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Applications of bioactive compounds extracted from olive industry wastes: A review

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Abstract

The wastes generated during the olive oil extraction process, even if presenting a negative impact for the environment, contain several bioactive compounds that have considerable health benefits. After suitable extraction and purification, these compounds can be used as food antioxidants or as active ingredients in nutraceutical and cosmetic products due to their interesting technological and pharmaceutical properties. The aim of this review, after presenting general applications of the different types of wastes generated from this industry, is to focus on the olive pomace produced by the two-phase system and to explore the challenging applications of the main individual compounds present in this waste. Hydroxytyrosol, tyrosol, oleuropein, oleuropein aglycone, and verbascoside are the most abundant bioactive compounds present in olive pomace. Besides their antioxidant activity, these compounds also demonstrated other biological properties such as antimicrobial, anticancer, or anti-inflammatory, thus being used in formulations to produce pharmaceutical and cosmetic products or in the fortification of food. Nevertheless, it is mandatory to involve both industries and researchers to create strategies to valorize these byproducts while maintaining environmental sustainability.

KEYWORDS

bioactive compounds, cosmetics, food fortification, olive wastes, pharmaceuticals

1 | INTRODUCTION

In the Mediterranean region, mainly in countries such as Spain, Italy, Portugal, Greece, Syria, Morocco, and Tunisia, the olive oil production is one of the most important industries for their economy. European Union countries produce about 69% of the world's olive oil, being the leading producer, consumer, and exporter of this product. In the last years, other countries such as Argentina, Australia, United States of America, and South Africa became olive oil producers (Dermeche et al., 2013; Roig et al., 2006) since the global consumption of olive oil has increased worldwide. As the olive oil benefits for human health are becoming widely recognized, the perspective is that of a continuous increase in its consumption (and consequent production) in the coming years.

The extraction of olive oil includes different processes such as olive washing, olive crushing, malaxing of the

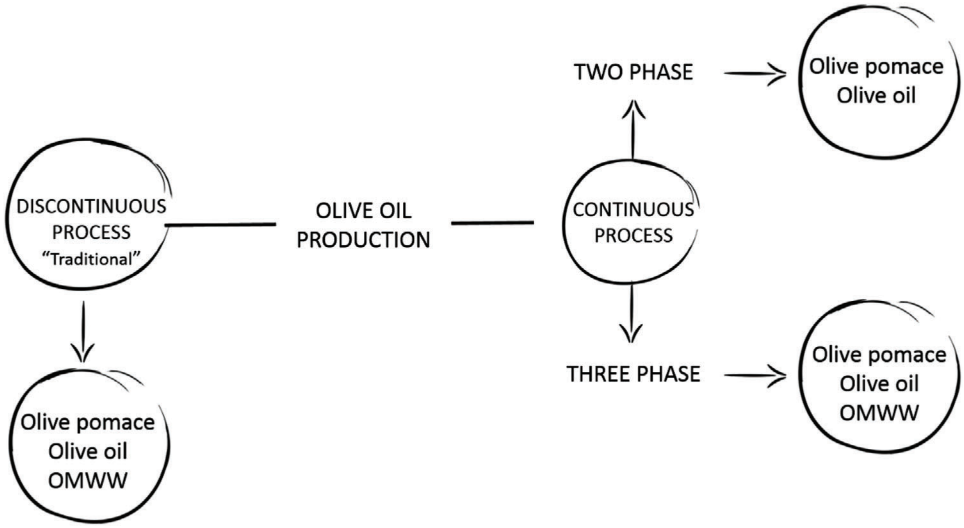

FIGURE 1 Different processes for olive oil production. OMWW, olive mill wastewater. Adapted from Rodrigues et al. (2015)

resulting pastes and the extraction itself (Roig et al., 2006; Zbakh & El Abbassi, 2012). The extraction of olive oil can be achieved through discontinuous (traditional pressing) or continuous (centrifugation) processes. Concerning the centrifugation processes, there are two possible systems, called three-phase and two-phase systems. In the three-phase system, a solid cake and two liquids, olive oil and large amounts of an aqueous liquid known as olive mill wastewater (OMWW) are generated. In the two-phase system, less water is used during the process which means that the volume of OMWW produced is reduced in comparison with the other process. In this system, besides olive oil, a semisolid residue (wet pomace or olive pomace) constituted by olive husk and OMWW is generated (Caporaso et al., 2018; Rodrigues et al., 2015). Figure 1 summarizes the processes for olive oil extraction. The two-phase system is used in the modern units replacing the three-phase technology, in order to minimize the wastewater volume and energy requirements (Dermeche et al., 2013). In fact, Azbar et al. (2004) indicated that two-phase technology saves process water by 80% and energy up to 20%. Nevertheless, its residues have a negative impact on the environment when they are discharged without treatment, due to their high toxicity and the resistance to biological degradation (Al-Khatib et al., 2009; Fiorentino et al., 2003; Khdair et al., 2019; Pavlidou et al., 2014).

Although some papers are found describing the composition of olive wastes and their applications in different areas (Bhatnagar et al., 2014; Galanakis, 2018; Rodrigues et al., 2015), there is no review that evaluated and compiled the possible applications for each of its main bioactive compounds, individually. To our knowledge, the only review describing the use of hydroxytyrosol as a functional food ingredient, not only as pure compound but also in the form of hydroxytyrosol-rich extracts, was published by Silva et al. (2020). In the present review, the applications of the different wastes generated from the olive oil industry will be described. After that, the review will focus on the solid residue (olive pomace) produced by modern two-phase system. Phenolic characterization and quantification will be discussed and the challenging applications of the individual compounds will be carefully explored.

2 | POTENTIAL APPLICATIONS OF OLIVE WASTES

Regardless of its negative environmental impacts, the potential added value of olive wastes for numerous sectors is well known. In the literature, there are a few reviews reporting the different applications for olive wastes (Dermeche et al., 2013; Roig et al., 2006).

Olive wastes have been used as soil amendment, to increase soil fertility and organic carbon stored in the agro-systems (Federici et al., 2017; Majbar et al., 2018; Regni et al., 2017). Fernández-Hernández et al. (2014) observed amended soils with higher content of nitrogen, phosphorus, potassium, and organic matter than the soil treated with inorganic fertilizer when using olive wastes composts mixed with different agro-industrial wastes applied to an olive grove in Spain. The increase of soil fertility produced an increase in the olive oil content of the fruits (Fernández-Hernández et al., 2014), although other researchers considered that recycling these wastes could promote soil phytotoxicity, considerable decline in soil germination capability, and necrosis of the olive leaves (Arvanitoyannis & Kassaveti, 2007).

Olive wastes can also be used as biomass to produce renewable fuels (Tayeh et al., 2014; Al Afif & Linke, 2019; Al-Addous et al., 2017; Messineo et al., 2020; Rincón et al., 2013; Romero-García et al., 2014; Serrano et al., 2017; Valenti et al., 2017). In a recent review paper, Messineo et al. (2020) reported the latest achievements in anaerobic digestion of olive mill residues in order to produce biofuels. In that review, the authors described not only the aspects of the process but also the existing pretreatments of olive wastes (Battista et al., 2016; Rincón et al., 2013; Siciliano et al., 2016) which are applied to induce the decomposition of the complex lignocellulosic structures before anaerobic digestion (Kumari & Singh, 2018). Serrano et al. (2017) proposed a thermal pretreatment and a subsequent phenolic recovery before the anaerobic digestion step to improve methane production. Furthermore, some chemical and physical pretreatment methods, such as ultrasonic pretreatment, basic pretreatment with sodium hydroxide, calcium carbonate, and/or hydrogen peroxide were used to optimize hydrogen and bioethanol production from olive oil production residues (Battista et al., 2016; Siciliano et al., 2016).

Other way to valorize olive wastes is to convert them into inexpensive adsorbents for water pollution control (Anastopoulos et al., 2015), in particular, heavy metals (Abdelhadi et al., 2017; Fernández-González et al., 2019; Fernando et al., 2009; Martinez-Garcia et al., 2006; Martín-Lara et al., 2013; Pagnanelli et al., 2003). Martinez-Garcia et al. (2006) observed that olive wastes maintained their adsorptive capacity over 10 cycles. Moreover, the ability of these biosorbents to adsorb several metal ions may increase their potential application on industrial wastewater treatment (Abdelhadi et al., 2017; Martinez-Garcia et al., 2006).

Other interesting and valuable use of olive mill wastes is to replace fresh water in brick manufacturing which contributes to a reduction of the water consumption (De La Casa & Castro, 2014; de la Casa et al., 2009; Eliche-Quesada et al., 2014; Mekki et al., 2006; Mekki et al., 2008). Comparing their physical properties with control products using fresh water, promising results have been obtained showing a significant increase in the volume shrinkage (10%) and the water absorption (12%), while the tensile strength remained constant (Mekki et al., 2008). Similar results were observed by de la Casa et al. (2009) also with the improvement by 33% of the dry-bending strength when compared to the control bricks.

In order to contribute to a more sustainable food production, the wastes generated from olive industry can also be transformed into animal feed (Dunne, 2019; Estaún et al., 2014; Gerasopoulos, Stagos, Kokkas, et al., 2015; Gerasopoulos, Stagos, Petrotos, et al., 2015; Molina-Alcaide et al., 2010; Rojas-Cano et al., 2014), although it is necessary to pay attention to their digestibility, palatability, and safety (Rojas-Cano et al., 2014). Rojas-Cano et al. (2014) demonstrated that the inclusion of olive soap stocks in the diet of growing crossbred Iberian pigs did not affect the apparent digestibility of nutrients or body protein accretion but increased the energy value of the diet. Also, Serra et al. (2018) found that the swine diet was improved by the inclusion of olive wastes. Lipid oxidation slowed down in the sausages despite the higher and lower contents in polyunsaturated fatty acids (PUFAs) and saturated fatty acids, respectively, compared to the controls. In another study, it was observed that feed blocks containing olive pomace could improve the quality of milk compared with a conventional diet with no impact on the milk yield and reducing the feeding costs (Molina-Alcaide et al., 2010). Similarly, for broiler chickens, the use of olive wastes extracts was effective in reducing the oxidative stress and led to higher antioxidant capacity in plasma and tissues (Gerasopoulos, Stagos, Kokkas, et al., 2015).

With increasing consumer demand for healthier food, the industry and the scientific community started to produce new functional ingredients for food and beverages. The recent pandemic situation also affected the food sector, mainly food safety and security, becoming more important in the development of sustainable and modern food systems (Galanakis, 2020; Galanakis et al., 2021). Thereby, the supplementation of consumers' diets with bioactive ingredients (vitamins, peptides, polyphenols, and lipids) can be an important key for the prevention or recovery from COVID-19 disease (Galanakis et al., 2020). The addition of OMWW and olive paste, individually or combined, to bread and pasta was assessed by Cedola et al. (2020) and Simonato et al. (2019). The results demonstrated that the enrichment of bread and pasta with OMWW slightly improved the chemical quality without compromising the sensory properties, whereas the enrichment with olive paste considerably improved both phenolic contents and antioxidant activity although the sensory acceptability was worse due to its bitter and spicy taste. The combination of the two byproducts in the fortification of bread and spaghetti increased the whole quality index, being higher for bread (Cedola, Cardinali, et al., 2020). The fortification of wheat pasta with olive pomace also enhanced the dietary fiber of the final product, while increasing its firmness and decreasing its cooking time (Simonato et al., 2019). In other study, the bread and rusks fortified with olive polyphenols (200 mg of polyphenols/kg) demonstrated higher antimicrobial activity and extended their shelf life from 10 to 15 days (Galanakis et al., 2018). Moreover, the addition of olive leaf extracts to poultry meat decreased the microbial growth and maintained both chemical quality and sensory attributes (Saleh et al., 2020), thus extending the shelf life of the meat when refrigerated for 15 days.

Olive byproducts are abundant sources of bioactive phenolic compounds (El-Abbassi et al., 2012; Madureira et al., 2020; Nunes et al., 2018; Yakhlef et al., 2018) that have promising potential as antioxidant, anti-inflammatory, and antimicrobial agents (Bulotta et al., 2014; Leouifoudi et al., 2014; Schaffer et al., 2010). Hence, the recovery of phenolic compounds from these wastes, after suitable purification, presents considerable interest for food and beverage (Araújo et al., 2015; Caporaso et al., 2018; Zbakh & El Abbassi, 2012), cosmetic (Galanakis et al., 2018; Rodrigues et al., 2017; Rodrigues et al., 2015), and nutraceutical (Vitali Čepo et al., 2018) industries, due to their interesting pharmaceutical properties. In the last years, the extracted phenolic compounds have also been used to produce biodegradable packaging materials for various types of food products to replace the synthetic ones (de Moraes Crizel et al., 2018; Lammi et al., 2018). de Moraes Crizel et al. (2018) studied the incorporation of 30% olive pomace flour in chitosan based films, protecting nuts against oxidation during 31 days. Lammi et al. (2018) developed biodegradable olive pomace-based fillers with lower stress and elongation at break and reducing costs.

3 | BIOACTIVE COMPOUNDS EXTRACTED FROM OLIVE POMACE

As previously discussed, in order to eliminate the OMWW generated in the three-phase system, the two-phase technology has emerged in the last 0 years, producing one major residue, olive pomace. Olive pomace comprises the olive husk and the OMWW, being one of the most polluting agricultural byproducts in the Mediterranean region (Papaioannou et al., 2013). Nevertheless, despite the very important polluting aspect, this waste contains high amounts of added value compounds, such as phenolic compounds, in variable amounts depending on several factors, such as olive variety and cultivar, harvest time, processing methods, and extraction process (Dermeche et al., 2013).

Cioffi et al. (2010) reported oleuropein (81.7–83.9 mg/kg of dry weight) and ligstroside aglycone (27.1–31.1 mg/kg of dry weight) as the most abundant compounds of olive pomace from Cilento National Park (Italy). In olive pomace from Algeria, oleuropein (144 mg/g of dry weight) was also detected as the major compound, and secoxyloganin (55 mg/g of dry weight), loganin (47 mg/g of dry weight), and cyanidin-3-glucoside (39 mg/g of dry weight) were observed for the first time in olive wastes (Moudache et al., 2020). On the other hand, Madureira et al. (2020) described hydroxytyrosol (25 mg/g of extract) as the main phenolic compound present in olive pomace from the region of Alentejo (Portugal), followed by hydroxytyrosol-1-β-glucoside (9.8 mg/g of extract) and tyrosol (5.9 mg/g of extract), which is consistent with the observations made by Malapert et al. (2018). These authors also described hydroxytyrosol (370.7 mg/L), hydroxytyrosol glucoside (165.2 mg/L), and tyrosol (148.4 mg/L) as the major compounds present in olive pomace from Baux-de-Provence (France). Additionally, Nunes et al. (2018) observed that hydroxytyrosol and comsegoloside represented about 79% of the total phenolics present in olive pomace from the region of Trás-Os-Montes (Portugal). On the other hand, Rubio-Senent et al. (2012) observed high quantities of 3,4-dihydroxyphenylglycol, elenolic acid derivatives, and comsegoloside besides hydroxytyrosol and tyrosol. Furthermore, verbascoside, gallic acid, caffeic acid, vanillic acid, oleuropein aglycone, *p*-coumaric acid, rutin, luteolin-7-*O*-rutinoside, and luteolin-7-*O*-glucoside were reported in lower amounts (Cioffi et al., 2010; Madureira et al., 2020; Malapert et al., 2018; Peralbo-Molina et al., 2012; Rubio-Senent et al., 2012).

Different methodologies for the extraction of these bioactive compounds from olive pomace can be performed using conventional and emerging technologies. Conventional techniques are based on solid–liquid extraction (Cardoso et al., 2005; Madureira et al., 2020; Suárez et al., 2009), but have some limitations namely long extraction times, high-energy dissipation, and low extraction selectivity and purity. In these ways, new and promising techniques were developed, such as ultrasound-assisted extraction (Goldsmith et al., 2018; Nunes et al., 2018), microwave-assisted extraction (Chanioti & Tzia, 2018; Xie et al., 2019), pressurized liquid extraction (Pavez et al., 2019), and supercritical fluid extraction (Caballero et al., 2020) in order to improve the extraction yield of phenolic compounds from olive pomace.

Table 1 describes the main phenolic compounds found in olive pomace and their MS data.

4 | APPLICATIONS OF THE MAIN BIOACTIVE COMPOUNDS EXTRACTED FROM OLIVE POMACE

The possible applications of the bioactive compounds from olive pomace in different areas, after suitable purification, can be the focus of a sustainable valorization in innovative products. This contributes not only to enhance the sustainability of the olive sector, but also for economic and environmental aspects.

Figure 2 shows the chemical structures of the bioactive compounds discussed in this review. Table 2 summarizes the major compounds present in olive pomace and their health benefits, while Table 3 outlines the existing patents on applications of these compounds and Table 4 the

TABLE 1 Main phenolic compounds identified in olive pomace and their MS data

Phenolic group	Compound	HPLC-DAD-MS(m/z)	LC-QqTOF MS/MS(m/z)	HPLC-DAD-MS(m/z)	UHPLC-DAD-MS(m/z)	LC-DAD-MS(m/z)
		Rubio-Senent, Rodríguez-Gutíerrez, Lama-Muñoz, and Fernández-Bolaños (2012)	Peralbo-Molina, Priego-Capote, and Luque De Castro (2012)	Nunes et al. (2018)	Malapert et al. (2018)	Madureira et al. (2020)
Phenyl alcohols	Hydroxytyrosol	153; 123	153.0560 (123.0450; 105.0339)	153 (123)	153	153 (123)
	Hydroxytyrosol glucoside	n.d.	315.1069 (123.0446; 153.0570)	n.d.	n.d.	315 (179, 161, 153, 135)
	Tyrosol	137	137.0608 (119.0505; 111.0098)	n.d.	137 (119)	137 (106)
Secoiridoids	Oleuropein	n.d.	539.1176 (377.1306; 307.0874; 275.0962)	n.d.	n.d.	n.d.
	3,4-DHPEA-EA	377; 307; 275; 149; 139	377.1440 (123.0446; 255.0869)	n.d.	377 (197, 153)	377 (331, 287, 179, 161, 143, 131, 119, 113, 101)
	Ligstroside	523; 361; 291; 259	n.d.	n.d.	n.d.	n.d.
	Elenolic acid	n.d.	n.d.	n.d.	241 (209, 165, 139, 127, 121, 101)	n.d.
Phenolic acids/aldehydes	Caffeic acid	n.d.	179.0352 (135.0449)	n.d.	179 (163, 135)	179 (135)
	p-coumaric acid	119	163.0403 (119.0503)	n.d.	163 (119)	n.d.
	Ferulic acid	n.d.	193.0514 (134.0377)	n.d.	n.d.	n.d.
	Gallic acid	n.d.	169.0150 (125.0246)	n.d.	n.d.	n.d.
	Vanillic acid	n.d.	167.0353 (108.0206; 123.0446)	n.d.	n.d.	n.d.
	Protocatechuic acid	109; 45	153.0193 (109.0295)	n.d.	n.d.	n.d.
	Vanillin	n.d.	n.d.	n.d.	n.d.	151 (136)
	Syringic acid	n.d.	n.d.	n.d.	n.d.	197 (153)
	Cinnamic acid	n.d.	147.0452 (147.0459)	n.d.	n.d.	n.d.
Flavonoids	Rutin	n.d.	609.1487 (301.0391)	n.d.	n.d.	n.d.
	Luteolin	n.d.	285.0420	n.d.	n.d.	n.d.
	Luteolin-7-*O*-glucoside	447; 285	447.0970 (285.0423)	n.d.	n.d.	n.d.
Phenylethanoid glycoside	Verbascoside	623; 461; 161	623.1973 (461.1744; 161.0254)	n.d.	623 (461, 477, 315)	623 (461, 315)
p-coumaric derivative	Comselogoside	535; 205; 145	n.d.	535 (491, 389, 345, 265)	535 (491, 389, 345, 307, 265, 163)	n.d.
Lignan	Pinoresinol	n.d.	357.1345	n.d.	n.d.	n.d.

n.d., not detected.

TABLE 2 Health effects reported for the main phenolic compounds present in olive pomace

Phenolic compound	Health effects	References
Hydroxytyrosol	Antioxidant, anti-inflammatory and anti-aging agent	Jeon and Choi (2018); Pérez-Bonilla et al. (2014); Takeda et al. (2014)
	Anticancer properties	Bernini et al. (2017); Imran et al. (2018); Romero et al. (2007)
	Antimicrobial properties	Medina et al. (2007)
	Protector against cardiovascular diseases	Bulotta et al. (2014; Tejada et al. (2016); Vilaplana-Pérez et al. (2014)
	Protector against high cholesterol	Illesca et al. (2019f); Tabern (2014)
	Protector against digestive disorders	Sánchez-Fidalgo et al. (2012)
	Skin protector	D'Angelo et al. (2005); Smeriglio et al. (2019)
	Prevention and treatment of osteoporosis	Hagiwara et al. (2011)
	Prevention of HIV infection and/or HIV-derived diseases	Bedoya et al. (2016); Lee-Huang et al. (2003, 2007)
Oleuropein	Antioxidant properties	Zbidi et al. (2009)
	Blood pressure lowering	Sun et al. (2017)
	Protector against cardiovascular diseases	Zhao et al. (2017)
	Neuroprotective properties	Sarbishegi et al. (2014)
	Anticancer properties	Imran et al. (2018); Ruzzolini et al. (2018); Shamshoum et al. (2017)
	Antimicrobial properties	Li et al. (2016); Liu et al. (2017)
	Skin protector	Kimura and Sumiyoshi (2009); Perugini et al. (2008)
	Hepatoprotective properties	Kim et al. (2014); Santini et al. (2020)
	Gastroprotective properties	Koc et al. (2018)
	Anti-diabetic properties	Annunziata et al. (2018); Qadir et al. (2016)
	Anti-obesity properties	Svobodova et al. (2014)
	Prevention of osteoporosis	Filip et al. (2014); Hagiwara et al. (2011)f
Tyrosol	Muscle damage inhibitor	Lee et al. (2018)
	Cholesterol efflux promotor	Berrougui et al. (2015)
	Intestine mucosa protector	Giovannini et al. (1999)
	Anti-diabetic properties	Chandramohan and Pari (2016); Zhang et al. (2019)
	Prevention of hypertension	Plotnikov et al. (2018)
	Protector against cardiovascular diseases	Samuel et al. (2008)
	Prevention of osteopenia	Puel et al. (2008)
Verbascoside	Antioxidant and anti-inflammatory properties	Cardinali et al. (2012); Chen et al. (2012); Funes et al. (2009); Funes et al. (2010); Qiao et al. (2019); Vertuani et al. (2011)
	Anticancer properties	Ma et al. (2020); Ohno et al. (2002)
	Hepatoprotective properties	Cui et al. (2018)
	Wound healing properties	de Moura Sperotto et al. (2018)
	Anti-hypertensive activity	Chen et al. (2012)
	Anti-diabetic properties	El-Marasy et al. (2020); Liu et al. (2013)
	Hypoglycemic activity	Morikawa et al. (2014)
	UV protector	Potapovich et al. (2013)
	Neuroprotective properties	Xia et al. (2018)
Oleuropein aglycone	Anti-neurodegenerative properties	Casamenti et al. (2015); Cordero et al. (2018); Grossi et al. (2013); Palazzi et al. (2018)

(Continues)

TABLE 2 (Continued)

Phenolic compound	Health effects	References
	Anticancer properties	Menendez et al. (2007)
	Lipid-lowering properties	Leenen et al. (2002)
	Anti-hyperglycemic properties	Rigacci et al. (2010)r
	Anti-obesity properties	Oi-Kano et al. (2017)
	Antimicrobial properties	Bisignano et al. (2014)

HIV, human immunodeficiency virus; UV, ultraviolet.

fortified food with the presented bioactive compounds.

As the most abundant bioactive compounds in olive pomace, hydroxytyrosol, oleuropein, and tyrosol will be discussed first in this section, followed by verbascoside and oleuropein aglycone, which are present in lower amounts in this residue but have beneficial properties and potential applications that should be explored.

4.1 | Hydroxytyrosol

Hydroxytyrosol (Figure 2), also known as 3,4-dihydroxyphenylethanol (DOPET), 3,4-dihydroxyphenolethanol (3,4-DHPEA), or 4-(2-hydroxyethyl)–1,2-benzenediol by the International Union of Pure and Applied Chemistry (IUPAC), is one of the most powerful naturally derived antioxidants with higher antioxidant potential than butylated hydroxytoluene (BHT), trolox and vitamins C and E (Pérez-Bonilla et al., 2014; Zbidi et al., 2009). Hydroxytyrosol is a main product of the hydrolysis of oleuropein (Liu et al., 2018) which occurs during the ripening of the olives, storage of the oil, and preparation of table olives, and it is responsible for the complexity and variety of the oil and olive flavors. Due to its amphipathic character, hydroxytyrosol can be found not only in olive and in olive leaf, but also in olive oil byproducts in a free form, as acetate form or as part of more complex compounds like oleacein, verbascoside, and oleuropein.

There are different patented methods to obtain purified hydroxytyrosol from products and byproducts of olive oil industry to be used in food, cosmetic, and pharmaceutical industries (Table 3). Thus, nanofiltration and reverse osmosis were patented as clean technologies to purify hydroxytyrosol (de Magalhães Nunes da Ponte et al., 2014), whereas a process using resins was patented by Fernandez-Bolaños Gusman et al. (2005).

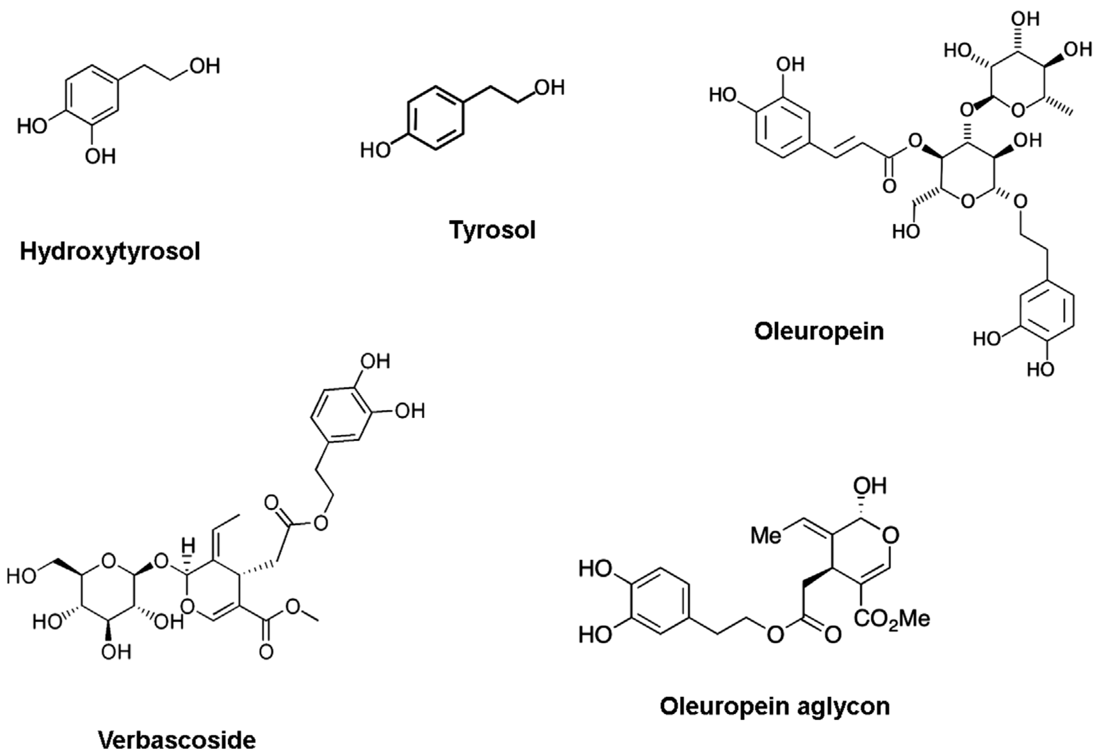

FIGURE 2 Chemical structures of some of the main phenolic compounds present in olive pomace, discussed in this review

TABLE 3 Patents on the application of phenolic compounds present in olive pomace

# Patent	Subject	Industry application	Year of publication	References
WO 2004/069218 A1	Cosmetic formulation containing verbascoside to use as a stimulant agent for the production of thermal shock proteins and as an inhibitor of collagenase and elastase and stimulant of hydroxylases.	Cosmetic industry	2004	Robin and Rolland (2004)
EP 1498131 A1	Medicinal preparation with verbascoside (5%–40%) as active ingredient of a drug used to prevent senile dementia and inhibit aggregation of blood platelets.	Pharmaceutical industry	2005	Tu et al. (2005)
WO 2007/012057 A2	Production of a hydroxytyrosol-rich formulation to treat skin inflammations, such as psoriasis, eczema, allergic dermatitis, phytohypersensitivity, dermatosis, and lichen urticatus.	Pharmaceutical industry	2007	Numano et al. (2007)
WO 2007/051829 A1	Production of a medication using oleuropein for preventing and/or treating peripheral vascular disease, particularly venous insufficiency.	Pharmaceutical industry	2007	Martín et al. (2007)
WO 2008/128629 A1	Production of a nutraceutical composition with hydroxytyrosol for regeneration and repair of cartilage injuries in joints.	Nutraceutical industry	2008	Raederstorff et al. (2008)
WO 2009/013596 A2	Process of production of food hydroxytyrosol-enriched products (fortified edible oils, fortified edible oil-containing products, and dietary supplements in the form of soft gel capsules containing fortified edible oils) to prevent or treat cardiovascular diseases, plaque build-up in the arteries, arterial hypertension, and metabolic syndrome.	Nutraceutical industry	2009	Más et al. (2009)
US 2010/0297330 A1	Production of yogurts with hydroxytyrosol to increase the antioxidant activity, preserving their organoleptic characteristics and stability for at least three months, having the role of preventing diseases.	Food industry	2010	Villanova et al. (2010)
WO 2010/070183 A1	Preparation of therapeutic compositions with oleuropein as active ingredient to induce angiogenesis and vasculogenesis.	Pharmaceutical industry	2010	Quesada-Gómez et al. (2010)
WO 2011/141611 A1	Pharmaceutical compositions containing oleuropein as the only active ingredient to heal wounds and ulcers in elderly people and/or diabetics.	Pharmaceutical industry	2011	Quesada-Gómez et al. (2011)
US 2011/0144040 A1	Compositions containing verbascoside and verbascoside-rich extracts to increase strength, muscle power, endurance, muscle protein content, and to reduce fatigue.	Nutraceutical industry	2011	Panyam and Chavanpatil (2011)
WO 2011/153647 A1	Pharmaceutical composition containing hydroxytyrosol and xanthohumol to treat asthma and rhinitis.	Pharmaceutical industry	2011	Ehrenberger and Bieberschulte (2011)

(Continues)

TABLE 3 (Continued)

# Patent	Subject	Industry application	Year of publication	References
US 2012/0260922 A1	New microbicide formulation containing hydroxytyrosol and other existing drugs to prevent sexually transmitted diseases, such as HIV-infection.	Pharmaceutical industry	2012	Gómez-Acebo et al. (2012)
US 8574635 B2	Methods and pharmaceutical compositions with oleuropein and its derivatives, to inhibit HIV-infections and also to treat obesity and type 2 diabetes, or related disorders.	Pharmaceutical industry	2013	Lee-Huang et al. (2013)
WO 2013/084249 A1	Dietary supplement containing a mixture of verbascoside and teupolioside for prevention of hypercholesterolemia. The invention is also related to the production of foodstuffs (milk, eggs, meat) with reduced cholesterol content, rich in vitamins A and E.	Nutraceutical industry	2013	Casamassima (2013)
US 2014/0011756 A1	Process of compositions production with hydroxytyrosol and oleuropein for treating HIV-associated neurological disorders, inflammation, and inflammation-associated disorders.	Pharmaceutical industry	2014	Crea (2014)
ES 2462565 A1	A dermocosmetic containing hydroxytyrosol to inhibit melanin synthesis and to reduce skin coloration, which can work as a whitening, lightening, and depigmenting agent of skin.	Cosmetic industry	2014	Codina and Monjo (2014)
WO 2016/087428 A1	Process to fortify edible oils with hydroxytyrosol to be used in all fields of nutrition.	Nutraceutical industry	2016	Bulbarello and Leuthardt (2016)
US 2017/0367995 A1	A method for production of a formulation comprising hydroxytyrosol (40%–90%) and at least one additional polyphenol to treat neurodegenerative diseases, such as Parkinson in early stage.	Pharmaceutical industry	2017	Crea (2017)
ES 2734600 A1	A pharmaceutical and nutraceutical composition using aloe vera gel (90%–99.9%) and hydroxytyrosol (0.1%–10%) for the production of a dietary supplement for the control off glycemic index and cholesterol or a medication for the treatment and/or prevention of metabolic syndrome and type 2 diabetes and as a food supplement.	Nutraceutical and Pharmaceutical industry	2019	Fernández Arche et al. (2019)
US 2019/012952 A1	Method for production of beverages containing hydroxytyrosol without changing smell and flavor.	Food industry	2019	Fuwa et al. (2019)f
US 2020/0390793 A1	Composition (food product or food supplement) with oleuropein to be administrated to treat, prevent, or reduce the progression of sarcopenia.	Nutraceutical industry	2020	Boutry et al. (2020)

HIV, human immunodeficiency virus.

TABLE 4 Fortified food with phenolic compounds present in olive pomace

Phenolic compound	Food	Benefits of fortified food	References
Hydroxytyrosol	Red and white wine	Improvement of the color for at least 6 months.	Raposo et al. (2016)
	Beer	5 g/L of hydroxytyrosol imparted a more soft and pleasant flavor and aroma.	Guglielmotti et al. (2020)
	Biscuits	Improvement of antioxidant activity, total phenol and flavonoid contents; Decrease of the levels of oxidized low-density lipoproteins in blood.	Cedola, Palermo, et al. (2020); Mateos et al. (2016)
	Sausages and meat patties	Increase of antioxidant activity and decrease of lipid and protein oxidation until 9 or 21 days of storage, maintaining color and texture; Reduction of undesirable fungi.	Balzan et al. (2017); Chaves-López et al. (2015); Muíño et al. (2017); Nieto et al., 2017a, 2017b)
	Fish patties	Delay of lipid oxidation; Preservation against pathogens, extending shelf life of the product.	Martínez et al. (2019)
	Yogurts	Improvement of the growth of lactic acid bacteria; Prevention of the spoilage during fermentation.	Georgakouli et al. (2016)
Oleuropein	Pasteurized milk	Extension of the shelf life by 60% with 7.57 mg oleuropein/100 ml milk.	Palmeri et al. (2019)
	Yogurts	Enhancement of rheological properties (higher firmness and viscosity and less syneresis).	Zoidou et al. (2017)
	Meat burgers	Delay of oxidation, increasing shelf life of the product.	Elama et al. (2017)
	Salmon burgers	Reduction of lipid oxidation.	Khemakhem et al. (2019)
Verbascoside	Sausages	Antifungal activity without compromising sensory characteristics.	Chaves-López et al. (2015)

This compound has been described as an antioxidant with many biological activities (Table 2) (Bertelli et al., 2020; Marković et al., 2019; Vilaplana-Pérez et al., 2014). There are many studies proving its antioxidant, anticancer, anti-inflammatory, and antimicrobial activities (Bernini et al., 2017; Bernini et al., 2015; Imran et al., 2018; Jeon & Choi, 2018; Medina et al., 2007; Pérez-Bonilla et al., 2014; Romero et al., 2007; Takeda et al., 2014). In addition, it was reported to act as a protector against high cholesterol blood levels (Tabern et al., 2014), metabolic diseases (Bulotta et al., 2014; Fki et al., 2020), genotoxicity, cytotoxicity and proapoptotic effects (Anter et al., 2014; Bernini et al., 2013), oxidative stress (Loru et al., 2009; Merra et al., 2014), and digestive disorders (Sánchez-Fidalgo et al., 2012). Other works have focused on the use of hydroxytyrosol in cardiovascular diseases (Bulotta et al., 2014; Tejada et al., 2016; Vilaplana-Pérez et al., 2014).

D'Angelo et al. (2005) and Smeriglio et al. (2019) demonstrated the dermatological properties of hydroxytyrosol to prevent protein damage induced by long-wavelength ultraviolet radiation in melanoma cells or to counteract atopic dermatitis, respectively. More specifically, Smeriglio et al. (2019) investigated the safety and efficacy of the Fenolia® Eudermal Cream 15 containing hydroxytyrosol in its formulation, which was demonstrated to be effective in improving the epidermal barrier effect, preventing inflammation, and repairing the skin. Actually, hydroxytyrosol is already used as an ingredient in different cosmetics, including anti-aging and lightening/whitening products. There are a few patents to produce cosmetics with hydroxytyrosol. Codina and Monjo (2014) patented a method to produce a dermocosmetic containing hydroxytyrosol to inhibit melanin synthesis, reduce skin coloration and work as a whitening, lightening, and depigmenting agent of skin. Another hydroxytyrosol-rich formulation was developed to treat skin inflammations, such as psoriasis, eczema, allergic dermatitis, photohypersensitivity dermatosis, or lichen urticatus (Numano et al., 2007).

Hydroxytyrosol has been proposed to promote fat and cholesterol metabolism, effectively protect the liver function, and cure and/or prevent the occurrence of obesity. In a study with high-fat diet fed mice, hydroxytyrosol was used as a nutritional supplement to amend dysfunctional white adipose tissue (Illesca et al., 2019). The supplementation caused an improvement on adipocyte hypertrophy and a decrease in oxidative damage, showing it as a promising alternative to prevent obesity and its associated metabolic disturbances. A pharmaceutical or nutraceutical composition was developed and patented by Arche et al. (2019) based on an aloe vera (90–99.9%) and hydroxytyrosol (0.1%–10%) gel to be used as a dietary supplement for the control of glycemic index and high cholesterol levels or a medication for the treatment and/or prevention of metabolic syndrome and type 2 diabetes.

An interesting study by Hagiwara et al. (2011) proposed the use of hydroxytyrosol on osteoporosis' prevention and treatment, since this compound stimulated the deposition of calcium in a dose-dependent manner. Furthermore, nutraceutical and pharmaceutical compositions with hydroxytyrosol were patented for regeneration and repair of cartilage injuries in joints (Raederstorff et al., 2008).

A formulation comprising hydroxytyrosol (40%–90%) and at least one additional olive polyphenol was developed for the treatment of neurodegenerative diseases such as Parkinson in the early stages of the disease (Crea, 2017). The inventors described the administration of daily doses of capsules (72 mg olive polyphenols, including 30 mg hydroxytyrosol) to subjects for some weeks, noticing considerable improvements in their movements and reduction of the tremor after the first weeks.

The use of hydroxytyrosol to prevent human immunodeficiency virus (HIV) infection and even to palliate HIV-derived diseases has also received special attention (Bedoya et al., 2016; Lee-Huang et al., 2007; Lee-Huang et al., 2003). Bedoya et al. (2016) observed that 5-hydroxytyrosol inhibited HIV-1 infections of recombinant or wild-type viruses in human lymphoblastic cells (MT-2 cell lines) and human peripheral blood mononuclear cells (PMBCs cell lines). The combination of this compound with other drugs already used as a preventive treatment against HIV-1 infections was also tested. Additive effects were found with lamivudine and emtricitabine, whereas the combination with tenofovir seemed to be synergistic. These findings, which suggested that 5-hydroxytyrosol could be an effective and low-cost new microbicide to prevent the HIV infection with particular interest in countries with high incidence of transmission were patented by Gómez-Acebo et al. (2012). Another method for producing pharmaceutical compositions with phenolic compounds extracted from olive byproducts, including hydroxytyrosol, for treating HIV-associated neurological disorders, inflammation, and inflammation-associated conditions was patented (Crea, 2014). This composition was produced to be preferably used as a tablet formulation for oral administration.

A formulation containing hydroxytyrosol and xanthohumol as active substances in the form of an intranasal spray was also patented to treat asthma and rhinitis as well as to treat colds (Ehrenberger & Bieberschulte, 2011).

The European Food Safety Authority (EFSA) concluded that there was sufficient scientific evidence to claim several health benefits for hydroxytyrosol and related olive oil polyphenols (EFSA Panel on Dietetic Products, Nutrition & Allergies, 2011), and that no concerns exist about its safety to be used in novel food preparations under proposed uses and levels (EFSA Panel on Dietetic Products, Nutrition & Allergies, 2017). A summary on the uses of hydroxytyrosol in fortified foods is collected in Table 4. A comprehensive review on the applications of hydroxytyrosol as a functional food ingredient, either in the form of pure compound or hydroxytyrosol-rich extracts, was recently published by Silva et al. (2020). In that review, the authors described the use of this compound in edible oils, beverages, bakery products and meat, fishery, and dairy products. Several food products with higher antioxidant activity (fortified edible oils, fortified edible oil-containing products, and dietary supplements in the form of soft gel capsules containing fortified edible oils) were patented by Mas et al. (2009) for preventing or treating cardiovascular diseases, plaque build-up in the arteries, arterial hypertension, and metabolic syndrome, based on their hydroxytyrosol-rich composition. Bulbarello and Leuthardt (2016) patented capsules for oral consumption of an edible oil fortified with hydroxytyrosol (more than 250 mg hydroxytyrosol/kg fortified oil) to be used in humans and animals in all the fields of nutrition. Besides its health benefits, the fortification with hydroxytyrosol can delay the oxidation of edible oils.

Moderate consumption of red wine has been suggested to protect against cardiovascular diseases mainly due to its high content in polyphenols (Santos-Buelga & González-Manzano, 2011). When hydroxytyrosol is added to red (Raposo et al., 2016a) and white (Raposo et al., 2016b) wines to replace the use of sulfur dioxide, an intensification of color was noticed. The improvement on color was maintained even after 6 months of storage for white wines, whereas red wines were oxidized. Based on these results, the authors suggested that the combination of sulfur dioxide with hydroxytyrosol could be a suitable condition to reduce the sulfur dioxide content without compromising the wine oxidation. Recently, Guglielmotti et al. (2020) incorporated hydroxytyrosol in beer using olive leaves as an ingredient in the form of dry crumbled leaves, infusion and atomized extract, so as to explore their contribution to bitterness and antioxidant activity of beer. The ingredients were added during boiling phase of brewing, in order to promote the hydrolysis of oleuropein of the leaves to hydroxytyrosol. The results demonstrated that the addition of 10 g/L of olive leaves imparted a sour/astringent taste and herbal aroma to the beers, whereas 5 g/L of olive left a softer and pleasant flavor and aroma in comparison to the control. Fuwa et al. (2019) studied the possibility of preparing a beverage containing hydroxytyrosol (0.5 to 50 mg/100 ml) to improve blood flow without changing smell and flavor. The authors formulated beverages comprising ethanol and/or propylene glycol (0.05% to 0.5% w/v), caffeine (10–210 mg/100 ml), and glucose and maltose. The beverages with the most favorable taste were found to be the ones with higher concentrations of caffeine (>110 mg of caffeine/100 ml) and 0.8–1.5 mg of hydroxytyrosol/100 ml. The beverages with the most favorable sense of quick sweetness were those containing 0.8–1.5 mg of hydroxytyrosol/100 ml and a ratio of glucose/maltose of 0.03–0.14.

Bakery products are also interesting products to incorporate hydroxytyrosol since they are consumed worldwide by people of different ages. Mateos et al. (2016) observed that the intake by volunteers of hydroxytyrosol-fortified biscuits (30 g biscuits providing 5.25 mg of hydroxytyrosol, after an overnight fast) could significantly decrease the levels of oxidized low-density lipoproteins (LDL) in blood, also finding that hydroxytyrosol was highly bioavailable, extensively metabolized, and rapidly eliminated. In another study by Cedola et al. (2020), the white wine used to produce the Italian biscuit "taralli" was replaced by an olive leaves extract containing hydroxytyrosol. An improvement on antioxidant activity (1.5-fold), total phenols (≥1.4-fold), and flavonoid content (4-fold) were observed, which could be responsible for the darker color of the fortified biscuits compared to the control ones.

Hydroxytyrosol has been also used in meat to improve the oxidative stability and sensory properties of lamb meat patties (Muíño et al., 2017), the nutritional profile of low-fat chicken Frankfurters (Nieto et al., 2017a) or to reduce the growth of undesirable fungi on dry fermented sausages (Chaves-López et al., 2015). Muíño et al. (2017) evaluated lamb meat patties enriched with omega 3 (fish oil) and hydroxytyrosol at different concentrations (100, 200, and 400 ppm), demonstrating that the presence of hydroxytyrosol increased the antioxidant activity of patties and decreased the lipid and protein oxidation at days 3, 6, and 9 of storage compared with control samples, while maintaining the color and texture. Hydroxytyrosol (50 ppm), in combination with olive oil and walnuts, was used to produce chicken sausages without loss of sensory attributes during storage at 4°C for 21 days. Furthermore, it was enough to maintain the color and reduce lipid and protein oxidation until 21 days (Nieto et al., 2017b; Nieto et al., 2017a). Fermented sausages added with hydroxytyrosol (100.23 ppm) showed lower lipid oxidation and volatile compounds and higher redness, as well as improved antifungal activity both in vitro and in situ (Chaves-López et al., 2015). Also, Balzan et al. (2017) prevented the lipid oxidation of pork sausages using a purified extract from the olive vegetation water containing a high amount of hydroxytyrosol.

In fishery products, hydroxytyrosol was efficient to inhibit the formation of lipid oxidation products in bulk cod liver oil (100 ppm of hydroxytyrosol), cod liver oil-in-water emulsions (100 ppm of hydroxytyrosol), and frozen minced horse mackerel (*Trachurus trachurus*) muscle (50 ppm of hydroxytyrosol) (Pazos et al., 2008); furthermore, the level of α-tocopherol and the ω-3 long-chain PUFAs was preserved. Hydroxytyrosol extracts were also able to delay the lipid oxidation and preserve fish patties against *Escherichia coli*, *Listeria monocytogenes*, and *Staphylococcus aureus* contributing to extend their shelf life (Martínez et al., 2019).

The production of yoghurts that include hydroxytyrosol (in a percentage between 0.1% and 0.01%) as an additional healthy component was patented by Villanova et al. (2010). The enriched yogurts preserved their organoleptic characteristics, improved their antioxidant activity, and maintained their stability for at least 3 months. In the same way, Georgakouli et al. (2016) verified that the addition of a commercial hydroxytyrosol-rich product obtained from olive fruits (Medoliva©) in yogurts (50 mg of polyphenols) improved the growth of lactic acid bacteria and contributed to preventing spoilage during fermentation, as well as to reduce LDL cholesterol, body weight, and blood pressure.

4.2 | Oleuropein

Oleuropein belongs to a very specific group of coumarin-like compounds, called secoiridoids and consists of hydroxytyrosol, elenolic acid, and a glucose molecule (Figure 2). It is one of the main polyphenols present in olive wastes, contributing to the bitter taste of olive oil and fruit.

Oleuropein possesses numerous pharmacological benefits (Table 2) mostly related with its strong antioxidant and anti-inflammatory activities (Hassen et al., 2015; Marković et al., 2019; Nediani et al., 2019). The antioxidant activity of oleuropein is related to the presence of hydroxyl groups in its chemical structure that can donate hydrogen to prevent oxidation (Hassen et al., 2015). In fact, oleuropein and oleuropein-rich extracts were reported to have higher antioxidant activity than the synthetic antioxidant BHT (Zbidi et al., 2009). Another interesting property of oleuropein is its blood pressure-lowering effect. Sun et al. (2017) found that oleuropein can protect the paraventricular nucleus (PVN) of hypothalamus from oxidative stress, being a promising strategy both for preventing and treating hypertension. Furthermore, oleuropein has been shown to have cardioprotective (Zhao et al., 2017), neuroprotective (Sarbishegi et al., 2014), anticancer (Imran et al., 2018; Ruzzolini et al., 2018; Shamshoum et al., 2017), and antimicrobial (Li et al., 2016; Y. Liu et al., 2017) activities. Also, it was proven to possess skin protectant (Kimura & Sumiyoshi, 2009; Perugini et al., 2008), hepatoprotective, gastroprotective, anti-diabetic and anti-obesity activities, and lipid regulating effects (Annunziata et al., 2018; Drira et al., 2011; Kim et al., 2014; Koc et al., 2018; Qadir et al., 2016; Santini et al., 2020; Svobodova et al., 2014). Based on the mentioned properties, oleuropein may be used for a variety of human disorders.

Martín et al. (2007) developed a patent on the use of oleuropein for the manufacture of a medication for preventing and/or treating a condition associated with peripheral vascular disease. A pharmaceutical composition with oleuropein (concentration between 10^{-7} and 10^{-4} M) as active ingredient was also patented to induce angiogenesis and vasculogenesis, that can be administered by oral, rectal, parenteral, intraperitoneal, intradermal, transdermal, intratracheal, intramuscular, intravenous, or inhalation (Quesada-Gómez et al., 2010). The same authors (Quesada-Gómez et al., 2011) patented a preparation containing oleuropein as the only active ingredient to be used for healing wounds and ulcers in aged and/or diabetics individuals in the form of gel, cream, or aqueous solution form.

The above mentioned medication, hydroxytyrosol based, for treating an AIDS-associated neurological disorders can also be prepared using a mixture of hydroxytyrosol and oleuropein (Crea, 2014). Lee-Huang et al. (2013) also patented a formulation able to inhibit not only the infectivity of HIV but also to treat and prevent obesity and related conditions, such as type 2 diabetes. Actually, interesting evidences have been found on the effects of oleuropein on the control of type 2 diabetes (Annunziata et al., 2018).

Oleuropein also has application in the treatment of osteoporosis. The BONOLIVE® supplement, consisting of a polyphenols mixture from olive leaf containing more than 40% of oleuropein, has been clinically proven to induce significant effects on bone health, stimulating bone building cells (osteoblasts), and improving blood lipid profiles in individuals after 12 months of treatment (Filip et al., 2014). Hagiwara et al. (2011) also reported that, as hydroxytyrosol, oleuropein may have critical effects on the formation and maintenance of bone, and that both could be used as effective medications for the treatment of osteoporosis symptoms.

Recently, Boutry et al. (2020) described a formulation to be used either as a food product or a food supplement, based on oleuropein to treat or prevent sarcopenia, indicated for elderly and/or frail individuals.

Oleuropein has been added as an active ingredient in milk and yogurt preparations for the production of novel foods with improved characteristics. Palmeri et al. (2019) observed that the addition of 5% olive leaf extract (corresponding to 7.57 mg of oleuropein/100 ml of milk) to pasteurized milk was able to extend its shelf life by 60%, thus leading to significant benefits in terms of costs linked to transport and to product returns to the dairy industry. The incorporation of oleuropein to fortify yogurts represents a major challenge for their taste and texture. Nevertheless, Zoidou et al. (2017) proved that the addition of olive leaf extract containing high amounts of oleuropein to yogurts improved their rheological properties, providing higher firmness and viscosity, and less syneresis.

Oleuropein can also be used for delaying the oxidation of meat. Elama et al. (2017) explored the possibility of using oleuropein as a natural antioxidant in frozen hamburgers to replace synthetic food antioxidants such as sodium erythorbate. Similar results were obtained for both oleuropein and sodium erythorbate, finding that a concentration of 0.5% was able to extend shelf life of hamburgers and hinder oxidation. The potential of oleuropein to preserve salmon burgers by reducing lipid oxidation during the storage at low temperatures was also demonstrated (Khemakhem et al., 2019).

4.3 | Tyrosol

Tyrosol (Figure 2), also named as 2-(4-hydroxyphenyl)-ethanol, *p*-hydroxyphenethyl alcohol, or 4-(2-hydroxyethyl)-phenol by the IUPAC, is a phenylethanoid compound naturally present in olive fruit, olive oil, and olive wastes both in their free form or as part of more complex molecules, mostly as esters of elenolic acid.

Several studies have demonstrated the potential of tyrosol as antimicrobial, anti-carcinogenic, anti-inflammatory, and antioxidant agent (Table 2). Tyrosol has been proposed to fight hypertension, atherosclerosis, coronary heart disease, chronic heart failure, insulin resistance, and obesity by modulating cluster of differentiation 14 (CD14) upregulation and inhibiting inflammation (Chang et al.,). In a study developed by Lee et al. (2018), tyrosol showed to be effective in inhibiting muscle damage from oxidative stress triggered by strenuous exercise. Tyrosol could also promote cholesterol efflux by enhancing the antiatherogenic properties of high-density lipoproteins (HDL) (Berrougui et al., 2015) and protect the intestine mucosa by preventing the oxidative damage induced by LDL, as shown in human colon adenocarcinoma cell line, Caco-2 (Giovannini et al., 1999).

Tyrosol may also play a role in the treatment of diabetes mellitus, exerting anti-inflammatory effects on the liver and pancreas via its antioxidant activity, as observed in streptozotocin-induced diabetic rats (Chandramohan & Pari, 2016). Furthermore, the intramuscular administration of tyrosol to diabetic hind limb ischemia mice significantly enhanced the formation of blood vessels which improved the recovery of blood perfusion (Zhang et al., 2019). Those authors also reported a cytoprotective function of tyrosol against hyperglycemia-induced oxidative stress in skeletal muscle cells and an increase in their proliferation.

Plotnikov et al. (2018) described that when tyrosol was administered to young spontaneously hypertensive rats (SHRs), the development of hyperviscosity syndrome was limited, the oxygen transport capacity was improved, and the microvascular rarefaction in the cerebral cortex was eliminated. The blood viscosity increased by 16%–26% in rats treated with tyrosol and the results were similar to those obtained with pentoxyphylline, a drug used for the treatment of peripheral circulation disorders (Plotnikov et al., 2007). Samuel et al. (2008) verified that a tyrosol treatment (5 mg/kg/day for 30 days) was capable of inducing myocardial protection against ischemia-induced stress in rats, which turns important in order to develop a new drug to combat cardiovascular diseases. Moreover, Puel et al. (2008) reported that the daily consumption of tyrosol during 84 days by ovariectomized rats increased bone formation, which was associated with its antioxidant properties, thus preventing osteopenia.

In spite of its interesting properties, the hydrophilic chemical nature of tyrosol could limit its use in foods, pharmaceutical formulations, and/or cosmetics. Paulo and Santos (2020a) developed a strategy to incorporate tyrosol in alternative polymer carriers as poly(D,L-lactide-*co*-glycolide), ethylcellulose, and polycaprolactone by water-in-oil-in-water double emulsion solvent evaporation technique. The obtained results revealed that these microparticles were thermogravimetrically stable in the temperature range of 30 to 261°C. Actually, the bioaccessibility of tyrosol improved by 1.9-fold when the compound was encapsulated (Paulo & Santos, 2020b). Being an antioxidant compound, the microencapsulation may also protect tyrosol from auto-oxidation processes. Other recent study reported the impact of two different carriers for the encapsulation of tyrosol: the oligosaccharide β-cyclodextrin and the polysaccharide chitosan (Pintillo et al., 2021). The results demonstrated that the coating promoted a sustained release of tyrosol and slowed down the initial burst effect observed from the inclusion complex. Also, this compound was shown to be a ctDNA groove binder. These outcomes bring new insights concerning the encapsulation of antioxidants for further incorporation in food, pharmaceutical, cosmetic, and/or nutraceutical matrices.

4.4 | Verbascoside

Verbascoside (Figure 2), also known as acteoside, belongs to the extensive family of phenylpropanoids and is a conjugated glucoside of hydroxytyrosol and caffeic acid. This compound has been demonstrated to have antioxidant protective effects on phospholipid membranes and modulation of plasma antioxidant activity in vivo (Chen et al., 2012; Funes et al., 2009; Funes et al., 2010). Cardinali et al. (2012) reported that verbascoside has a high antioxidant capacity, acting as an effective scavenger of biologically active free radicals and an inhibitor of lipid peroxidation, so that it can be used for treating oxidative stress-related diseases, which may be interesting for application in cosmetics, nutraceuticals, or functional foods. Furthermore, antitumor, antimicrobial, anti-inflammatory, anti-thrombotic, and wound healing properties have also been described (Cui et al., 2018; de Moura Sperotto et al., 2018; Ma et al., 2020; Ohno et al., 2002; Qiao et al., 2019; Vertuani et al., 2011).

Chen et al. (2012) reported that verbascoside (10 mg/kg body weight) has anti-hypertensive activity, lowering both systolic and diastolic blood pressures in hypertensive rats. Its anti-inflammatory potential was also reported by Qiao et al. (2019) on rats with osteoarthritis, a chronic arthritis, through the inactivation of JAK/STAT signaling pathway. Vertuani et al. (2011) demonstrated the stability of verbascoside in suppositories which is an interesting pharmaceutical form to apply in treatment of inflammation of the intestinal mucosa. This compound also presents antitumor activity possibly by increasing p53 levels, as well as by inhibiting KLK expression and angiogenesis, making it a potential candidate for the treatment of advanced hepatocellular carcinoma in the clinic (Ma et al., 2020).

Hepatoprotective (Cui et al., 2018) and anti-diabetic effects (El-Marasy et al., 2020; Liu et al., 2013) have also been described and hypoglycemic activity and improved glucose tolerance were found by Morikawa et al. (2014) in starch-loaded mice.

Potapovich et al. (2013) suggested that verbascoside could inhibit inflammatory response and metabolic disorders caused by solar UV irradiation in human keratinocytes. Similarly, wound healing activity was reported, as it was demonstrated to be capable of increasing the migration of keratinocytes and inhibiting inflammation mediators (de Moura Sperotto et al., 2018).

Xia et al. (2018) described the capacity of verbascoside in attenuating oxidative stress and neuronal apoptosis in middle cerebral artery occlusion/reperfusion rats. Its administration seemed to reduce infarct volume and brain edema and improve neurological deficits, thus suggesting that it can be successfully used to treat cerebral ischemia–reperfusion injury. A review on the biological effects of verbascoside and its potential clinical utility have been published by Alipieva et al. (2014).

Casamassima (2013) patented a dietary supplement containing verbascoside and teupolioside for prevention of hypercholesterolemia and the production of foodstuffs (particularly in meat, milk, and eggs) with reduced cholesterol content.

NuLiv Science (https://nulivscience.com/), which works on the research and development of proprietary ingredients for nutraceuticals industry, produced two products containing verbascoside: Acteolin™ and Verbasnol™. Acteolin™ is an ingredient claimed to provide benefits for cognitive and memory functions, lung, and eye health. Verbasnol™ helps boost the skin's natural ability and sweeps away the adverse effects of sunlight, oxidative stress, and dryness while maintaining skin hydration and elasticity. Robin and Rolland (2004) patented a formulation containing verbascoside to use in cosmetics as a stimulant agent for the production of thermal shock proteins and as an inhibitor of collagenase and elastase in the skin cells.

In recent years, there has been a growing interest to improve athletic performance and body composition (the ratio of lean to fat mass). Panyam and Chavanpatil (2011) patented preparations containing verbascoside or verbascoside-rich extracts to be administrated in capsule, pill, powder, edible bar, or liquid form in order to increase strength, muscle power, endurance, muscle protein content, and to reduce fatigue. Tu et al. (2005) patented a drug with verbascoside (5%–40%) as an active ingredient to prevent senile dementia and inhibit aggregation of blood platelets.

Concerning the use of this compound in food, Chaves-López et al. (2015) demonstrated that verbascoside-rich (135.20 ppm) extracts incorporated to fermented sausages had antifungal activity without inducing significant changes on sensory characteristics, thus being considered a potential alternative to synthetic antifungal compounds.

4.5 | Oleuropein aglycone

Oleuropein aglycone (Figure 2), also known as 3,4-DHPEA-EA (i.e., 3-4-DHPEA-elenolic acid mono-aldehyde, IUPAC name: methyl (2R,3Z,4S)−4-{2-[2-(3,4-dihydroxyphenyl)ethoxy]−2-oxoethyl}−3-ethylidene-2-hydroxy-3,4-dihydro-2H-pyran-5-carboxylate), is a secoiridoid formed from the deglycosylation of oleuropein, which can be produced by enzymatic, acid or acetal hydrolyses (Xu et al., 2018). Several studies referred to it as the main polyphenol present in olive oil (e.g., Cordero et al., 2018; Xu et al., 2018), but it is also abundant in olive wastes. In recent times, this compound has gained attention due to its biological activities, including anti-neurodegenerative diseases, anti-breast cancer, anti-inflammatory, anti-hyperglycemic, antioxidant, and lipid-lowering properties (Grossi et al., 2013; Menendez et al., 2007; Oi-Kano et al., 2017; Palazzi et al., 2018; Rigacci et al., 2010; Xu et al., 2018).

Oleuropein aglycone has the ability of promoting the autophagy, thus being associated with a reduction of symptoms of Alzheimer's disease and cognitive impairment (Casamenti et al., 2015; Cordero et al., 2018). Grossi et al. (2013) found that the administration of oleuropein aglycone in young/middle-aged TgCRND8 mice for 8 weeks could improve memory and animal behavior by interfering with Aβ aggregation. Oleuropein aglycone was also seen to slow down amyloid aggregation by stabilizing α-synuclein monomers, thus hampering their progression to cytototoxic amyloids, which could be helpful in the prevention of Parkinson's disease. In addition, it may also hinder the binding of α-synuclein aggregates to cell membrane components thus preventing cell oxidative damage (Palazzi et al., 2018). Leri and Bucciantini (2016) reported that oleuropein aglycone could inhibit the toxic effects of transthyretin (TTR) amyloid and be important to prevent or treat heart and liver complications. It has also been shown to be capable of preventing or delaying the progression of type 2 diabetes (Rigacci et al., 2010) and obesity (Oi-Kano et al., 2017). Oi-Kano et al. (2017) reported that it reduced the visceral fat content in high-fat diet-induced obese rats by enhancing noradrenaline secretion via β-adrenergic action following transient receptor potential ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) activation. Oleuropein aglycone was found to protect LDL in plasma against oxidation (Leenen et al., 2002) as well as to enhance the antioxidant defense system against experimental atherogenesis, which was attributed to its 3,4-dihydroxyphenyl ethanol group (Jemai et al., 2008).

Menendez et al. (2007) reported that, among the polyphenols present in olive oil, oleuropein aglycone was the most potent compound in decreasing breast cancer cells viability, by inhibiting the proteolytic processing of human epidermal growth factor receptor2 (HER2).

In a study developed by Bisignano et al. (2014), oleuropein aglycone was found to be effective against American Type Culture Collection (ATCC) and clinical isolates of *S. aureus* (minimum inhibitory concentrations [MIC] values between 125 and 250 μg/ml) and *Staphylococcus epidermidis* (MIC values between 7.81 and 62.5 μg/ml). Although further studies have to be performed in order to understand the mechanisms responsible for these results, this compound could be a potential natural antimicrobial for the treatment of skin infections.

5 | CONCLUSION

The compounds present in the wastes generated during the olive oil extraction process may have considerable health benefits and be used, after suitable purification, as food antioxidants or active ingredients in nutraceutical and cosmetic products, because they possess a range of recognized bioactivities, technological, and pharmaceutical properties. Further research on their potential applications should be granted in order to valorize them and maintain environmental sustainability. In addition, it is imperative for the development of green and efficient extraction methods to ensure higher recovery of these compounds and the cooperation between industry and researchers to generate sustainable added value to these byproducts, thus contributing to the circular economy.

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AUTHOR CONTRIBUTIONS

Joana Madureira: Data curation; investigation; visualization; writing—original draft, review, and editing. Fernanda M. A. Margaça: Funding acquisition; visualization; writing—review and editing. Celestino Santos-Buelga: Conceptualization; funding acquisition; supervision; visualization; writing—review and editing. Isabel C. F. R. Ferreira: Conceptualization; funding acquisition; project administration; writing—review and editing. Sandra Cabo Verde: Conceptualization; funding acquisition; supervision; visualization; writing—review and editing. Lillian Barros: Conceptualization; funding acquisition; supervision; writing—review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Meet the Microbes: The Role of Microorganisms in the Safety, Quality, and Shelf life of Meat and Meat Products

Free Virtual Seminar | December 2, 2021 | 12PM EST

Microorganisms in meat play a significant role in the safety, quality, and shelf life of meat and meat products. Pathogenic organisms such as Salmonella, E.coli 0157:H7, Campylobacter, and Listeria monocytogenes represent important food safety hazards and public health threats. Other microorganisms are involved in spoilage, quality issues, and reduced shelf life.

In this webinar, we will explore major pathogens in meat and the public health burden of foodborne illness outbreaks involving these pathogens, issues dealing with sampling and the microbiological testing of meat, and industry and regulatory approaches for assuring the safety and quality of meat and meat products. We will also discuss the 25th anniversary of HACCP regulation for meat and meat products, and its impact on meat safety.

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