells [121]. The oleuropein was also known to inhibit the other inflammatory agents such as leukotriene B4 production and lipoxygenase activity [122].

The anti-inflammatory mechanism of oleocanthal phenolic compound of olive oil was found very similar to ibuprofen which is a non-steroidal anti-inflammatory drug. Oleocanthal was found to inhibit the inflammatory enzymes such as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) in invitro studies. The inhibition was dose dependent and oleocanthal was found more efficient than ibuprofen in inhibiting these inflammatory enzymes at equimolar concentrations (Beauchamp et al., 2005). The oleocanthal was found to attenuate inflammatory mediators such as inducible iNOS which plays a role in the pathogenesis of joint degenerative disease [123-124].

HXT of olive oil exhibited anti-inflammatory property in an animal model. HXT had reduced the pro-inflammatory cytokines such as TNF α and IL-1β expressions in inflammatory diseases [125]. In In vitro conditions, HXT was found to attenuate the pro-inflammatory agents such as iNOS, COX-2 and TNF α in LPS-challenged human monocytic THP-1 cells [126]. 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 [127].

LPS stimulated J774 murine macrophages cell lines shown an increased m-RNA level of nitric oxide synthase and cyclooxygenase-2 as well as ROS generation. The HXT treatment found to blocks the activation of nuclear factor-κB (NF-κB), signal transducer, transcription-1α (STAT-1α) and interferon regulatory factor-1 (IRF-1). HXT treatment down regulates iNOS and COX-2 gene expression, prevents NF-κB, STAT-1α and IRF-1 activation. Because of these properties HXT may represent a potential non-toxic agent for the control of inflammation [128].

5.2.2. Terpenoids of olives as anti-inflammatory agents

Terpenoids including UA, OA, MA, and Uvaol have been investigated and considered as potent anti-inflammatory agents [129-130]. In the presence of allergens, OA suppresses the eosinophil infiltration, allergic airway inflammation, down-regulation of IL-5, IL-13, and IL-17 [131]. It was found to reduce the degranulation of mast cell, phospholipase A2 type-IIA (sPLA2-IIA), T helper cell-2 (Th2) type cytokines, capillary permeability and type I allergic reactions [132]. OA has inhibited the relinquishment of high mobility group box 1 (HMGB1) and HMGB1-dependent adhesion and migration of the monocytic cell line THP-1. In addition to this it has been found to suppress the expression of HMGB1 receptor thereby preventing HMGB1-dependent pro-inflammatory effect by down regulating nuclear factor (NF) and tumour necrosis factor (TNF) [133]. It was also found to lower the acetic acid induced hyper-

permeability and carboxymethyl cellulose induced leukocyte migration and activation of TNF and NF [134].

The In-vitro/In-vivo inflammatory models were used for assessing anti-inflammatory activity of UA [135]. The pro-inflammatory cytokines such as IL-2, Interferon (IFN) and TNF from Th-2 cell of arthritic balb/c mice were found to be down-regulated after UA treatment [136]. The UA has also been found to deactivate the proinflammatory enzyme like sPLA2 [137]. It was found to down-regulate the expression of E-selectin by inhibiting NF-k translocation into the nucleus [138]. It was also found to down-regulate the gene expression of advanced glycation (AGEs) end products along with another inflammation causing molecules such as iNOS and cyclooxygenase-2 (COX-2) [139]. The neuroprotective effect was shown by UA in LPS stimulated cognitive deficit mice model [140]. UA not only reduces the tumour growth but was also found to improve and increases the survival rate by inhibiting the STAT3, Akt, and IKKa/b mediated signalling pathways [141-142].

The anti-inflammatory effect of MA was first evaluated by Banno et al. (2005), in a potent tumour promoter, 12-O-tetradecanoylphorbol-13- acetate (TPA) [143]. MA was known to regulates inflammation through the inhibition of iNOS and COX-2 expression by inhibiting the activity of NF-κB, a transcription factor which binds to the promoter sequence of these two enzymes [144]. NF-κB is recognized as a stress-regulated transcription factor, which plays a key role in the control of inflammatory responses [145]. In addition to this, MA was able to suppress the activation of activator protein 1 (AP-1) [146] and blocked NF-κB phosphorylation, nuclear translocation, and DNA-binding activity by down regulating receptor of NF-κB expression [144].

Martin et al. (2006) and Allouche et al. (2011), have reported the anti-inflammatory effects of triterpenes of olive oil [147-148]. Asthma reproduces the eosinophilic inflammatory response identified as a key alteration in the pathogenesis of allergic diseases. The anti-inflammatory properties of uvaol involving inhibition of eosinophil infiltration and the IL-5 concentrations. As, IL-5 plays an important role in eosinophil infiltration and in allergic inflammation. Considering that, inhibition of eosinophil accumulation in tissue has been a therapeutically useful strategy in the treatment of allergic diseases [149]. Inhibiting the phosphorylation of mitogen-activated protein kinases (ERK1/2) which can suppress the inflammatory response in an asthma model by reducing inflammation, remodelling, and mucus production in the airways [150]. The allergic challenge provoked changes in lung parenchyma as an increase in the number of collapsed alveoli [151-152]. Uvaol could reduce the growth of myofibroblasts

by down regulating the phosphorylation of ERK1/2 and decrease the perivascular fibrosis [153].

Uvaol in human mononuclear cells mediates a decrease in IL-1β secretion, a cytokine important for expression of the adhesion molecule in eosinophils [147]. The anti-allergic effect of other triterpenes like UA, lupeol and astilbic acid were able to significantly inhibit antigen-induced IL-5 production [154-156]. Uvaol attenuates eosinophilic allergic inflammation, mucus secretion, and alveolar collapse that seems to involve the reduction of IL-5 concentration. Therefore, uvaol represent a new anti-allergic agent with several pharmacological properties.

5.3. Phenolics and terpenoids of olives as Anti-modulatory agents

Immunomodulator is a component which able to regulate the immune system involving both innate and adaptive immune responses. Various bioactive compounds derived from medicinal plants and oils have become a substance for exploration to modulate immune system [157].

5.3.1. Phenolics of olives as anti-modulatory agents

Teressa vezza et al. (2017), studied the anti-inflammatory and immunomodulatory effects of olive leaf extract [158]. The anti-inflammatory effects of olive leaf extract (0.5-25 mg/kg) containing oleuropein was studied in DSS and DNBS mice models of colitis. The immune modulatory effects were studied using the extract (0.1-100 μg/mL) in various cell types and In vivo organ cultures of mucosal explants of healthy donors and Crohn's disease (CD) patients. The extract was found to reduce the expression of pro-inflammatory mediators (IL-1β, TNF-α, and iNOS) in both the models and improved the epithelial barrier integrity restoring expression of ZO-1, MUC-2, and TFF-3. The production of pro-inflammatory mediators (IL-1β, IL-6, IL-8, and TNF-α) were reduced in intestinal mucosal samples from CD patients. They concluded that, the ant-inflammatory activities of oleuropein was related to its immune modulatory properties and capacity to restore the intestinal epithelial barrier. Additionally, the extract could also regulate the activity of cells involved in inflammatory response

5.3.2. Terpenoids of olives anti-modulatory agents

Pentacyclic triterpenes have several pharmacological properties including immunomodulatory. The pentacyclic triterpenes were evaluated for their effects on T-cell proliferation and OA was found to induce T-cell proliferation. While, UA was found to inhibit T-cell proliferation with IC50 values greater than 50 μg/mL and 3.01 μg/mL respectively. OA and UA have similar chemical structure and differ in the position of methyl group at ring E and this has imparted the different functionality. OA stimulates more of NO

and TNF-α production of macrophage cells [159-160]. Whereas, UA showed suppression effects. Compared to OA, UA had shown strong activity in inhibiting T-cell proliferation [161].

The pentacyclic triterpenes are classified as acid and alcohol based on the presence of carboxyl group and methyl at C-17 position. Inhibitory activities of UA against T-cell proliferation showed that UA which has six E rings was found more potent. The position of methyl group on E ring of pentacyclic triterpene is probably conferring the inhibitory properties. Four pentacyclic triterpenes that include OA, MA, erythrodiol and uvaol from olive oil have been evaluated for their immunomodulatory activity on cytokine production of human mononuclear cells. Erythrodiol demonstrated strongest activity in reducing IL-6 production. In case of their activity on TNF-α production, uvaol and OA at the highest concentration of 100 μmol/L have significantly inhibited TNF-α production, while erythrodiol at the similar concentration did not affect these pro-inflammatory cytokines [153]. MA-enriched diet has inhibited the formation of polyps in small intestines of ApcMin/+ mouse model by regulating genes associated with modulatory pathways. The ApcMin/+ is a mouse model having point mutation (multiple intestinal neoplasia) in APC gene. MA was found to suppress chronic inflammation, which has contributed to the development and sustainability of intestinal adenomatous polyps in ApcMin/+ [162]. The MA fraction has demonstrated anti-modulatory activity comparable with that of dexamethasone but, the effect was depending on the specific compound and cytokine.

5.4. Phenolics and terpenoids of olives as anti-thrombotic agents

Thrombosis is the process of forming blood clots (thrombus) inside blood vessel, which prevents the circulation of blood [163]. It is a critical event in the vascular disorders which is responsible for worldwide morbidity and mortality [164]**.** The plant and olive oil secondary metabolites were reported to have antithrombotic effects [165].

5.4.1. Phenolics of olive oil as anti-thrombotic agents

Thrombosis is a cause of death and closely related to a series of cascades including adhesion, aggregation, and secretory functions of activated platelet [166]. Coagulation and fibrinolysis are the two processes of thrombosis. The phenolics such as HXT, oleuropein, aglycone and luteloin were reported as potent inhibitors of platelet aggregation in several studies [167]. The consumption of virgin olive oil containing high phenolic compounds (400 mg/kg) had shown decreased platelet aggregation through inhibition of various procoagulant factors (CH plasminogen activator inhibitor and factor VII) in hyper cholesterol patients [168]. There are various reports on inhibitory effects of tyrosol and oleacein on platelet aggregation and

production of oxylipins was also observed [169]. These studies indicate the anti-platelet aggregation and protective mechanisms of olive oil phenols.

Jose et al. (2009), evaluated antithrombotic effect of hydroxytyrosol acetate (HXT-AC) and compared the results with HXT and acetylsalicylic acid (ASA) [170]. The study was designed to measure the In vitro platelet anti-aggregating activity of HXT-AC in human whole blood and compared the results with that of HXT and ASA. HXT-AC and HXT inhibited platelet aggregation induced by ADP, collagen or arachidonic acid in both whole blood and platelet-rich plasma (PRP). ASA and HXT-AC had a greater effect in whole blood than in PRP when ADP or collagen was used as an inducer. ASA and HXT-AC have shown greater effects in PRP þ leucocytes than in PRP alone. All three compounds inhibited platelet thromboxane B2 and leucocyte 6-keto-prostaglandin F1a (6-keto-PF1a) production. The thromboxane/6-keto-PGF1a inhibition ratio (as an indirect index of the prostanoid equilibrium) was 10·8 (SE 1), 1·0 (SE 0·1) and 3·3 (SE 0·2) for HXT-AC, HXT and ASA respectively.

5.4.2. Terpenoids of olive as Anti-thrombotic agents

MUFA reduce platelet aggregation, a key step in the blood-clotting process [171-172]. Platelet activating factor (PAF) causes platelets to aggregate and is a strong inflammatory lipid mediator essential for the activation of leukocytes and their binding in the endothelial cells [173]. PAF antagonists have been shown to exert a protective action against platelet aggregation and atherosclerotic development [174]. Olive oil terpenoids or particularly a polar lipid fraction is PAF antagonists as compared to other seed oils [175].

The derivatives of the olive terpenoids were found to inhibit human platelet reactivity in experimental studies [176]. Brzosko et al. (2002), conducted in vivo study to check impact of virgin olive oil on thrombosis and found that thrombotic occlusion gets delayed in the aortic loop [177]. They also observed reduction in the fibrinogen concentration with less platelet wall interactions [177]. In another study by Cruz et al. (2000), used saturated fatty acid-enriched diet (SFAED) with 15 % olive oil and showed reduction in platelet activation and vascular thrombogenicity in rabbit [178].

The molecular mechanism by which MA regulate platelet aggregation was determined. The platelet aggregation was induced by both mechanisms such as activation of protein kinase C (PKC) and by increase in cytosolic Ca^{2+}. The effects of MA on PKC activation were studied by analysing the phosphorylation level of myristoylated alanine-rich C kinase substrate (MARCKS), which is a phosphorylation substrate of PKC in human platelets and showed that MA treatment inhibited PKC [179].

Ca^{2+} and PKC induce the granule secretion and activation of glycoprotein PAC- 1 (GPIIb/IIIa) that functions as the final receptor of platelet aggregation. MA downregulate platelet aggregation via its suppression of PKC activation and Ca^{2+} ions. MA also suppresses platelet aggregation by reducing the expressions of P- selectin and PAC- 1 in platelets. The regulation of vasomotion from the controlled production of nitric oxide and endothelin 1 (ET- 1) enables adequate maintenance of vascular homeostasis [180-181]. The effects of MA on the levels of nitric oxide (NO) and ET- 1 were determined to further provide a mechanistic understanding of the MA mediated inhibition of platelet aggregation.

5.5. Phenolics and terpenoids of olives as anti-oxidative agents

Oxidizing agents are compounds with low-molecular-weight, severely damages the cell walls/membranes and releases the internal cellular components to oxidize them, which leads to cell death. The olive oil secondary metabolites showed to have anti-oxidative properties in humans [182]. The anti-oxidative properties of phenolics and terpenoids found in olives are discussed in this section.

5.5.1. Phenolics of olives as anti -oxidative agents

Oleuropein was found to inhibit the copper sulphate mediated oxidation of low-density lipoproteins (LDL) [183-184], reported the oleuropein nitric oxide (NO) scavenging capacity and it was found to increase the iNOS expression in the cell [185]. Visioli et al. (2002), demonstrated the scavenging activity of oleuropein using hypochlorous acid (HOCl) which is an oxidative agent. HOCl mainly produced at the site of inflammation by neutrophil myeloperoxidase and can cause potential damages to the proteins [183]. Coni et al. (2000), in their study found that feeding rabbits with olive oil rich in oleuropein was found to increase resistance of LDL oxidation and lower free, esterified and total cholesterol in plasma [186]. De la Puerta et al. (1999), in their study determined antioxidant and anti-eicosanoid effects of phenolic compounds (oleuropein, tyrosol, hydroxytyrosol and caffeic acid) of polar fractions of olive oil in leukocytes [122]. In another study Visioli et al. (2000), it was found that, the administration of oleuropein into human body was found to decrease the excretion of 8-iso-PGF2α, in dose dependent manner indicate the reduced lipid peroxidation [187].

The HXT of olive oil is a powerful natural antioxidant and 2 times more potent than coenzyme Q10 [188]. The HXT has structural affinity for certain groups of compounds containing amino groups. The simple structure of HXT makes it easy to assimilate by human body. After assimilation it reaches blood plasma within 15-20 minutes and don't create any toxicity problem. This is a good transporter through the human body and it can penetrate the cellular membrane easily. The molecular structural and transporting property of HXT

provides many beneficial aspects in the organism [189]. 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 [190]. The consumption of HXT regulate the concentration of glutathione and provides antioxidant enzymes to adipose tissue (Schaffer et al., 2007). The In vivo study in rat model with induced diabetes mellitus shown that, the HXT consumed rats have shown reduced diabetic vasculopathy and reduced cell proliferation in the vascular wall [191]. This compound was found to controls the intracellular redox state and protects the cell damage by oxidative stress. The anti-oxidant properties of HXT could prevent the various diseases such as cancer, diabetes, inflammation or cardiovascular and neurodegenerative diseases, where reactive oxygen species are produced and damages the tissues [192].

5.5.2. Terpenoids of olives as anti-oxidative agents.

MA also shown antioxidant activity by suppressing the expression of COX-2 and inducible iNOS at protein and mRNA levels [193]. MA significantly inhibits the enhanced production of NO induced by LPS, measured by the nitrite production with an IC50 value. The inhibition of NO production by OA and MA were described by Yang et al. in murine RAW 264.7 cells [194].

MA decreases the production of reactive oxygen species (ROS) in breast cancer cells [148]. Triterpenes can protect cells against H2O2-induced DNA damage in several leukemic 96 and human breast cancer cell lines [148, 195]. Triterpenes decreases the ROS, NO levels and reduces the expression of vascular endothelial growth factor (VEGF) [196].

Apoptosis was induced through the mitochondrial pathway, and this could be due to ROS generated by mitochondrial fatty acid oxidation. The arrest of cell cycle and induction of apoptosis in human pancreatic cancer cell line (Panc-28) by ROS-mediated mitochondrial depolarization and lysosomal membrane permeabilization [194]. OA exhibited inhibitory effects through induction of apoptosis and cell cycle arrest [106, 197].

OA reduces the H2O2 or MMP+ induced cell death and release lactate dehydrogenase (LDH), which leads to alleviated oxidative stress in PC12 cells. It spares glutathione (GSH), raising the activity of superoxide dismutase (SOD) and catalase which reduces the release of IL-6 and TNF-α [198-199]. Another, antioxidant effect of OA was to reduce ROS and proteins related with oxidative stress, showing neuroprotective effects In-vivo [200].

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

In this COVID-19 pandemic it is recommended to control the transmission of SARS-CoV-2 virus 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 these challenges scientists are looking for some alternative options using natural compounds which are safe, effective and economical [201]. The triterpenoids of *Olea europaea* L., can destroy the infectious agents. The triterpenoids found in olive gum oil were used for fumigation [202-203]. Oleanane triterpenes the derivative of oleanolic acid were reported to inhibit the coronavirus, hence these derivatives can be used as an ingredient in preparation of disinfectants [204].

Scientist are continuously researching on various natural biomolecules to find out the effective ones against SARS-CoV-2 using various tools such as molecular dock, computer simulation, In silico absorption, distribution, metabolism and excretion (ADMET). The molecular docking is used to analyse the interaction between ligand and target molecules. In this simulation study binding affinities of ligand to the target molecule and conformational changes were analysed [205-206]. The main protease (Mpro/6LU7) and chymotrypsin like protease ($3CL^{pro}$) parts of COVID-19 are important for replication of the virus and these two are main targets for many potential drugs. These proteases have been structured and deposited in protein data bank (PDB) and is accessible to public for research [207], performed the molecular docking studies with oleuropein of olive oil and Mpro of virus [208]. They have used Autodock 4.2, Pymol version 1.7.4.5 Edu, and Biovia Discovery Studio 4.5 with the Lamarckian Genetic Algorithm. They have analysed the probability of docking of oleuropein with Mpro (6LU7). In the study it was found that, oleuropein forms hydrogen bonds with the 6LU7 amino acids (Tyr54, Leu141, His163, and Glu166) and shown the binding energy of -7.83 kcal/mol for Mpro. Similarly, the oleanolic acid found in *Olea europaea* was analysed for their inhibitory activity on proteases of SARS-CoV-2 using molecular docking [209]. Two proteases 6LU7 and 6Y2E of SARS-CoV-2 were used for this study. The protein-ligand and structure interactions were visualized by PyMOL and Biovia Discovery Studio 20.1.0. The results suggest that oleanolic acid have -7.8 and -8.0 binding affinities (kcal/mol) for 6LU7 and 6Y2E proteases respectively. These affinity results indicate that oleanolic acid is effective in binding with viral proteases and is predicted to inhibit the virus replication. In another study Vardhan and Sahoo (2020), used maslinic acid as a ligand against receptor binding domain (RBD) of SARS-CoV-2, S protein [210]. The

maslinic acid shown -9.3 binding affinity (Kcal/mole) for RBD and was mainly interacting with three different sites of S protein. Maslinic acid shown to affect the binding of viral S protein with ACE2 receptor of target cell, thereby it could inhibit the entry of SARS-CoV-2 into host cell. They have also tested the interaction of maslinic acid with 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 3CLpro protease of SARS-CoV-2. The protease $3CL^{pro}$ is very essential for translation and replication of virus. They found that OA and UA both have binding affinity of -8.9 for $3CL^{pro}$ protease. Therefore oleuropein, oleanolic acid, maslinic acid and ursolic acid were found potential COVID-19 inhibitors. However, further research is necessary to investigate their further medicinal use for control of COVID-19.

7. Conclusion

Olive plant and its products are rich sources of various plant secondary metabolites. The oleuropein, hydroxy tyrosol, oleanolic acid and maslinic acid from olives have been used as an effective antiviral agent and for treating other diseases as well. In molecular docking studies it was found that, the oleuropein, oleanolic acid and maslinic acid have shown highest affinity to Mpro and $3CL^{pro}$ part of SARS-CoV-2 which are essentially required for virus replication and found promising future drugs against COVID-19. Apart from antiviral properties these bioactive compounds found to interfere and modulate various signalling pathways and possess various properties such anti-inflammatory, anti-modulatory, anti-thrombotic and anti-oxidant properties. These compounds were known to control the cytokine storms which is observed during various viral infection and other diseases. The virgin olive oil which is produced from olive fruit by mechanical press is a rich source of all the bioactive compounds. Hence, the olive oil should be a part of our daily diet to harness the potential health benefits and to boost the 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 olive plant was reported as 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 as an ingredient in preparation of hand sanitizers, body lotions /soaps to control the COVID-19. With all these proven scientific evidences of antiviral, potential health benefits and their 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 for proving the efficacy and to provide an affordable and risk-free treatment to COVID-19.

8. Declarations

8.1. Authors' contributions

As a team, all the authors have equally contributed for writing review article titled "Therapeutic Potential of Olive's Bioactive Compounds in COVID-19 Disease Management.

8.2. Conflicts of Interest

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

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