

The olive (*Olea europaea*) and the almond (*Prunus amygdalus*) related phytonutrients, and the associated health-promoting biological effects, a review

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SUMMARY

With the increasing attention to the health promoting activities of the bioactive compounds from some plants, many researchers are focusing on the biological potential and mechanisms of certain cultivated plant species. In this review, we survey the olive and almond based extracts specific phytoconstituents and their associated health promoting effects that have been evaluated in experimental and clinical studies.

Keywords: olive; almond; anti-inflammatory effect; antimicrobial effect; Mediterranean diet

INTRODUCTION

Food safety and security together with the plant-based healthy diet are global challenges with increasing importance that are further substantiated by the growing number of research projects and published studies. Against all the odds, the attention of specialists is becoming steadily shifted towards developing cereals, fruits and vegetables-based high value-added foodstuffs like functional and/or medical foods together with nutraceuticals (Jones and Jew, 2007; Siro et al., 2008). It seems that our ancestral diet has to be reinvented but this time must be combined with personalized facts like genome/epigenome, health status, pathologic condition, etc. (Jew et al., 2008). Present day acclaimed Mediterranean diet efficiently combines versatile sources of macro and micronutrients that are rich in antioxidants and anti-inflammatory bioactive compounds (Dernini et al., 2017). In the following, we will focus on the olive (*Olea europaea*) and the almond (*Prunus amygdalus*) species that are important crop plants grown in the Mediterranean area, and their inclusion in the diet seems to be associated with many health-promoting biological effects mostly attributed to their rich phenolic content (Gorzynik-Debicka et al., 2018).

The olive tree/branch and fruit besides their nutritional importance, also hold deep religious meaning. The olive tree was the symbol of the whole Mediterranean area during ancient times, serving as a source of food and olive oil. Also, along with the oak, another mythical tree, it was well respected and revered in Greece, so that the olive branch was the symbol of peace or victory. The olive was mentioned 7 times in the Quran (زيتون); being considered a blessed fruit in Islam and a gift from heaven. In the Bible, there are also 200 references to olive, and olive tree indicating the worth it holds, and it is mentioned in the Torah as well (אֵיל), symbolizing peace, light, and longevity.

Through the years, people across the world believed in the healing and health-promoting properties of olive and almond, leading to the improvement of cultivation and food processing technologies.

In the past decades, due to the advent of system biology, the assessment of plants and their extracts containing several phytonutrients were gaining growing interest among scientists since they were able to combine multiple high through output methods to define the complexity of plant-derived matrices composition and the generated biological effects in the case of the exposed animal and/or human consumers. The phytonutrients are secondary metabolites of plants that when consumed by animals or humans could exert multiple health-promoting effects (Cicero and Colletti, 2016; Howes and Simmonds, 2014) correlated with antimicrobial (Pisoschi et al., 2018), anti-inflammatory (Jurenka, 2009), anti-cancer (Sadeghi et al., 2018; Baraya et al., 2017; Vigh et al., 2016), anti-oxidant (Shaygannia et al., 2016; Baptista et al., 2018), anti-stress (Mishra et al., 2000), and immunomodulatory (Sultan et al., 2014) properties.

It is important to notice that among the phytonutrients the polyphenols do represent a very important and well-studied category (Joseph et al., 2016). These plant derived phenolic compounds are critical for the human diet as they generate multiple beneficial health-promoting effects (Somerville et al., 2017). From simple phenolic molecules to complex macromolecules, increasing body of evidence suggests that consumption of plenty of phenolic compounds may lower the risk of pathologies because of their antioxidant, anti-glycemic, immunomodulatory, anti-inflammatory and microbiota maintaining activities (Yahfoufi et al., 2018; Guasch-Ferré et al., 2017; Kim et al., 2016; Duda-Chodak et al., 2015). When added to foods, antioxidants control rancidity development, retard the formation of toxic oxidation products, maintain nutritional quality, and extend the shelf-life of products (Shahidi et al., 2015).

In the current paper, we will review the most important published data regarding the olive and almond species-related phytonutrients and the associated health claims.

MATERIALS AND METHODS

The current literature, analyzing the beneficial effects of *Olea europaea* and *Prunus amygdalus* has been contextualized in this review. The search was conducted using digital libraries such as Pubmed, Science direct and Google scholar. The search examined studies published until June 2020, utilizing the words: *Olea europaea*, extra-virgin olive oil, lignans, biological activities of extra-virgin olive oil, *Olea* by-products, *Prunus amygdalus*, *Prunus amygdalus* biological effects and *Prunus amygdalus* health activities. At about a thousand papers were included into the current study.

RESULTS AND DISCUSSION

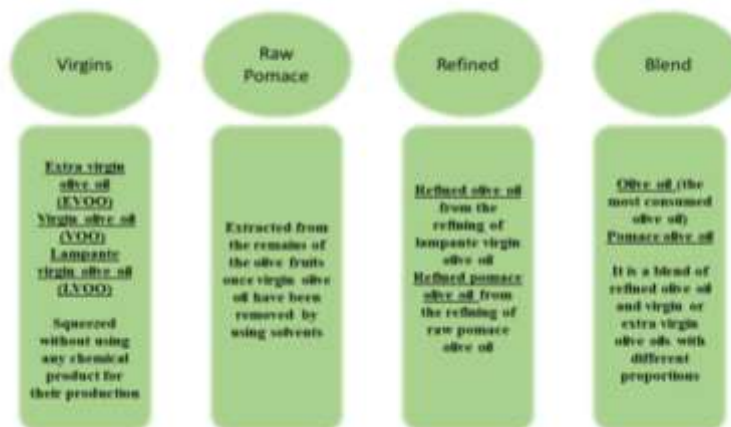
Olive (*Olea europaea*)

General aspects. In present days, the economic importance of olive is increasing, however, the unfortunate appearance of *Xylella fastidiosa*, an aerobic invasive bacteria, has affected thousands of hectares of olive plantations across Southern European countries threatening the EU's olive industry. The pathogenic bacteria is spread by plant-sucking insects such as the meadow froghopper (*Philaenus spumarius*), and the induced bacterial leaf scorch type of diseases are affecting not only the olive but the oleander and almond tree species too (Saponari et al., 2013). The production of olive oil is one of the most profitable agribusiness in the Mediterranean area (Baniyas et al., 2017). From the antiquity, the olive fruit, oil and leaves have alimentary, healing and ritualistic uses (Talhaoui et al., 2018), and they are an inherent part of Mediterranean culture and diet (Navarro et al., 1994). The health-promoting

properties of olive oil have been acknowledged for centuries, and its popularity is increasing steadily across the world. Actually, the Mediterranean people were using olive oil like nourishing food, health-giving drug, and cosmetics for centuries, and it became also the topic of much scientific attention in the past few decades, confirming its potential for future applications (Ghanbari et al., 2012). There are 4 different types of olive oils according to European law. *Figure 1* summarizes these types of olive oils and indicates some of the differences between them. The virgin, raw pomace, refined and blended types of olive oils are all available on the markets across the World.

The virgin oils are the most natural ones obtained only by mechanical processing, and based on their quality, they could be divided into extra virgin, virgin and lampante olive oils categories. The first two olive oils are suitable for human consumption, while the last one is of an unpleasant taste and smell that is not suitable for direct consumption, so it is necessary to refine it. The remains of the olive fruits, in the mills once producing virgin olive oil, could be removed, and they are called raw pomace representing the second product type of olive processing. The pomace contained olive oil can further extracted by solvents, and is named raw pomace olive oil that falls into the third, the so-called refined olive product category together with the lampante oil. Both the lampante and the raw pomace oils are not marketable, and they must be processed in refineries because of their unpleasant taste and smell. The resulted refined olive oils are colorless, tasteless and odorless, albeit they cannot be sold directly to the consumer. The fourth olive product type is called blended olive oil, and products falling into this category are of lower quality yet widely marketed around the World. Such a blended olive oil is a mixture of refined olive oil and virgin or extra virgin olive oils. The proportion, which does not usually appear on the label, is between 10 and 15% of virgin oil.

Figure 1. Classification of different types of olive oil according to the European Union law



One should also notice that besides the above presented EU law based definition of olive products, there could be many more types of classifications or subtypes evoked mainly attributed to explanations related to cultural thoughts. Therefore within the extra virgin olive oil could be distinguished subcategories like (1) cold pressed, being produced by pressing at a temperature below 27 °C; (2) cold extracted, with the extraction process taking place at a temperature below 27 °C; (3) integrated production, produced following the rules of a given regulatory board; (4) ecological (Bio), meaning that the product was obtained following the rules of specific regulatory board(s); (5) origin denomination, being a promotional label and awarded by a specific regulatory board. It therefore seems likely that telling the difference between the olive oil types solely based on processing technology could be relatively problematical, and with the large scale product adulteration, there is an urgent need to redefine the traceability and quality parameters. Luckily, recent advances in analytical chemistry can overcome the aforementioned problems by applying near-infrared spectroscopy and chemometric techniques (Kesen, 2019; Vanstone et al., 2018), but attention should be paid to the careful assessment of the olive products specific phytonutrient profiles too.

Olive-specific phytonutrients. Olive and olive oil have been of major importance in the Mediterranean diet for centuries, it has been present in almost all dishes. Therefore, a huge number of studies have been conducted to highlight the phytonutrient profile of different olive oils and leaf extracts. Many active compounds have been identified, isolated and reported so far in different varieties of olive products (Miho et al., 2018). Various environmental factors like soil and climatic conditions, harvesting time, and processing technologies can significantly modify the composition of oil constituents (Inglese et al., 2010). Studies are also indicating that the cultivated olive varieties can greatly influence the type and amount of the obtained yields. The Manzanillo, Ascolano, and Kalamata olive varieties with an oil content of less than 12% are suitable for table olive type of products, while the varieties having increased oil content like Verdial, Gemlik, Hojiblanca, Arauco, and Nychati are preferably used to obtain oils (Ryan and Robards, 1998). When it comes about the chemical composition, half of the weight of olive leaves and fruits is due to their water content, while the major carbohydrates found in olives are the cellulose and sugar. Minerals like copper, manganese, magnesium, potassium, and have been detected in both olive leaf and fruits (Hernández et al., 2010). It was also observed that during fruit maturation, the carbohydrate content decreases and concomitantly, the oil content will raise.

The most important active compounds are monounsaturated fatty acids (MUFA), and the presence of various minor components including α -tocopherol, squalene and polyphenols (namely derivatives of oleuropein and ligstroside), (Boskou, 2006; Stark et al., 2002). Stearic acid (C18:0), palmitic acid (C16:0), palmitoleic acid (C16:1), oleic acid (C18:1), and

linolenic acid (C18:3) are the major fatty acids present in olives. Gadoleic (C20:1), myristic (C14:0), and margaric (C17:0) acids are present in small amounts, while the traces of eicosenoic and 11-cis-vaccenic acids have also been detected (Ghanbari et al., 2012). It is also interesting that further chemical analysis of the olive oils, besides the triacylglycerols (TAGs), revealed additional components like organic acids, sterols, phospholipids, pigments (carotenoids, chlorophylls), and flavor influencing volatiles and phenols, together with odor determinants like alcohols, ketones, esters, and hydrocarbons. These groups of compounds play a significant role in the quality and purity analyses, in the evaluation of authentication and lately in VOO (Virgin Olive Oil) traceability and health (Conte, et al., 2019).

The olive leaves have also attributed important beneficial effects that are very much related to their polyphenol content that seems to vary substantially among samples, depending on the used raw materials and extraction manufacturing methodology (Medina et al., 2019). *Table 1* shows some of the most important bioactive compounds identified and reported for extra virgin olive oils (EVOO) and olive leaf extracts (Romani et al., 2019; Kiritsakis et al., 2010). It should be noticed that the in particular phenolics like hydroxytyrosol (HT), oleuropein (OLE), oleocanthal (OLC), and lignans found in EVOO, olive oil by-products and leaves are of major interest (Romani et al., 2019).

Table 1. Extra Virgin Olive Oil (EVOO) minor polar components (Romani et al., 2019; Kiritsakis et al., 2010)

Secoiridoids	(a)	Oleuropein aglycone
	(b)	Deacetoxy oleuropein
	(c)	Oleocanthal and oleacin
	(d)	Ligstroside aglycone
Phenolics	(a)	Hydroxytyrosol
	(b)	Tyrosol
	(c)	Hydroxytyrosol glycole
Phenolic acids	(a)	Gallic acid
	(b)	Protocatechuic acid
	(c)	p-hydroxybenzoic acid
	(d)	vanillic acid
	(e)	Caffeic acid
	(f)	syringic acid
	(g)	p- and o- coumaric acid
	(h)	Ferulic acid
	(i)	Cinnamic acid
Flavonoids	(a)	Luteolin
	(b)	Apigenin
Lignans	(a)	(+) Pinoresinol
	(b)	(+) Acetoxypinoresinol

The data were taken from Romani et al., 2019; Kiritsakis et al., 2010.



Olive derived bioactive compounds associated health effects

Olive oils and leaf extracts generated biological effects at the level of different model species (bacteria, fungi, laboratory animals) and humans are intensively studied. In the following, we will review some of the most relevant biological effects found to be associated with polyphenol content that varies substantially among the olive oil types. Usually, the polyphenol content of virgin oil has the highest value at about 150–400 mg kg⁻¹, the raw pomace oil shows 10–30 mg kg⁻¹, blended olive oils display 10–100 mg kg⁻¹ and the refined olive oils features 0–5 mg kg⁻¹ contents. Despite the emphasized polyphenol content, olive oils and leaf extracts should be seen as complex matrices that could generate multiple additives and/or synergistic health effects.

Anti-oxidant effects. The total polyphenolic fraction of an extra virgin olive oil (EVOO) was assessed on several human cell lines and found that the total polyphenol extract improved the redox profile of all cell lines, by inducing elevated glutathione levels (Kouka et al., 2018). Interestingly, some human studies indicated that olive polyphenols decreased the oxidized-LDL levels in plasma, and positively affected several biomarkers of oxidative damage (Raederstorff, 2009). These effects were attributed to the hydroxytyrosol that is considered the most abundant olive polyphenol. Moreover, experimental observations are suggesting that olive oil together with polyphenols in the Mediterranean diet, could induce health improvement in the case of the non-alcoholic fatty liver disease - NAFLD patients (Abenavoli et al., 2019). In a study carried out on *C. elegans*, it was demonstrated that the ROS level was reduced, while the expression of hsp-16.2 was increased to protect the organism against the increasing ROS (Luo et al., 2019). The level of malondialdehyde (MDA) also decreased sharply. The activities of inner antioxidant enzymes, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-PX) were potentiated showing that the olive specific *in vivo* and *in vitro* antioxidant activities are significant properties. It was also demonstrated that the olive oil and leaf extract could protect against fluoxetine-induced liver injury in rats through the decreasing of oxidative stress, inflammation, apoptosis and liver lipid peroxidation, and by ameliorating the liver glutathione, superoxide dismutase, catalase and glutathione peroxidase (Elgebaly et al., 2018).

Antimicrobial effects. Olive oil is a leading edible oil worldwide due to its positive effects on the inhibition of foodborne pathogens, stimulation of growth of beneficial microorganisms as well as altering gut microbiota besides the antioxidant activity (Gavahian et al., 2019). Moreover, in a study done by Ghomari et al., (2019) the ethanol olive leaf extract proved to have antibacterial activities against five pathogenic bacteria *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Listeria monocytogenes*.

Olive oil has an antibacterial effect against *Helicobacter pylori* that was linked to the majority of peptic ulcers and to some types of gastric cancer, together with the resistance of the microorganism to antibiotic treatments (Romero et al., 2007). A very high bactericidal activity of olive oil extracts against several strains of *H. pylori* was also reported in *in vitro* conditions (Romero et al., 2007; Castro et al., 2012). Another study by Gilling et al. (2019) has proven that the olive extract had antimicrobial activity against *Escherichia coli* after an exposure time of 30 minutes. Furthermore, a cellulose-based antimicrobial hydrogel was prepared from seed and husk cellulosic fibers of olive industry residues by a load of silver nanoparticles onto grafted acrylamide monomer cellulosic fibers (Dacroy et al., 2018). The obtained hydrogel exhibited efficient antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. Another olive powder was found to inhibit the growth of *Bacillus cereus* a facultative anaerobic spore-forming bacterium implicated in foodborne illnesses (Marco et al., 2011; Ferrer et al., 2009). The *in vitro* antimicrobial effect of olive leaf extract was also shown in the case of *E. coli* and *C. albicans* (Markin et al., 2003), together with *C. dubliniensis* (Zorić et al., 2016).

Anti-diabetic effects. As a general remark, one can say that the nutritional intake of olive oil has been associated with the prevention and management of many chronic diseases including T2D. The olive oil phytonutrients like monounsaturated fatty acids, hydroxytyrosol and oleuropein have been suggested to inhibit inflammation, to lower blood glucose and reduce carbohydrate absorption, by increasing insulin sensitivity and modulating the expression of relevant genes (Alkhatib et al., 2018). In another study, the olive leaves extract was shown to overcome the diabetes-induced adverse effects on testicular tissues presumably by normalizing testicular steroidogenesis (Soliman et al., 2019). Recent observations are indicating that the intake of oleanolic acid (OA)-enriched olive oil reduces the risk of developing diabetes in prediabetic patients (Santos-Lozano et al., 2019). In a study to survey the possible links between olive oil intake and the incidence of T2D, it was observed that increased olive oil intake is associated with a modestly lower risk of T2D in USA women (Guasch-Ferré et al., 2015).

Anti-inflammatory effects. The olive oils exert anti-inflammatory effects on the skin, and promote wound healing of the skin (Lin et al., 2017). Extra virgin olive oil can be used for the prevention and treatment of immune-mediated inflammatory diseases (Santangelo et al., 2018). Other evidence are indicating that the extra virgin olive oil has anti-inflammatory and cardio-protective roles in the prevention of atherosclerosis-related conditions (Wongwarawipat et al., 2018). Moreover, studies on inflammatory and cancer cell models have demonstrated that olive leaf polyphenols have anti-inflammatory and anti-cancer effects by protecting against DNA damage initiated by free radicals. The NF-κB inflammatory response and

the oxidative stress response (Boss et al., 2016) pathways were shown to be the most affected. Furthermore, other experiments were suggesting that the reduced TNF α secretion in polymorphonuclear cultured cells in response to olive leaf extract treatment indicates an anti-inflammatory effect, and the oleuropein is the major extract bioactive compound responsible for this effect (Qabaha et al., 2018).

Interestingly in the virgin olive oil it was discovered the oleocanthal a phenolic compound that possesses similar anti-inflammatory properties to ibuprofen. This pharmacological similarity leads to a few studies confirming the oleocanthal anti-inflammatory and potential therapeutic actions (Lucas et al., 2011).

Hydroxytyrosol (3,4-dihydroxyphenyl-ethanol), is an important phenol derived from olive oil featuring anti-inflammatory and anti-oxidant activities *in vitro* which may explain the chronic-degenerative diseases preventive properties of olive oil. The hydroxytyrosol reduced efficiently some inflammatory markers like COX2, TNF- α and oxidative stress *in vivo* on a mouse model of systemic inflammation (Fuccelli et al., 2018). It has been also demonstrated that olive oil with a natural content of phenolic compounds attenuates adipose tissue hypertrophy and inflammation and exerts antiatherosclerotic effects in mice (Luque-Sierra et al., 2018).

Recently the anti-inflammatory effects of a phenolic fraction, from olive leaves and fruits, have been tested for a potential application in gut inflammation based on the *in vitro* irritable bowel disease animal models (Larussa et al., 2019). The performed studies looked promising in the case of Crohn's disease and ulcerative colitis.

Furthermore, an olive leaf extract has been shown to suppress placental inflammation and inhibit NLRP3 inflammasome activation and may be used as a supplement for the treatment and prevention of human placenta-specific inflammatory diseases (Kaneko et al., 2019).

Anti neuro-inflammatory effects. The olive oil phenols can generate neuroprotective effects against cerebral ischemia, spinal cord injury, Huntington's disease, Alzheimer's diseases, multiple sclerosis, Parkinson's disease, aging, and peripheral neuropathy (Khalatbary, 2013). In another experimental setup, the results showed that the virgin olive oil derived polyphenolic extract prevented microglia cell death, and decreased the lipopolysaccharide (LPS)-induced activation of toll-like receptor 4 (TLR4)/NOD-like receptor pyrin domain-containing-3 (NLRP3) signaling cascade (Taticchi et al., 2019). The levels of TLR4 and NF- κ B were reduced, similar to the NLRP3 inflammasome and interleukin-1 β (IL-1 β), Cyclooxygenase-2 (COX-2) isoenzyme and ionized calcium binding adaptor molecule 1 (Iba-1) inflammatory mediator. It seems therefore likely that the virgin olive oil polyphenolic extract pretreatment significantly reduced the mRNA expression of inflammatory mediators along the TLR4/NLRP3 axis and suppressed the cytokine secretion. All these results

suggest that olive oil polyphenols could exerts neuroinflammatory activity on brain cells.

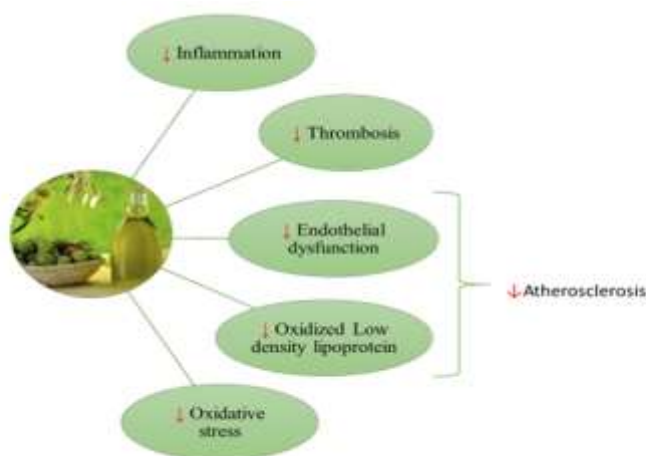
Interestingly the oleuropein as a phenolic compound from olive leaf, suppressed the LPS-induced increase in pro-inflammatory mediators, such as nitric oxide, and pro-inflammatory cytokines, by the inhibition of ERK/p38/NF- κ B pathway and reactive oxygen species (ROS) generation (Park et al., 2017). The oleuropein it suppressed also the LPS-induced excessive mitochondrial fission, which regulates mitochondrial ROS generation, and the pro-inflammatory response by diminishing *Drp1* dephosphorylation. All these data are suggesting that oleuropein could be implicated in the prevention of microglial inflammation-mediated neurodegenerative disorders.

Cardiovascular protective effects. The fact that the Mediterranean diet has cardioprotective properties that were first mentioned by Keys A. et al., 1986 for the first time and further investigated by many others. In the last few decades, numerous epidemiological studies and meta-analyses, as well as intervention trials, confirmed this observation, pointing out the protective role of the Mediterranean diet on primary and secondary cardiovascular diseases (Figure 2) (Minelli and Montinari, 2019; Romani et al., 2019).

The reduction of blood pressure could be considered another protective effect related to the consumption of extra virgin oil is (Davis et al., 2017). When spontaneously hypertensive rats were provided extra virgin olive oil enriched in bioactive compounds from olive fruits and leaves, there were observed reduced plasma levels of Angiotensin II and total cholesterol, and the urinary levels of endothelin-1 and oxidative stress biomarkers, while pro-inflammatory cytokines were unaffected (Vazquez et al., 2019). Such experiments are suggesting that the supplementation of extra virgin olive oil with olive leaf extract could be an effective anti-hypertensive treatment instrument for reducing blood pressure and cholesterol levels. Other elegant experiment on isolated diabetic rat hearts demonstrated the cardioprotective effect of olive oil against ischemia reperfusion-induced cardiac arrhythmia (Bukhari et al., 2020).

Among the olive specific bioactive compounds the hydroxytyrosol implication in cardiovascular protection is relatively well documented. It exerts antioxidant, anti-inflammatory, anti-platelet aggregation and anti-atherogenic activities in *in vitro* and animal models (Tejada et al., 2017). Hydroxytyrosol greatly ameliorates endothelial dysfunction, decreases oxidative stress, and is neuro- and cardio-protective (Bertelli et al., 2020). In another experiment where the hypoxic myocardial cell line H9c2 cells were treated with live leaf extract, it was observed that the expression of GRP78 and CHOP genes got reduced in relation to endoplasmic reticulum stress, which could be a new target for the prevention and treatment of cardiovascular diseases (Wu et al., 2018).

Figure 2. EVOO and its cardioprotective action on the cardiovascular system according to the European Food Safety Authority claims



It is important to mention that other *in vitro* and *in vivo* studies are describing the phenolic compounds, such as hydroxytyrosol, tyrosol, and their secoiridoid derivatives to reduce the expression of adhesion molecules and consequent migration of immune cells. Such phytonutrients can act upon signaling pathways and modify the transcription profile (like blocking the NF- κ B), inhibit the action of enzymes responsible for the production of eicosanoids, and consequently, decrease the circulating levels of inflammatory markers (Souza et al., 2017).

In a randomized, double-blind, controlled, crossover trial to investigate the effects of a phenolic-rich olive leaf extract (OLE) on blood pressure and a number of associated vascular and metabolic features, there were observed many positive effects (Lockyer et al., 2017). Blood pressure, total cholesterol, LDL cholesterol and triglycerides together with interleukin-8 were also reduced by OLE as compared to control, whilst other markers of inflammation, vascular function and glucose metabolism were not affected. Having seen some of the most relevant studies indicating that the daily olive oil intake modulates beneficially the inflammatory markers including cytokines, it is advisable considering the inclusion of olive products in the diet of individuals at risk for cardiovascular diseases.

Anti-tumor/cancer effects. The oleuropein found in olive leaf, showed strong anti-breast cancer properties by exhibiting specific cytotoxicity against breast cancer cells that underwent apoptosis via the mitochondrial pathway (Elamin et al., 2013). The oleuropein was also blocking progression through cell cycle at S phase and up-regulated the cyclin-dependent inhibitor p21. Furthermore, oleuropein inhibited the anti-apoptosis and pro-proliferation protein NF- κ B and its main oncogenic target cyclin D1. Moreover, the oleuropein was tested on human melanoma cells, and stimulated apoptosis, affected cell proliferation and induced the downregulation of the pAKT/pS6 pathway (Ruzzolini

et al., 2018). Moreover, in a study done by Mohsen Gavahian et al., 2019, the oral intake of extra virgin olive oil proved to be beneficial in both preventing cancer and type 2 diabetes.

It has been suggested that the olive oil and leaf extracts could modulate the gut microbiota, with a possible role in cancer prevention, while the produced active metabolites may exert chemopreventive action (Borzi et al., 2018).

Immunomodulatory effect. Certain experimental observations are indicating that olive leaf extracts could behave like modulators of the human immune response (Magrone et al., 2018). When the peripheral blood mononuclear cells from healthy donors were cultured in the presence of olive leaf extracts, the IFN- γ production increased together with the absolute numbers of CD8+ and NK cells that could indicate a reinforcement of the anti-tumor activity. Similarly the NO levels raised that could generate some cardioprotective vasodilation activity. Moreover, the olive leaf extract could generate an equilibrium between T regulatory cells and Th17 cells as evidenced by unmodified levels of interleukin (IL)-IL-10 and IL-17, respectively. All these observations are suggesting that the olive leaf extract could also be used for the treatment of chronic inflammatory diseases, reducing the negative outcome of cardiovascular events.

More on olive leaf extracts composition and the attributed biological effects. Olive leaves are an important source of bioactive compounds in comparison to olive oil and fruit (Brahmi et al., 2012). Among the phenolic compounds present in olive leaves, the essential ones are the hydroxytyrosol, tyrosol, catechin, caffeic acid, rutin and oleuropein (O. Benavente-García, et al., 2000). It was also mentioned in a study done by da Silva et al. (2019) that the olive leaves extract had photoprotective, anti-mutagenic and antioxidant effects. Several studies describing the beneficial effects of olive leaf extracts were already mentioned in the previous paragraphs, but there are

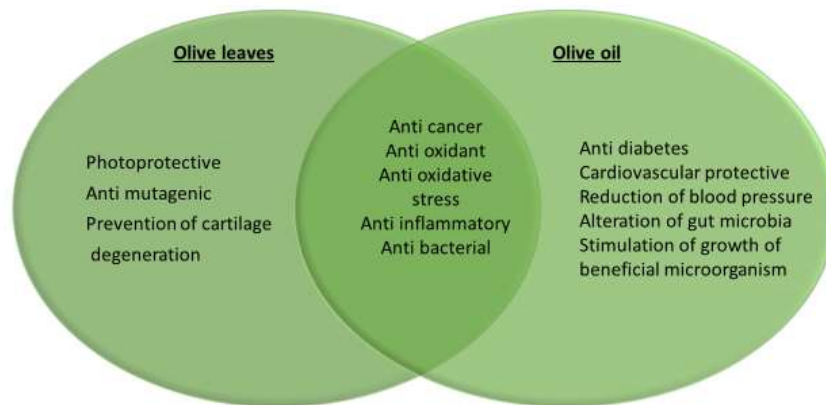
many more relevant issues that should be further assessed in order to clarify the cause –effect type of correlations (Cittan and Celik, 2018). These are the following:

- Counteracting cell proliferation and cyst growth in an *in vitro* model of autosomal dominant polycystic kidney disease (Toteda et al., 2018);
- The oxidative damage protecting effect on human erythrocytes (Lins et al., 2018);
- Counteracting epithelial to mesenchymal transition through the inhibition of TGFβ1 signaling (Lupinacci et al., 2018);
- Preventing cartilage degeneration in osteoarthritis of STR/ort mice (Takuma et al., 2018);
- Reducing induced hepatotoxicity by attenuating oxidative stress, inflammation and apoptosis (Elgebaly et al., 2018);

- Modulating the human immune response (Magrone et al., 2018).

The olive oils and leaf extracts relevance for health-promoting and preventive or therapeutic nutrition is increasing, and due to the advent of molecular cell biology more and more molecular mechanisms are getting revealed shedding light on the cause - effect type of correlations. It is also interesting that the olive leaf extracts associated beneficial potential is of a large spectra. It has been observed that the metabolic and vascular protective effects of olive leaf extract in diet-induced obesity in mice are related to the amelioration of gut microbiota dysbiosis and to its immunomodulatory properties (Veza et al., 2019). The complexity of the olive associated health-promoting effects are shown on *Figure 3*.

Figure 3. Summary of the biological and health effects of Olive oil and Olive leaves



Almond (*Prunus amygdalus*)

General aspects. The almond (*Prunus dulcis* or *Prunus amygdalus*) is a species of tree native to Iran but is also widely cultivated in the Mediterranean and some Asian regions, being one of the earliest domesticated trees in the history of mankind. The almond is also the name of the edible seed of this tree. The fruit of the almond is not a nut but a drupe, consisting of an outer hull and a hard shell with the seed. Interestingly, many parts of the almond fruits can be used for different purposes, and recent studies are yielding many papers describing challenging observations. Commercially, almonds can be found in the shell, shelled, and peeled. The peeled almonds (removal of seed coat or skin) are used as a raw material for foodstuff manufacturing. The almond nuts are rich in healthy fats, proteins, minerals and vitamins like calcium, copper, iron, magnesium, phosphorus, potassium, zinc, manganese, thiamine, riboflavin, niacin, and vitamin E (Kalita et al., 2018). The blanching of almond does yield valuable byproducts

like the almond skin that possess antioxidant activities both *in vitro* and *in vivo*, while they are rich in fiber and phenols, having the potential for valorisation in functional foods, nutraceuticals, and/or food additives (Esfahlan et al., 2010). The almond nuts are very widely used in Mediterranean diet (Casas-Agustench et al., 2011), and in baking and as a flavoring agent in Middle East and South Asia cuisine. In addition to its nutritional values, several studies are reported the almond nuts and skins having health-promoting values that may be supportive towards preventing and/or treating of some pathological conditions. It seems worthwhile to name some of the almonds nuts specific pharmacological properties such as the anti-stress (Bansal et al., 2009), anti-oxidant (Pinelo et al., 2004), immunostimulant (Puri et al., 2000), lipid lowering (Spiller et al., 1998), laxative (Sharma et al., 1981), anti-inflammatory, and anticancer effects (Kumar et al., 2020). The almond nut is also highly beneficial in preserving the metabiota of the colon (Holscher et al., 2018; Liu et al., 2016). In the following some of the



most relevant almond-specific health-related effects are presented (see also *Figure 4*). Despite all the beneficial effects of almond, one should not underestimate its allergic triggering effects too (Zhang and Jin, 2020).

Cardiovascular effects. Some experiments with almond nuts showed efficiency in treating cardiovascular conditions by not only reducing LDL-C (low-density lipoprotein-cholesterol) levels, but also maintaining HDL-C (high-density lipoprotein-cholesterol) levels that were more likely to be a characteristic of the South Asians population (Kalita et al., 2018). Other observations carried out on experimentally induced hyperlipidemic mice fed with almonds, clearly indicated major positive changes in relation to the serum lipid profile so that the levels of total cholesterol, triacylglycerol, low-density lipoprotein cholesterol and very LDL-C were decreasing (Tarmoos et al., 2019). Other human studies were also indicating that the dietary almond intake reduced substantially the total cholesterol, LDL cholesterol, body weight, HDL cholesterol, and apolipoprotein B, together with the fasting blood glucose, diastolic blood pressure, and body mass index (Lee-Bravatti et al., 2019). In the same experiments there were also observed that the triglyceride, systolic blood pressure, apolipoprotein A1, high-sensitivity C-reactive protein values were not influenced by the almond intake. Moreover, it has been demonstrated that the typical Korean diets featuring almond like snack could assist slightly overweight/obese individuals to improve nutritional status and reduce the risk for cardiovascular diseases (Jung et al., 2017). Interestingly, the U.S. Food and Drug Administration accepted the health claim that 42.5 g per day of nut intake may reduce the risk of cardiovascular disease, and as such is a cost-effective method to try to prevent cardiovascular disease in the short and long term, too (Wang et al., 2020).

Anti-inflammatory effects. In Persian medicine the almond, hazelnut and walnut were acknowledged for their brain-protective activity that today has been proven to interfere with several mechanisms in Alzheimer disease pathogenesis such as amyloidogenesis, tau phosphorylation, oxidative stress and cholinergic pathways (Gorji et al., 2018). Moreover, some not neurodegenerative features of almond intake has also been seen including cholesterol lowering and anti-inflammatory properties, as well as an effect on neurogenesis. In a study that proposed to investigate the mechanism of the anti-inflammatory and anti-obesity effects of almond skin polyphenol extract (ASP) in differentiated 3T3-L1 adipocytes, it was observed that the AMP-activated protein kinase (AMPK) was phosphorylated that increased the activity of adipose triglyceride lipase and hormone-sensitive lipase, including the inhibition of adipogenesis-related transcription factors. In addition, ASP inhibited the TNF- α -induced inflammatory response (Huang et al., 2017).

Antidiabetic effects. It has also been proven that the *Prunus amygdalus* extract down-regulated hyperglycemia, hyperlipidemia and oxidative stress in diabetic rats, through biochemical essays showing the

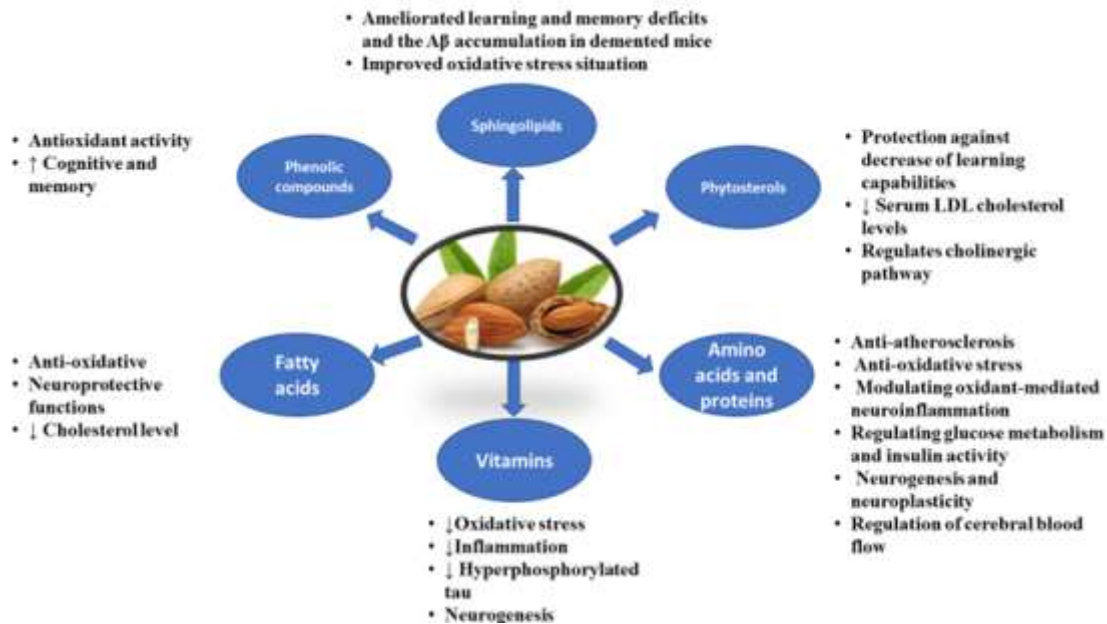
inhibition of metabolic enzymes or amelioration of oxidative stress (Kumar et al., 2020). In a complex study that intended to compare the effect of peanuts and almonds, incorporated into a low-carbon-diet, on cardio-metabolic and inflammatory aspects in patients with T2DM, there been observed similar effects with respect to improving fasting and postprandial blood glucose level among patients, but the body mass index, the blood lipid profile or interleukin-6 (IL-6) values did not increase (Hou et al., 2018). Other experiments revealed on Asian Indian T2D patients that the incorporation of almonds in a well-balanced healthy diet would induce multiple beneficial effects on glycemic and cardiovascular disease risk factors (Gulati et al., 2017). Significant improvements were observed for parameters like waist circumference, waist-to-height ratio, total cholesterol, serum triglycerides, low-density lipoprotein cholesterol, glycosylated hemoglobin and CRP.

Antimicrobial effects. A study done by Musarra-Pizzo et al., (2019) proved that the phenolic compounds in the almond extract possessed antibacterial activities against different strains of *Staphylococcus aureus*. The effect of phenolic compounds on bacterial cells involved damage of the cellular membrane, binding of the cell wall, enzyme inactivation, DNA damage. In the same study, the anti-viral activity of the phenolic compounds found in almond was also proven against *Herpes simplex virus-1* (HSV-1). The authors suggested that it might be due to the effect of the almond extract on HSV gene expression at early or late stages of viral replication.

The almond peel/skin related effects. The peels and hulls of the nuts were also chemically and biologically analyzed (Qureshi et al., 2019). The antibacterial and antiviral effects of a mix of polyphenols present in natural almond skin were observed against the *Staphylococcus aureus* and HSV-1, (Musarra-Pizzo et al., 2019). It was proposed that the natural products from almond skin extracts are an extraordinary source of antiviral agents and provide a novel treatment against HSV-1 infections (Bisignano et al., 2017). Others have investigated the effect of almond skin extracts on the production of pro-inflammatory and anti-inflammatory cytokines in human peripheral blood mononuclear cells, either infected or not by HSV-2 (Arena et al., 2015). Again, the antiviral effect has been demonstrated so that the production of inflammatory IL-17 was inhibited, while the releasing of anti-inflammatory IFN- α , IFN- γ and IL-4 in cellular supernatants could be detected. The neuroprotective effect of almond skin was demonstrated using a spinal cord injury mouse model that featured severe injury with edema, tissue damage, production of inflammatory mediators and apoptosis by reducing several inflammatory parameters like neutrophil infiltration, NF- κ B activation, iNOS expression and apoptosis (Mandalari et al., 2011).

Furthermore, the almond peel extracts were shown to have some renal chemo-protective potential by modulating multiple molecular pathways (Pandey et al., 2017), and had beneficial effects on serum lipid profile in male rats (Safarian et al., 2016).

Figure 4. Bioactive compounds of almond and the mechanisms involved in its biological effect



CONCLUSIONS

The plant-based diet's popularity seems to increase in developed countries. There have been invoked plenty of health claims in the context of plant-based diets, though they do carry some risk of inadequate protein, vitamin, and mineral intake that can be readily overcome by the proper balancing of macro- and micronutrients together with the necessary phytonutrients. Going back to prehistorical times, the hominid diet was substantially changed with the emergence of African savannas in the Pleistocene, which increased the abundance of high-quality plant (nuts and tubers) and animal foods (Kaplan et al., 2000). Next the adaptation of bipedality freed the hands for tool use, which increased the efficiency of gathering and hunting that ultimately resulted into a plant-meat combined diet. Currently our nutrition appears not to be

properly balanced in the context of our lifestyle, and the consequence is visible looking at the burden of the chronic diseases. It seems logic that we must undertake effective actions to adjust our nutrition and reduce the incidence of chronic diseases with nutritional implications. In this respect turning our attention towards plants and becoming focused on bioactive phytonutrients holds the promise of a health-promoting nutrition.

Our paper is focused on the olive and almond, two cultivated plant species with benefic effects. We surveyed many studies that emphasized the role of these two plants in generating health-promoting activities. However, it should be noted, that the functional outcomes of the natural compounds of the olive and the almond would vary on a large scale. Both plants displayed anti-inflammatory, antimicrobial, anti-diabetic, and cardioprotective effects.

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