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Applications of by-products from the olive oil processing: Revalorization strategies based on target molecules and green extraction technologies

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ABSTRACT

Background: During the last decades, olive oil consumption has experienced a continuous increase due to its unique organoleptic properties and its related beneficial properties. Consequently, waste and by-products derived from the olive production have also increased causing environmental problems and economic losses. However, the low-cost and huge availability of these by-products is an opportunity for their valorization and the obtaining of high added-value compounds such as tyrosol, hydroxytyrosol (HT), oleocanthal, oleuropein (OLE), ligstroside, squalene, fatty acids, etc. The development of innovative extraction and characterization technologies is a key factor for the olive sector. In addition, a deeper knowledge about the biological properties of the compounds present in the recovered products and their mechanism of action is crucial to allow their reintegration in the food chain and their potential uses in the food and pharmaceutical industries.

Scope and approach: This review encompasses all these aspects showing the advances achieved to date in the olive oil by-products valorization focusing on their biological properties, including cardioprotective, antioxidant, anticancer, anti-inflammatory and antidiabetic effects.

Key findings and conclusions: The by-products derived from the *Olea europaea* L. processing industry are secondary but valuable products, from which different biologically active molecules can be recovered by green extraction technologies (PLE, SFE, *etc.*) and reused for food, pharmaceutical and cosmetic purposes following the circular economy policies. One of the main advantages on recovering valuable molecules from olive by-products is their incorporation to functional foods. A direct effect was proved between the use of olive by-products in human consumption and the heath claims. In this context, different food industries have used the phenolic fraction of olive by-products, holding mostly HT and OLE, as food additives and as preserving agents due to their antioxidant properties.

1. Introduction

The term "superfoods" is becoming popular in the food sector to named foods that claim health benefits (Galanakis, Aldawoud, Rizou, Rowan, & Ibrahim, 2020). In the last two decades, the food industry is looking for ingredients in food products that increase health benefits. To follow this trend, several additives and active compounds from different sources are being investigated as antimicrobial, anti-inflammatory, and potential antiviral agents (Galanakis, 2020; Galanakis et al., 2020).

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Abbreviations

General Terms

EVOO	Extra Virgin Olive oil
OO	Olive oil
HVED	High voltage electrical discharges
HT	Hydroxytyrosol
MUFAs	Monounsaturated fatty acids
OLE	Oleuropein
OMWW	Olive mill wastewater
OP	Olive pomace
PUFAs	Polyunsaturated fatty acids
SFAs	Saturated fatty acids
TPC	Total phenolic content
GAE	Gallic acid equivalents
dw	Dry weight
TAG	Triacylglycerols
VOO	Virgin olive oil
EFSA	European Food Safety Authority
HDL	High-density lipoprotein
LDL	Low-density lipoproteins

Extraction Techniques

EAE	Enzyme-assisted extraction
IR-AE	Infrared-assisted extraction
MAE	Microwave-assisted extraction
MEAE	Microwave-enzyme-assisted extraction
PLE	Pressurized liquid extraction
UAE	Ultrasound-assisted extraction
US–LLE	Ultrasound-assisted liquid-liquid extraction
SWE	Subcritical water extraction
SC-CO_2	Supercritical carbon dioxide extraction
SFE	Supercritical fluid extraction

Assays and Bioactivities

ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
COX-2	Cyclooxygenase-2
DPPH	2,2-diphenyl-1-picrylhydrazyl radical scavenging
FRAP	Ferric reducing ability of plasma
iNOS	Inducible nitric oxide synthase
ORAC	Oxygen radical absorbance capacity
PGE2	Prostaglandin E2
PPARGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1 alpha
MMP-9	Matrix metallopeptidase-9
Nfr2	Nuclear factor (erythroid-derived 2)-like 2
LPS	Lipopolysaccharide
NO	Nitric oxide
NF-κB	Nuclear factor κ-B
IL	Interleukin
MAPK	Mitogen-activated protein kinase
HO-1	Heme-oxygenase-1
ERK	Extracellular signal-regulated protein kinases
ROS	Reactive oxygen species
TEAC	Trolox-Equivalent antioxidant capacity
TNF-α	Tumor necrosis factor-alpha

Moreover, the food industry is considering the new period post-pandemic COVID-19 in which consumers are concerned about ingesting products to enhance their immune systems and to increase the heathier diets (Galanakis, 2020; Galanakis, Rizou, Aldawoud, Ucak, & Rowan, 2021). Thus, the production of bioactive compounds to develop functional foods may become a bottleneck, being necessary to identify new sources of bioactive compounds to increase the availability of healthy food products. In this sense, the food industry should consider innovations that disrupt the way we consume food being one approach to valorize the vast range of bioresources (Galanakis et al., 2021). It is worthy to accelerate efforts in developing sustainable and modern food systems including large food supply chains based on by-products, reducing the cost of food waste treatment, and their reutilization in the food chain.

The by-products derived from the *Olea europaea* L. processing industry are secondary but valuable products, from which different bioactive molecules such as polyphenols, anthocyanins, tannins, flavonoids, and dietary fiber (pectin) can be recovered and reused for several purposes following the circular economy policies (Markhali, Teixeira, & Rocha, 2020). One option to separate these bioactive compounds from agricultural wastewaters is by traditional extraction techniques such as the use of organic solvent and filtration processes (membrane) (Galanakis, 2015). Processes of phenols recovery include condensing steps (thermal concentration, filtration or lyophilization) and then, sequential extraction steps with methanol, ethanol or hydro-alcoholic solutions (Rahmanian, Jafari, & Galanakis, 2014). In this sense, the bibliography describes numerous process about the recovery and purification of phenolic compounds from olive mill wastewater (OMWW) and olive vegetable water (OVW) with membrane treatment such us microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO) (Kaleh & Geiβen, 2016; Russo, 2007; Servili et al., 2011; Zagklis, Vavouraki, Kornaros, & Paraskeva, 2015). Different membrane separation techniques of vegetable wastewater for the recovering of hydroxytyrosol (HT) in pilot plants with fixed process parameters were investigated. Results showed RO concentrate can be used as pharmacological preparations due to the content of low MW polyphenols, which are the principal products for food, pharmaceutical and cosmetic industries (Russo, 2007). Hydrophilic phenols were recovered from fresh OVW in an industrial plant by innovative techniques like membrane filtration prior enzymatic treatment (Servili et al., 2011). This novel approach yielded a crude phenolic concentrate which was utilized in a virgin olive oil (VOO) extraction process with the aim of improving VOO phenolic content. In fact, the economic feasibility of a system based on membrane filtration and RO processes for phenolic compound extraction and considering their subsequent reuse to enrich Extra Virgin Olive Oil (EVOO) during the malaxation phase shows to be economically viable showing a reduction of the waste product (La Scalia, Micale, Cannizzaro, & Marra, 2017).

In addition, selective concentration by green extraction technologies including high-hydrostatic pressure, ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE), pulsed electric field, radio-frequency drying, high voltage electrical discharge, and supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE) can also be used (Galanakis, 2021). These processes aim either to recover a particular phenol (HT) in pure form or in the recovery of a phenol's mixture as a crude product. The application of emerging technologies on different food components (lipids, minerals, vitamins, polyphenols, aroma compounds, and enzymes) keep their effectiveness and bioactive content and bioavailability since they are not based on high temperature avoiding damage the compound structure. These techniques can also improve their functional and culinary properties and increase the recovery yields from agricultural products. Besides, these techniques are environmentally friendly, provide high efficiency, rapid temperature increase, short extraction time, improve the process monitoring and consume low energy consumption (BursaćKovačević et al., 2018; Nagarajan et al., 2019; P. Otero, Quintana, Reglero, Fornari, & García-Risco, 2018; Sarfarazi, Jafari, Rajabzadeh, & Galanakis, 2020). However, the optimization of operational parameters is vital to avoid degradation of macromolecules and the oxidation of labile compounds [11,12].

2. Olive oil production process and main by-products

The tree species *Olea europaea* L., commonly known as olive tree, is distributed throughout the Mediterranean (Jimenez-Lopez et al., 2020). Olive worldwide farming covers about 11.6 million hectares, whereas in Spain the total area under olive cultivation is 2.7 million hectares (Fonseca, Mateo, Roberto, Sánchez, & Moya, 2020). In fact, the European Union (EU) is responsible for the 70% of the world's olive production, generating 7 × 10^9 €/year and being a key factor for agro-industrial, social and economic development (Jimenez-Lopez et al., 2020).

In the last years, olive oil (OO) production has experienced a growing economic situation, which is partially due to its beneficial properties, mostly attributed to EVOO (Contreras, Romero, Moya, & Castro, 2020; Domingues, Fernandes, Gomes, Castro-Silva, & Martins, 2021; Rodrigues, Pimentel, & Oliveira, 2015). OO plays a vital role in the Mediterranean diet, and it has been associated with several beneficial properties due to its high content in polyunsaturated fatty acids and various minor compounds (*i.e.* sterols). About 85% of OO composition is unsaturated fatty acids (due to its high content in oleic acid, C18:1), followed by saturated fatty acids. Minor compounds are represented by phenolic compounds or tocopherols. These phenolic compounds help protecting against oxidative stress and contribute to make OO a healthier product. Because of this rising demand, OO production grows and so does waste production. For instance, Turkey's annual OO production is currently 200,000 tons and therefore, approximately 650,000 tons of olive pomace per year are generated (Çelekli, Gün, & Bozkurt, 2021). Hence, the large amount of waste generated has always been of great concern. However, the search for waste management strategies in the OO industry still needs more development to limit its environmental and economic impact (de la Casa, Bueno, & Castro, 2021; P.; Gullón, Gullón, Astray, et al., 2020). In this perspective, and considering the composition of OO and its by-products, it is important to select the appropriate extraction technology and determine specific applications for these bioactive compounds, thus different approaches have been employed (Table 1). For this purpose, conventional techniques such as maceration, and less traditional techniques such as microwave-, infrared- or ultrasound-assisted extraction, among others, have been used. These extraction methodologies have certain advantages over conventional ones, since there is a minimum degradation of compounds, fewer solvents are needed, and better extraction yields are obtained (G. S. da Rosa et al., 2021).

In respect of the production of OO, this is a mechanical process that can be developed according to three main types: pressing (traditional process), two-phase centrifugal separation and three-phase centrifugal separation (Domingues et al., 2021). In turn, this process generates flows of OO and the different residues (olive cake, pomace, stones and olive mill wastewater) (Fig. 1) (Galanakis & Kotsiou, 2017). In the two-stage process, solid residues are formed and reused in drying processes to recover the remaining OO, but new wastewater is generated as well (Domingues et al., 2021). More concretely, the process begins with the olives batch washing. Larger residues are separated using mechanical means and water, while smaller waste is separated using other separation methods, such as a vibrating screen and air blowing. Then, in the oil mill, they are reduced to a smaller size together with the olive stones. After this process, a homogeneous paste consisting of water, oil and solids remains. In the traditional separation process, this paste is then pressed between two mats to obtain the solid part together with a liquid fraction composed of oil and water (known as pomace), which over time can be separated into two parts (P. Gullón, Gullón, Astray, et al., 2020). In the two-phase separation, a two-phase decanter is used to separate the oily part and the part consisting of solids and water. Then, this remaining solid residues are dried or extracted to recover oil. In the third

Table 1
Extraction technologies, conditions and yields of the main bioactive compounds from olive oil production by-products.

Technique	Conditions	Molecules	Yield (mg/g dw)[a]	Ref.
Leaves				
Maceration	Wt, 25 °C, 24 h	TPC	57.28 mg/g dw	Cazals et al. (2019)
		OLE	0.051 mg/g dw	
		HT	0.027 mg/g dw	
	40% EtOH, 25 °C, 24 h	TPC	98.14 mg/g dw	(G. S. da Rosa et al., 2019)
	70% EtOH, 25 °C, 24 h	TPC	115.75 mg/g dw	
MAE	Wt, 1000 W, 86 °C. 3 min	TPC	104.22 mg/g dw	Cazals et al. (2019)
		OLE	14.46 mg/g dw	
		HT	0.59 mg/g dw	
	40% EtOH, 1000 W, 5 min	TPC	114.29 mg/g dw	(G. S. da Rosa et al., 2019)
	70% EtOH, 1000 W. 5 min	TPC	130.09 mg/g dw	
UAE	Wt, 450 W, 27 °C, 29 min	TPC	80.51 mg/g dw	Cazals et al. (2019)
		OLE	6.91 mg/g dw	
		HT	0.547 mg/g dw	
	51.3% EtOH, 15 min	TPC	42 mg/g dw	Martínez-Patiño et al. (2019)
	47% EtOH, 50 min	TPC	0.31 mg/g dw	Contreras, Lama-Muñoz, et al. (2020)
		OLE	4.19 mg/g dw	
	50% AC, 60 °C, 10 min	TPC	37.44 mg/g dw	Irakli, Chatzopoulou, and Ekateriniadou (2018)
IR-AE	55% EtOH, 90 °C, 220 min	TPC	36.23 mg/g dw	(A.-M. Abi-Khattar et al., 2020)
		OLE	14.01 mg/g dw	
PLE	60% EtOH, 190 °C, 5 min	OLE	63.35 mg/g dw	(A. D. da Rosa et al., 2019)
	80% EtOH, 60 °C	TPC	386.42 mg/g dw	
		OLE	73.65 mg/g dw	
HVED	50% EtOH, 9 min	TPC	65.99 mg/g dw	Žuntar (2019)
SFE	80 °C, 80 min	TPC	30.2–36.1 mg/g dw	Caballero, Romero-García, Castro, and Cardona (2020)
Pruning biomass				
Maceration	50% EtOH, 55 °C, 90 min	TPC	23.85 mg/g dw	(B. Gullón et al., 2018)
UAE	54.5% EtOH, 70% amplitude, 15 min	TPC	31.0 mg/g dw	Martínez-Patiño et al. (2019)
SFE	EA, 50 °C, 60 min, 200 bar	TPC	7.94 mg/g	Caballero et al. (2020)
		HT	0.03 mg/g	
	EA, 50 °C, 60 min, 300 bar	TPC	10.39 mg/g	
		HT	0.18 mg/g	
SWE	180 °C, 10 min	OG	37.5 g/L	Cara et al. (2012)
Aqueous olive mill wastewater				

(continued on next page)

Table 1 (*continued*)

Technique	Conditions	Molecules	Yield (mg/g dw)[a]	Ref.
Maceration	Wt, 30–70 °C, 60 min	PP	1.8 mg/L	Conidi et al. (2019)
SFE	CO_2, 70 °C, 25 MPa, 420 min	SQ	0.967 mg/kg	(Gallego, Bueno, & Herrero, 2019;
	CO_2+0.25% EtOH, 480 min	PP and SQ	10.86 mg/kg	Schievano et al., 2015)
US-LLE	EA, 100W 10 min	TPC	1.84 mg/mL	(Jerman Klen & Mozetič Vodopivec, 2011)
	DE, 100W 10 min	TPC	1.15 mg/mL	
Olive cake				
Maceration	MetOH, 60 °C, 60 min	TPC	4.07 mg/g	Alu'datt et al. (2010)
UAE	LA: GLC with 15% Wt	PP	ns	(P. Gullón, Gullón, Romaní, et al., 2020)
SC-CO2	40.2 °C, 43.8 MPa, 30min	PP, TP and SQ	145 mg/g dw	Durante et al. (2020)
Olive pomace				
Maceration	Wt, 100 °C, 30 min	GLC, P and MA	64%	Manzanares et al. (2020)
	Wt, 210 °C, 4 min	GLC	74%	Manzanares et al. (2020)
UAE	Wt, 160 W, 25 °C, 5 min	TPC	0.40 mg/mL	Nunes et al. (2018)
		OLE	1.18 mg/mL	
MAE	100% EtOH, 600 W, 35–60 °C, 17 min	TPC	118.0 mg/g	Macedo et al. (2021)
		HT	128.4 mg/kg	
	NADES, 200 W, 60 °C, 30 min	OLE	5–7.56 mg/g dw	Xie et al. (2019)
		HT	0.43–0.89 mg/g dw	
SFE	EA, 50 °C, 60 min, 200 bar	TPC	9.18 mg/g	Caballero et al. (2020)
		HT	0.91 mg/g	
	EA, 50 °C, 60 min, 300 bar	TPC	14.01 mg/g	
		HT	1.25 mg/g	
SWE	130 °C, 30 min	OG	14.7 g/100 g	Miranda et al. (2019)
EAE	50 °C, 120 rpm, 2 h	TPC	153–372 mg/g	Macedo et al. (2021)
		HT	17.16 mg/kg	
MEAE	EtOH, 600 W, 35–60 °C, 17 min + 2.0% enzymes	TPC	0.341 mg/kg	Macedo et al. (2021)
		HT	24.4 mg/kg	
		EO	1029 mg/kg	
Olive stones				
HAE	MetOH, 40 °C, 90 min	TPC	211.63 mg/kg dw	(Nakilcioğlu-Taş & Ötleş, 2019)
		OLE	36.99 mg/kg dw	
	MetOH, 40 °C, 60 min	HT	26.85 mg/kg dw	
S/L	Dilute acid, 130 °C, 90 min	TPC	120 mg/100 g dw	Lama-Muñoz, Romero-García, Cara, Moya, and Castro (2014)

TPC: Total phenolic content, OLE: Oleuropein, HT: Hydroxytyrosol, OG: Oligosaccharides, PS: Polysaccharides, XYL: Xylose, GLC: Glucose, SQ: Squalene, PP: Polyphenols, P: Phenols, TP: Tocopherols, MA: Mannitol, Wt: water, EtOH: Ethanol, MetOH: Methanol, AC: Acetone, EA: Ethyl acetate, DE: Diethyl ether, LA: Lactic acid EO: Elenolic acid, MAE: Microwave-assisted extraction, UAE: Ultrasound-assisted extraction, IR-AE: Infrared-assisted extraction, PLE: Pressurized liquid extraction, HVED: High voltage electrical discharges, SFE: Supercritical fluid extraction, SWE: Subcritical water extraction, SC-CO2: Supercritical carbon dioxide, EAE: Enzyme-assisted extraction, MEAE: Microwave-enzyme-assisted extraction, US -LLE: Ultrasound – assisted liquid – liquid extraction, ns: not specified, HAE: Heat assisted extraction, S/L: Solid to liquid extraction.

[a] TPC yield is expressed in GAE (Gallic Acid Equivalents).

extraction phase, a separation by densities takes place in a three-phase decanter. In this stage, water is usually added to separate and clean the oil, thus obtaining a clarified oil and residual water, separately (Peri, 2014). Once the extraction process has been completed, OO holds solid particles that are in suspension, so filtration and solid-liquid separation is conducted. Finally, it is stored and packaged until shipped for marketing (P. Gullón, Gullón, Astray, et al., 2020). As a result of the OO production process, obtained by-products can be classified in the following parts: leaves and pruning biomass, aqueous olive mill wastewater, olive cake and olive pomace, which will be described below.

2.1. Leaves and pruning biomass

This by-product is composed of branches and leaves that, given the perennial nature of olive tree, accumulate during the maintenance of olive groves. It includes pruning or harvesting and also the cleaning of the olives prior to processing (P. Gullón, Gullón, Astray, et al., 2020). Both in the olive mill (accumulation of leaves, stones, pomace and the main product) and during olive trees pruning, a large amount of biomass is generated (Contreras, Romero, et al., 2020). Within this biomass, around 50% of weight is generated from fine branches, 25% from leaves and the remaining 25% is made up of coarse branches or wood (P. Gullón, Gullón, Astray, et al., 2020). Most of this biomass is partially used on-site in the form of energy, but new alternatives to produce high added-value products for food and/or pharmaceutical markets are continuously appearing (Manzanares et al., 2020).

Different chemical compounds can be found in this matrix, which may vary according to several factors such as: the selected extraction technology, analysis systems or cultivation methods, among others. Nevertheless, the chemical composition of olive leaves resembles to lignocellulosic materials (P. Gullón, Gullón, Astray, et al., 2020). In addition, major phenolic groups, such as simple phenols, flavonoids and secoiridoids can also be found. Among these compounds, the most common is the oleuropein (OLE) followed by hydroxytyrosol (HT) (5 times lower) (de Bock et al., 2013) and followed by tyrosol (up to 8 times less than HT) (Lamprou, Vlysidis, & Vlyssides, 2017), together with phenolic acids, such as caffeic, gallic or vanillic acids (Flamminii et al., 2021). One of the main roles of HT and OLE in olive leaves is to confer a natural defense against biological predators. Regarding industrial applications, OLE can be used as an alternative to synthetic preservatives and antibiotics for their antioxidant and antimicrobial properties. A recent study has tested both the antioxidant and antimicrobial activity of olive by-products (*i.e.* extracts from olive leaves) and it has been verified that they can be used in the food sector to improve the nutritional profile of food products and provide biological protection through their antimicrobial action (G. S. da Rosa et al., 2021). The phenolic composition of these by-products has led to add olive leaf extracts to VOO and other food products as a functional additive (Benincasa, Santoro, Nardi, Cassano, & Sindona, 2019). A study shows the protective attributes of OLE from olive trees are reflected typically by their inhibiting effects against oxidation, microbial disorders, inflammation, and platelet aggregation. In addition, OLE is found to be effectively capable of re-building the tissue damage, caused by cisplatin in stomach and lung organs (Markhali et al., 2020).

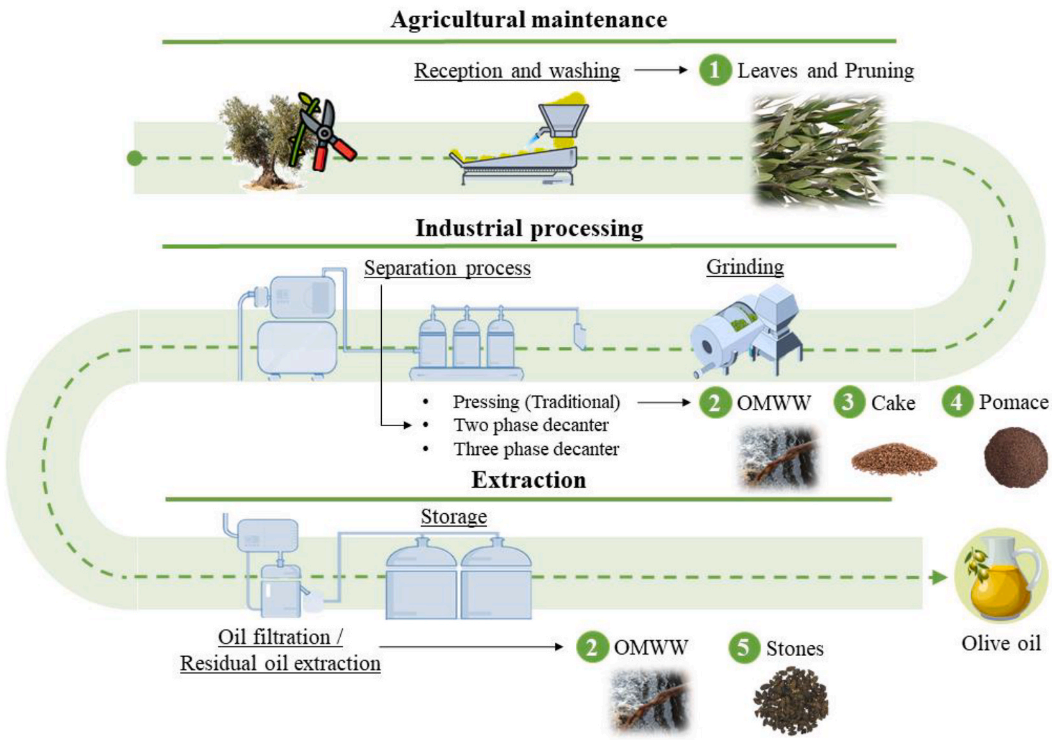

Fig. 1. By-products of the olive oil industry from agricultural maintenance (leaves and pruning biomass) and industrial process (aqueous olive mill wastewater, cake, pomace and stones).

Today, this by-product has not been exploited, and its disposal requires a cost. It is usually eliminated through burning or burying with other by-products on the ground and can occasionally be used as animal feed (Cazals et al., 2019). The latter has been assessed as an alternative for enriching animal feeds in order to obtain better quality meat combined with increased weight gain (Mattioli et al., 2018). Additionally, olive leaves have been described to possess high concentrations of polar bioactive compounds, which has led to add leaf phenolic extracts to OOs in order to further enhance their antioxidant properties (Paiva-Martins, Correia, Félix, Ferreira, & Gordon, 2007). For this reason, revalorization approaches of this by-product have been proposed. In this context, the extraction of bioactive compounds is considered a potential alternative, thus, extraction techniques are essential to obtain enriched extracts with target molecules and to optimize extraction yields (Table 1). Traditional extraction techniques like maceration can be applied to both leaves and pruning biomass and also novel techniques such as UAE (*e.g.* using water and ethanol also at different extraction times) and SFE (*e.g.* using ethyl acetate at different times and pressures) (A. M. Abi-Khattar et al., 2019; Cazals et al., 2019; G. S. da Rosa, Vanga, Gariepy, & Raghavan, 2019; P. Gullón, Gullón, Astray, et al., 2020). In leaves, extraction techniques such as infrared-assisted extraction (IR-AE) have showing more efficiency compared to conventional extraction. MAE has also been used (*e. g.*, using both ethanol, water, and acetone, but at different extraction times). PLE proved to obtain higher content of total phenolic content (TPC) and OLE than traditional techniques. Also, high voltage electrical discharges (HVED) displayed higher yield of phenolic compounds using ethanol as solvent (P. Gullón, Gullón, Astray, et al., 2020). In biomass pruning, extraction techniques such as steam explosion and subcritical water extraction (SWE) have been used for the recovery of glucose and xylose sugars (Manzanares et al., 2020). In this case, the technique that showed the highest yield for TPC extraction, compared to the other techniques, was UAE with 31.0 mg of gallic acid equivalents (GAE) per gram of dry weight (dw).

2.2. *Aqueous olive mill wastewater*

Olive mill wastewater (OMWW) is a complex effluent of different nature depending on the process that olives undergo and the crops' characteristics (Domingues et al., 2021). In general terms, OMWW can be considered as a mixture of oil, mucilage, sugars, tannins and organic acids (Flamminii et al., 2021). This mixture originates from the three-phase process during traditional decanting, but large quantities also originate from washing and extraction process stages (P. Gullón, Gullón, Astray, et al., 2020). In addition, over the years, it has been considered the most polluting waste in the Mediterranean area (P. Gullón, Gullón, Astray, et al., 2020). So, due to the major problem it causes, OO production is changing from a three-stage process to a two-stage process, and *n*-hexane has been included for its extraction (Domingues et al., 2021). After going through the two-stage process, these waters can become dark brown and increase its moisture content (Torrecilla & Cancilla, 2021). Actually, water content represents between 70 and 90% of the total weight of OMWW and it usually has a pH ~5 (slightly acidic) (Flamminii et al., 2021). However, this improvement does not totally solve the OMWW problem on its own, it only releases the olive mills from the environmental burden and concentrates the problem in the oil extraction industry. Therefore, new treatment of a real effluent from an OO extraction industry are proposed, using the Fenton's process integrated with coagulation.

OMWW is composed of a high concentration of organic compounds like carbohydrates, proteins, fatty acids (FA), carotenoids, tocopherols and phenolics, thus being a promising source of high added-value bioactive compounds (P. Gullón, Gullón, Astray, et al., 2020). It is also characterized by high biological and chemical oxygen demand values (40–80 g/L and 50–159 g/L, respectively), which may be due to its high content of organic acids and sugars (Flamminii et al., 2021). It has also shown an elevated phenolic content and pectin. However, these phenolic substances can sometimes present phytotoxicity, which limits OMWW use for agricultural purposes as soil amendment (Despoudi et al., 2021; Di Nunzio et al., 2020; Domingues et al., 2021). However, if well treated to reduce the toxicity of the phenolic compounds in these waters, their recovery and application as fertilizers or compost could be a potential alternative, in addition to the high added-value products that can be recovered for further use in food, cosmetic or pharmaceutical applications (Sánchez-Arévalo, Jimeno-Jiménez, Carbonell-Alcaina, Vincent-Vela, & Álvarez-Blanco, 2021). A study used heat-assisted extraction (HAE) combined with mixtures of different solvents, such as ethanol, to obtain a dietary fiber-containing material composed only of pectin from this by-product. Therefore, this material could serve as a gelling agent although there is still a lack of studies on its rheological behavior (Galanakis, Tornberg, & Gekas, 2010a).

From an economic point of view, OMWW management presents a high cost; its disposal is around 3.25 €/m^3 and, if transferred from biomass or composting, 6–10 €/m^3 (Flamminii et al., 2021). Nevertheless, a correct recovery of target compounds from this by-product, such as polyphenols, will not only improve the economic situation of OO producers, but will be less toxic too. So, the recovery of bioactive extracts through extraction techniques, such as maceration, is mandatory (Table 1) (Conidi, Egea-Corbacho, & Cassano, 2019). In addition, there are other types of extraction for the recovery of phenols in OMWW, such as ultrasound-assisted liquid-liquid extraction (US–LLE), which was more efficient ethyl acetate as solvent than diethyl ether (Table 1). As a result, this technique constitute a good alternative to conventional solvent extractions (Jerman Klen & Mozetič Vodopivec, 2011).

2.3. Olive cake

Olive cake, also called "*orujillo*", is the dry extracted pomace. It is a weathered solid that is formed when olive pomace is processed to recover the residual or pomace oil (P. Gullón, Gullón, Astray, et al., 2020). It mainly comes from multiphase decanters that generate around 55% of the total weight of the olive and is composed of the pulp and skin, without including the stones (Durante et al., 2020).

Concerning its chemical composition, it contains a diversity of phytochemicals such as phenolic compounds and other hydrophilic and lipophilic bioactive molecules, including sterols, pentacyclic triterpenes, tocochromanols, carotenoids and mono- and polyunsaturated fatty acids (PUFAs) (Durante et al., 2020; P.; Gullón, Gullón, Astray, et al., 2020). Among phenolic compounds, HT, tyrosol, secoiridoids derivatives and phenolic acids can be found (Tufariello et al., 2019).

Regarding its current use, olive cake possesses a high oil content and a calorific value of 17.6 MJ/kg, therefore, it is considered a suitable material for the production of heat and electricity by direct combustion (Gálvez-Pérez et al., 2021). Olive cake has also been used in food industry, *e.g.* spaghetti enriched with 10% of this by-product have been developed to increase their total polyphenol content, also showing anti-ageing effects on human fibroblast cells (Tufariello et al., 2019). It has also been applied for other purposes as proven in a study with goats which showed that this by-product could be used as alternative animal feed (El Otmani, Chebli, Hornick, Cabaraux, & Chentouf, 2021). The use of olive cake for the animal feeding was studied by different research groups with significant effects both on the animal wellbeing, productivity and quality of meat and milk product (Cibik & Keles, 2016; Estaún, Dosil, Al Alami, Gimeno, & De Vega, 2014; Tzamaloukas, Neofytou, & Simitzis, 2021).

Also, different extraction techniques have been performed to obtain bioactive molecules from this by-product (Table 1). These techniques include maceration with methanol, able to extract most of the phenolic compounds present in their free forms, or UAE using 15% lactic acid in water, resulting in an effective extraction of both polar and nonpolar compounds (Alu'datt et al., 2010; P.; Gullón, Gullón, Romaní, Rocchetti, & Lorenzo, 2020). Finally, supercritical carbon dioxide extraction (SC–CO2), has been applied for the efficient recovery of high-value natural bioactive from this by-product. In particular, a recent study applied response surface methodology to maximize oil extraction, resulting in a higher content of phytosterols, tocopherols and squalene (Durante et al., 2020).

2.4. Olive pomace

Olive pomace (OP) is a by-product resulting from the solid part of the extract after the removal of crude olive pomace oil, consisting mainly of the stone, the peel and the pulp (Çelekli et al., 2021). It stands for 35–40% of the total weight of the olive processed in the mill, considered as the main residue of the OO extraction production process. It is produced at the two-phase and three-phase system, more specifically from the insoluble phase, being useful in subsequent processes (P. Gullón, Gullón, Astray, et al., 2020).

OP possesses a high content of organic matter, fats, carbohydrates and water-soluble phenolic substances (Rodrigues et al., 2015). It also contains proteins, although its composition comes from lignocellulosic biomass (30–41.6% lignin, 35.3–49.0% cellulose, pectic polymers, hemicelluloses, oils, and minerals) (P. Gullón, Gullón, Astray, et al., 2020). OP composition may vary depending on whether a two-phase (the most used in Spain) or a three-phase production process is used. OP is a coarse brown sludge that, depending on the extraction system applied, presents different moisture content: in this sense, after the application of the two-stage system OP moisture reaches up to 70%, which are significantly higher than those derived either from the three-stage system, with moisture values of 45% in the residue, or the separation system of traditional OO mills with moisture values of 22–25%. All this situation makes difficult to handle and apply treatments, and explains the diversity between the different olive pomaces (P. Gullón, Gullón, Astray, et al., 2020; Manzanares et al., 2020). In general, processing 1000 kg of olives with the traditional system produces 400 kg of OP, 800 kg in the two-phase systems and 500 kg in the three-phase system (Flamminii et al., 2021).

OP can become a potential low-cost material, rich in bioactive phenols, for instance to produce healthier and added-value foods. In one study, the reuse of this by-product as a functional ingredient to produce biscuits and bread with different flours and fermentation protocols had promising results, *viz.* The bread that was made with conventional fermentation enriched with 4% olive pomace had the greatest anti-inflammatory effects (Di Nunzio et al., 2020). In addition, OP is considered an undervalued waste, although it has been employed in multiple applications, such as biofuel production, in the OO production industry itself, or as feedstock in biorefineries (Miranda et al., 2019). In this sense, OP can be used in the production of refined OO, throughout an additional stage of solvent extraction coupled with a refining process to eliminate or reduce all the substances or impurities that can affect oil quality (P. Gullón, Gullón, Astray, et al., 2020). In Spain, OP is extracted with solvents such as hexane (traditional system), by physical procedures, or centrifugation (Manzanares et al., 2020).

Furthermore, to obtain bioactive molecules from OP, different extraction methods have been applied (Table 1). MAE allowed better extraction of polyphenolic compounds, through an environmentally friendly process that transforms energy into heat due to electromagnetic radiation, (Xie et al., 2019), while UAE has been often used due to its properties as a cost-effective, fast and highly efficient technique. In general, both MAE and UAE have demonstrated its ability to recover high-value compounds from OP reporting differential results (Table 1), obtaining higher yields in TPC by MAE (Xie et al., 2019). Besides these widely applied extraction techniques, enzyme-based extraction techniques have been also applied to OP. Enzyme-assisted extraction (EAE), and its combination with MAE (microwave-enzyme-assisted extraction, MEAE) can be highlighted. These techniques use enzymes (*e.g.* cellulases, pectinases, and tannases) and have been reported to promote higher extraction yields in terms of phenolic compounds, phenolic alcohols and acids concentrations (Macedo et al., 2021).

2.5. Olive stones

Olive seeds or stones (OSs) are a lignocellulosic low moisture by-product that can be obtained after the separation through horizontal centrifugation of the OP (crushed seeds, peels and pulp) (Matos, Barreiro, & Gandini, 2010; Padilla-Rascón et al., 2020; Rodríguez et al., 2008). Nowadays, the two-phase separation system is the most used by the OO industry. This process generates high amounts of solid residues and consequently, the separation of OS from OP is becoming a more frequent practice to valorize these by-products (Matos et al., 2010; Padilla-Rascón et al., 2020).

OSs are considered as a source of dietary fiber, but also lipids and proteins (Maestri et al., 2019). Cellulose contribution varies around 30–34%, whereas lignin and hemicellulose content is between 21 and 28% (Matos et al., 2010). OS is especially rich in oleic and linoleic acids, both major compounds of OO. Mild concentrations of tocopherols, squalene, sterols, and other triterpenoids can be found in OS as well. Regarding the phenolic profile, it is especially rich in secoiridoid

Table 2
Main bioactive compounds identified in olive oil and principal by-products of its production. Average concentration calculated on reported means is presented.

Group	Compounds ([a])	OO	Principal residues O	S	OMWW	Ref.
Fatty acids	Oleic acid	~70000	~2000	~14000	~3000	(Hannachi et al., 2020; Maestri et al., 2019; Martins et al., 2021)
	Linoleic acid	~12000	~350	~4500	–	
Phytosterols	β-Sitosterol	~96	200	~200	–	(Maestri et al., 2019; Ranalli et al., 2002; Sánchez-Gutiérrez et al., 2017)
	Campesterol	~3	~13	80	–	
	Stigmasterol	~1	100	~6	–	
Triterpenoids	Squalene	~450	~300	~300	~25	(Fernández-Cuesta et al., 2013; Maestri et al., 2019; Martins et al., 2021; Sánchez-Gutiérrez et al., 2017)
	Maslinic acid	~47	~400	Nd	~18	(De La Torre et al., 2020; Mwakalukwa et al., 2020; Romero et al., 2018; Sánchez-Gutiérrez et al., 2017)
	Oleanolic acid	~39	~350	Nd	~8	
Phenolic acids and derivatives	Gallic acid	~4	~10	~3	–	(Alu'datt et al., 2011, 2010; Cioffi et al., 2010; Dagdelen et al., 2013; Martins et al., 2021)
	Caffeic acid	~3	~5	~140	~9	(Alu'datt et al., 2010; Cioffi et al., 2010; De Marco et al., 2007; Khadem et al., 2019)
	p-coumaric acid	~1	~10	~300	~5	(Alu'datt et al., 2011; Khadem et al., 2019; López-Yerena et al., 2019; Martins et al., 2021)
	Hydroxybenzoic acid	~1	~10	~5	–	(Alu'datt et al., 2011, 2010; De Marco et al., 2007; López-Yerena et al., 2019)
	Ferulic acid	~4	~20	~30	–	(Alu'datt et al., 2011, 2010; Cioffi et al., 2010)
	Vanillic acid	~1	~30	~10	~20	(Alu'datt et al., 2010; Cioffi et al., 2010; De Bruno et al., 2020; Khadem et al., 2019; López-Yerena et al., 2019)
	Verbascoside	–	~8	INd	~15	(De Marco et al., 2007; Maestri et al., 2019; Obied et al., 2008; Pérez-Serradilla et al., 2008)
Flavonoids	Luteolin	~2	~6	~60	~20	(Ahmad-Qasem, Barrajón-Catalán, Micol, Mulet, & García-Pérez, 2013; Bakhouche et al., 2013; De Marco et al., 2007; López-Yerena et al., 2019; Pérez-Serradilla et al., 2008)
	Apigenin	~5	~4	~30	~4	(Alu'datt et al., 2011; Bakhouche et al., 2013; De Bruno et al., 2020; López-Yerena et al., 2019; Maestri et al., 2019)
	Rutin	~5	~2	~70	~5	(Alu'datt et al., 2010; De Bruno et al., 2020)
Secoiridoids	Tyrosol	~3	~	~70	~20	(Angelino et al., 2011; Benincasa, La Torre et al., 2019; De Bruno et al., 2020; De Marco et al., 2007; González-Hidalgo, Bañón, & Ros, 2012; Khadem et al., 2019; Pérez-Serradilla et al., 2008)
	Hydroxytyrosol	~	2000	~40	~20	[22,26,35,36,42,45–48]
	Oleuropein	~14	~3500	~30	Nd	(Cioffi et al., 2010; González-Hidalgo et al., 2012; Nakilcioğlu-Taş & Ötleş, 2019; Pérez-Serradilla et al., 2008; Romero et al., 2018)
	Oleocanthal	~6	30	–	~1	(Adhami et al., 2015; Cioffi et al., 2010; La Scalia et al., 2017; López-Yerena et al., 2019)
	Oleacein	~1	20	–	~70	(Angelino et al., 2011; Gómez-Alonso, Salvador, & Fregapane, 2002; La Scalia et al., 2017; Paiva-Martins et al., 2007)
	Ligstroside	~5	~50	–	~9	(Ahmad-Qasem et al., 2013; Cioffi et al., 2010; De Marco et al., 2007; López-Yerena et al., 2019)
Lignans	Pinoresinol	~9	~3	~3	~4	(Bakhouche et al., 2013; De Bruno et al., 2020; Nunes et al., 2018; Oliveras López et al., 2008)
	1-acetoxypinoresinol	~2	~2	–	~0.1	(Bakhouche et al., 2013; Mwakalukwa et al., 2020; Oliveras López et al., 2008)
Tocopherols[b]	α, β. γ, and δ	~18	~30	~30	~2	(Aggoun et al., 2016; Bengana et al., 2013; de Lucas, Martinez de la Ossa, Rincón, Blanco, & Gracia, 2002; González-Hidalgo et al., 2012; Maestri et al., 2019; Yanık, 2017)

[a] Concentrations have been calculated to mg/100 g dry weight unless indicated otherwise.
[b] Tocopherols are expressed as sum of α, β. γ, and δ tocopherols; **OO**: Olive oil; **O**: Olive pulp; **S**: seeds; **OMWW**: Olive mill waste-water; INq: Identified but not quantified; Nd: Not detected.

compounds and nüzhenide derivatives (Maestri et al., 2019; Rodríguez et al., 2008), and some experiments have been focused on the extraction optimization of target polyphenols, such as HT, OLE and syringic acid (Nakilcioğlu-Taş & Ötleş, 2019). Among them, HT and OLE have been recovered from OS by conventional extractions such as HAE, showing a yield of ≈27 and 37 mg/kg dw, respectively (Table 1). In the same way, PLE has been also performed to obtain cholesterol-lowering compounds from OS obtaining an extraction yield up to 60% (Vásquez-Villanueva, Plaza, García, & Marina, 2020).

With respect to the current applications of OS, its high calorific value (18 MJ/kg) has prompted its use on thermal processes for the production of electricity and in heating systems, as well as in diverse applications, ranging from activated carbon or fuel production, to sugar, furfural or other valuable compounds production (Padilla-Rascón et al., 2020; Rodríguez et al., 2008). Furthermore, stones powder has been used as flour substitute in biscuits improving their TPC and antioxidant activity (Bolek, 2020).

The characterization of the different by-products generated during the OO production chain, as well as the extraction techniques that can be applied to obtain target molecules with bioactive properties, are essential to define workable valorization strategies of these residues and move towards a more sustainable system based on circular economy approach.

3. Target bioactive components of olive oil by-products

The wide variety of bioactive molecules present in OO should be the responsible ones of the benefits attributed to the potential consumers. These bioactive components can be found not only in OO, but also at significant levels in its processing by-products, such as leaves and pruning biomass, seeds, pomace, cake, or OMWW, and could be easily extracted from waste biomass and yield added-value products and ingredients (Cicerale, Lucas, & Keast, 2012; Parkinson & Cicerale, 2016). The predominant bioactive compounds of OO and their residues include fatty acids, phytosterols, triterpenoids, phenolic compounds (namely phenolic acids, flavonoids, secoiridoids and lignans) and tocopherols, but some other bioactive compounds have been described in low quantities, like carotenoids or chlorophylls (Hannachi et al., 2020; Parkinson & Cicerale, 2016). The content of these bioactive molecules varies depending on the by-product considered and also according to other factors that influence the chemical composition of olives, such as variety, ripeness, climatic conditions, growth conditions, etc. (Romero, Medina, Mateo, & Brenes, 2018). The recovered compounds from olive pulp, seeds and OMWW (as the principal by-products of OO industry) are presented in Table 2. In addition, the distribution of these compounds among the by-products and also the chemical composition of olive pulp, seeds and OMWW is presented in Fig. 2, based on the data compiled in Table 2. Briefly, the sum of the main bioactive compounds found in olive pulp, seeds and OMWW was used to calculate the % of a given compound in each by-product, thus obtaining the % of the compound in the bioactive fraction. On the other hand, the sum of the main content of a given compound in the OO and residues was used to evaluate the distribution of the compound among by-products.

3.1. Triglycerides containing fatty acids

Olive fruits are rich in oil, composed entirely by triglycerides containing fatty acids (FA), especially oleic, palmitic and linoleic acids (Fig. 3). Most of FA are extracted in the OO process (~80%), and thus, their concentration is much lower in olive by-products (~20%) (Alu'datt et al., 2017) (Fig. 2A). After oil extraction, olive pulp still contains about a 10% of residual oil, rich in FA (Peršurić, SaftićMartinović, Zengin, Šarolić, & KraljevićPavelić, 2020), specially the bioactive FA, oleic and linoleic acid. The content of these FA reaches up to 2000 mg and 350 mg per 100 g dw, respectively (Nunes et al., 2018). Considering the compounds compiled in Table 2, FA content corresponds to about 55.0% of the bioactive composition of the olive pulp (Fig. 2B). OSs are considered as a valuable source of unsaturated FA, being oleic and linoleic acids the most prevalent FAs. According to recent studies, seeds contain on average about 14,000 mg and 4500 mg/100 g dw of oleic acid and linoleic acid, respectively (Hannachi et al., 2020; Maestri et al., 2019), corresponding to 91.7% of the chemical composition (Fig. 2B). Finally, a recent study reported that OMWW contained about 3000 mg/100 g dw of oleic acid, but no linoleic acid was detected (Martins, Martins, & Braga, 2021). Thus, FA content stands for the 92.9% of OMWW's compounds (Fig. 2B).

3.2. Phytosterols

Although phytosterols are extracted during OO production, generally higher levels have been described in the residues (Mateos, Sarria, & Bravo, 2019). According to the data compiled, these compounds are distributed as follows: a ~10% of the total phytosterols are found in OO, whereas around ~80% are present in the by-products (Fig. 2A). OO contains about 100 mg of phytosterols/100 g dw, which corresponds to a 0.1% of the main bioactive compounds found in its chemical composition (Fig. 2B). The major phytosterols found on this product are β-sitosterol, campesterol and stigmasterol (Fig. 3), with a content about 96, 3 and 1 mg/100 g dw, respectively (Ranalli et al., 2002). Regarding by-products, phytosterols have been detected in olive pulp and in OSs, but not in OMWW (Table 2, Fig. 2). The total phytosterol content in olive pulp is around 380 mg/100 g dw (200, 80 and 100 mg/100 g dw for β-sitosterol, campesterol and stigmasterol, respectively), while it is lower in seeds, around 219 mg/100 g dw (200, 13 and 6 mg/100 g dw for the previously indicated compounds) (Maestri et al., 2019; Ranalli et al., 2002). According to the bioactive compounds present in these residues, phytosterols correspond to an average of 8.9% and 2.7% of the bioactive composition of olive pulp and seeds, respectively (Fig. 2B).

3.3. Triterpenoids

According to the compiled data, only about a 33% of triterpenoids is extracted during OO production, thus, about a 67% of these compounds is present in the by-products (Fig. 2A). Specifically, triterpenes correspond to a 0.6, 17.6, 1.5, and 0.8% of the bioactive composition of OO, OP, OS and OMWW, respectively (Fig. 2B). Among triterpenoids, squalene, maslinic and oleanolic acids are the most representative compounds (De La Torre et al., 2020; Fernández-Cuesta, León, Velasco, & De la Rosa, 2013) (Fig. 3, Table 2). Squalene is the main component of unsaponifiable matter, constituting more than 90% of OO hydrocarbons and containing up to 450 mg/100 g dw (Beltrán, Bucheli, Aguilera, Belaj, & Jimenez, 2016; Fernández-Cuesta et al., 2013). Regarding by-products, squalene content is lower, reaching 300 mg/100 g dw both in olive pulp and seeds and 25 mg/100 g dw in the case of OMWW (Maestri et al., 2019; Martins et al., 2021; Sánchez-Gutiérrez, Ruiz-Méndez, Jiménez-Castellanos, & Lucero, 2017). On the other hand, the presence of maslinic and oleanolic acids has been reported in OO, olive pulp and OMWW, but not in seeds (Table 2). In OO, the content of maslinic and oleanolic acids is about 47 and 39 mg/100 g dw, respectively (De La Torre et al., 2020). This content is higher in olive pulp, with a content of 400 and 300 mg/100 g dw, respectively (Sánchez-Gutiérrez et al., 2017), while lower levels have been reported in OMWW (18 mg of maslinic acid and 8 mg of oleanoic acid per 100 g dw (Mwakalukwa, Amen, Nagata, & Shimizu, 2020; Romero et al., 2018)).

3.4. Phenolic compounds

Phenolic compounds present in OO and its by-products are greatly heterogenous and include mainly phenolic alcohols, phenolic acids, flavonoids, secoiridoids, and lignans, among others (Servili et al., 2004, 2014). They are the primary group of bioactive molecules derived from olive and appear at markedly different concentrations among residues.

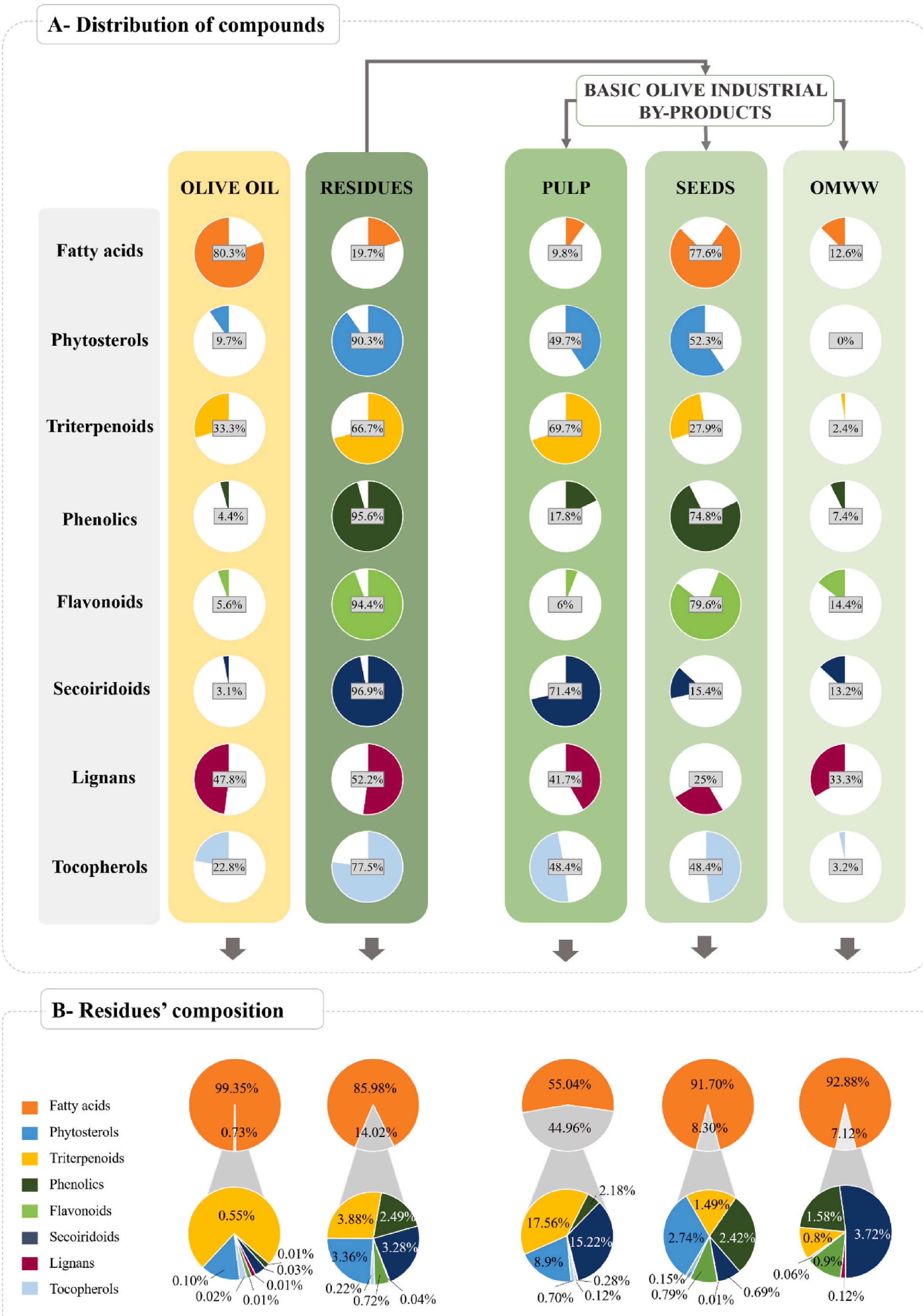

Fig. 2. Distribution and relative percentage of the bioactive compounds in olive pulp, seeds and OMWW.

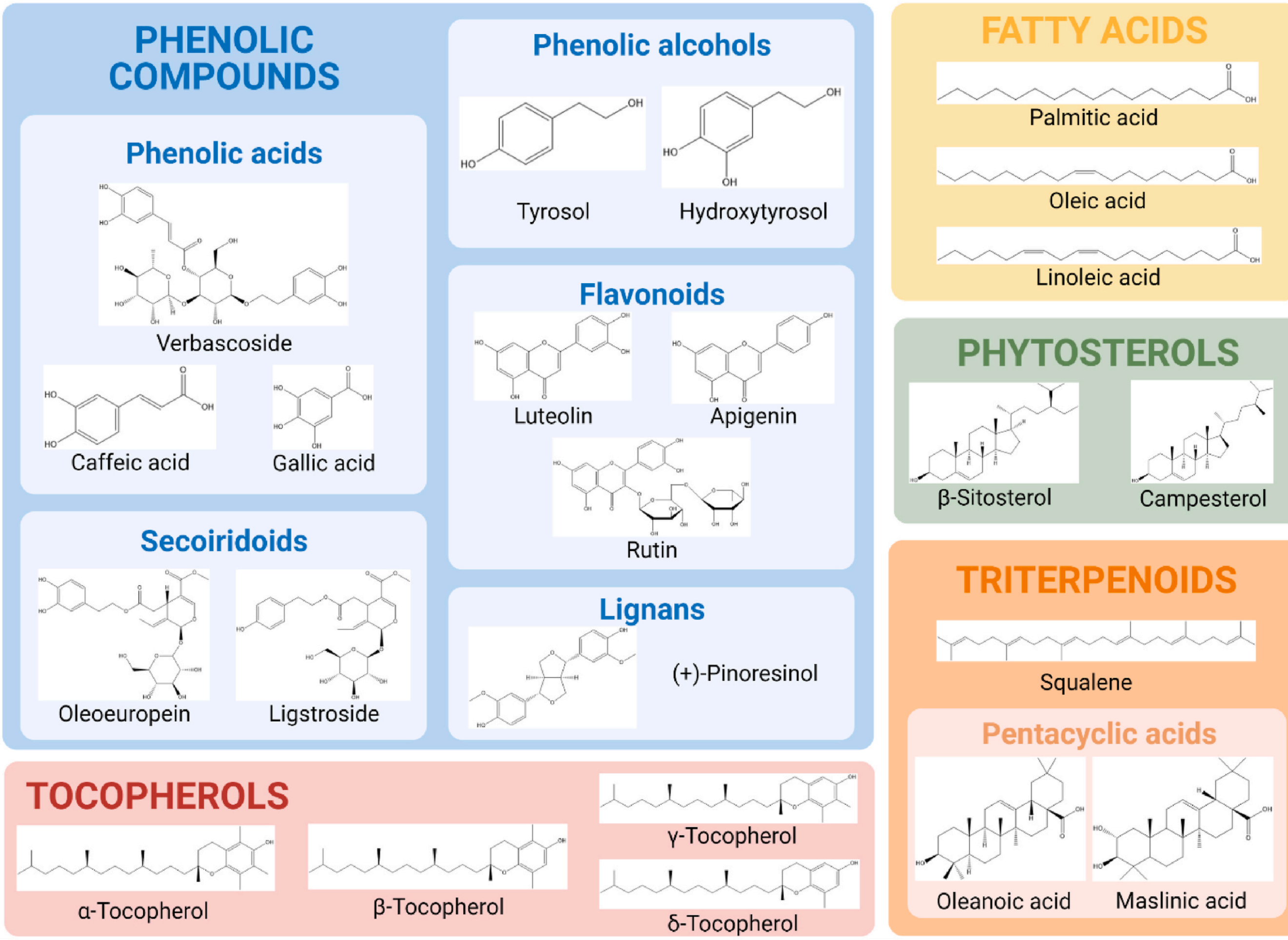

Fig. 3. Chemical structure of main bioactive compounds found in olive oil and by-products.

As it could be seen in Fig. 2A, the diverse groups of phenolic compounds are generally present in higher amounts in the residues, except for lignans.

3.4.1. Phenolic alcohols

The most relevant phenolic alcohols found in OO and by-products are HT and tyrosol, which can be found in variable amounts, depending on the olive variety and maturation stage *(Wani et al., 2018)*. Their high prevalence is due to their derivation from the most abundant phenolic compounds of OO, the secoiridoids oleoeuropein and ligstroside *(Cardoso, Falcão, Peres, & Domingues, 2011)*. Thus, HT is mainly produced from the hydrolysis of oleoeuropein, whereas tyrosol derives from ligstroside degradation *(Wani et al., 2018)*. From a biosynthetic point of view, both HT and tyrosol are derived from L-DOPA and L-tyrosine, respectively, suffering further sequential enzymatic modifications to give rise to the final compounds, which are incorporated into the secoiridoid compounds as the phenolic moiety through a biosynthetic pathway that is not fully elucidated, to date *(Sánchez, García-Vico, Sanz, & Pérez, 2019)*. Nevertheless, as bioactive compounds it is assumed that all HT-containing molecules in OO are the major responsible for its associated biological properties *(López de las Hazas et al., 2016)*.Phenolic acids.

The main phenolic acids found in OO and the selected residues are gallic, caffeic, *p*-coumaric, hydroxybenzoic, ferulic and vanillic acids, together with some derivatives, such as verbascoside (a glycosylated phenylethanoid, derived from hydroxycinnamic acid) (Table 2). Comparing their distribution, a 4.4% of these compounds is present in OO, while the remaining 95.6% can be found in the residues (Fig. 2A). Previous data have reported a phenolic acid content of approximately 14,000 mg/100 g dw of OO (Cioffi et al., 2010; Dagdelen, Tümen, Özcan, & Dündar, 2013; López-Yerena et al., 2019), which corresponds to an average 0.01% of the main bioactive compounds reported in this product (Table 2, Fig. 2B). Among residues, seeds stand out, with an average content of 488 mg/100 g dw (Alu'datt et al., 2011; Khadem, Rashidi, & Homapour, 2019) (2.4% of the main bioactive compounds), followed by the olive pulp, with 93 mg/100 g dw (Alu'datt et al., 2010; Pérez-Serradilla, Japón-Luján, & De Castro, 2008) (corresponding to a 2.2% of the bioactive fraction) (Table 2, Fig. 2B). Finally, only caffeic, *p*-coumaric and vanillic acids and verbascoside have been detected in OMWW, containing an average content of 49 mg/100 g dw (De Marco, Savarese, Paduano, & Sacchi, 2007; Martins et al., 2021; Obied, Bedgood, Mailer, Prenzler, & Robards, 2008), which corresponds to a 1.6% of bioactive compounds.

3.4.2. Flavonoids

Regarding flavonoids, some of the most widely identified in OO and by-products include the flavones luteolin and apigenin, and the flavanol rutin (Table 2, Fig. 3). Like in previous compounds, their content is higher in the by-products than in OO. Thus, the distribution of flavonoids is as follows: about a 5.6% is present in the OO, while the remaining 94.4% can be found in the residues (Fig. 2A). OO has been described to contain an average content of 2000 mg of luteolin and 5000 mg of apigenin and rutin per 100 g dw (Bakhouche et al., 2013; López-Yerena et al., 2019), accounting for a 0.01% of OO's main bioactive compounds (Fig. 2B). Regarding residues, luteolin is the predominant flavonoid in pulp and OMWW, while rutin is the major flavonoid of seeds. On average, olive pulp, seeds and OMWW contain up to 12, 160 and 29 mg of these flavonoids per 100 g dw (Alu'datt et al., 2011, 2010; De Marco et al., 2007; Khadem et al., 2019; Maestri et al., 2019; Pérez-Serradilla et al., 2008), which represent the 0.3, 0.8 and 0.9% of the bioactive compounds found in these matrices (Table 2, Fig. 2B).

3.4.3. Secoiridoids

Secoiridoids (Fig. 3) are the most abundant and distinctive phenolic compounds present in OO and olive by-products. The main secoiridoids are oleuropein, biosynthetically derived from the esterification of HT with elenolic acid, and ligstroside, derived from the esterification of tyrosol with oleoside 11-methyl ester, a methylated derivative of elenoic acid (Bianchi, 2003; Czerwin, Kiss, & Naruszewicz, 2012). As expected, the content of these compounds is higher in the different residues, presenting a 96.9% of total secoiridoids, compared to 3.1% found in OO (Fig. 2A). According to the previously available bibliography, secoiridoids content has been described to be more abundant in olive pulp (≥5000 mg/100 g dw) and OMWW (≥4000 mg/100 g dw), while this content is much lower in seeds (~140 mg/100 g) (Angelino et al., 2011; Khadem et al., 2019; Martins et al., 2021; Tufariello et al., 2019). Considering the bioactive compounds of residues, the amount of secoiridoids represents a 15.2, 0.7 and 3.7% of the bioactive fraction of olive pulp, seeds and OMWW, respectively (Table 2, Fig. 2B).

3.4.4. Lignans

Unlike other phenolic compounds, similar lignans distribution has been observed between OO and the different residues: 47.8 and 52.2%, respectively (Fig. 2A). The two main bioactive lignans described in OO are (+)-pinoresinol and (+)-1-acetoxypinoresinol (Fig. 3), whose content has been estimated in 9 and 2 mg/100 g dw, respectively (Bengana et al., 2013; De Bruno, Romeo, Piscopo, & Poiana). The lignans content stands for a 0.01% of the bioactive compounds present in OO (Fig. 2B). Regarding by-products, both compounds have been identified in olive pulp (~3 and ~2 mg/100 g dw, respectively) and OMWW ~ (4 and ~0.1 mg/100 g dw, respectively), but only (+)-pinoresinol was detected in seeds (~3 mg/100 g dw) (Mwakalukwa et al., 2020; Nunes et al., 2018). Specifically, lignans represent a 0.1, 0.01 and 0.1% of the bioactive compounds of olive pulp, seeds and OMWW, respectively (Fig. 2B).

3.5. Tocopherols

OO is rich in tocopherols (isomers of vitamin E), which may be present as α-, β-, γ- and δ-tocopherol isoforms (Fig. 3). Considering the distribution of tocopherols, higher amounts have been reported in by-products (77.5%) than in OO (22.8%) (Fig. 2A). Specifically, tocopherols content (the sum of all isoforms) in OO is generally reported to be around 18 mg/100 g dw (Bengana et al., 2013), representing a 0.02% of the main bioactive compounds (Table 2). In olive by-products, tocopherols are reported at varying concentrations, being α-tocopherol the most common isoform (Boskou, 2015; Moghaddam et al., 2012). In olive pulp and seeds, this content reaches around 30 mg/100 g dw, while a lower content is observed in OMWW, ~2 mg/100 g dw (Aggoun et al., 2016; Maestri et al., 2019; Yanık, 2017) (Fig. 2B).

4. Bioactivities of olive oil by-products

Diverse types of biological properties have been attributed to olive and OO by-products, including antioxidant, anti-inflammatory, anticancer, and others. In general, these properties have been linked with the diverse, previously-mentioned bioactive compounds, especially phenolic compounds (like HT, OLE, oleocanthal, etc.) (P. Gullón, Gullón, Astray, et al., 2020). In this section, several activities associated with olive by-products will be described, as well as the mechanism of action of the involved compounds (Table 3).

Table 3
Biological properties of compounds present from olive oil by-products.

Activity	Compounds	Main Mechanisms	Ref.
Antioxidant	HT and D	Ability to scavenge free radicals and chelate metals. Reduction of lipid peroxidation. Reduction of mitochondrial dysfunction. Activation of Nrf2 and upregulation of antioxidant genes.	(Araújo et al., 2015; Karković; Kouka et al., 2017; Marković et al., 2019; Robles-Almazan et al., 2018)
	OLE and D	Ability to scavenge ROS and RNS. Reduction of lipid peroxidation. Activation of Nrf2 and upregulation of antioxidant genes.	(Czerwin et al., 2012; Janahmadi et al., 2017; Jemai et al., 2008; Sherif, 2018; Yin et al., 2019)
Anti-inflammatory	HT and D	Inhibition of pro-inflammatory molecules (*e.g.*, NO, PGE2, TNF-α, NF-κB)	(Aparicio-soto et al., 2017; Bigagli et al., 2017; Fki et al., 2020; Plastina et al., 2019; Robles-Almazan et al., 2018)
	OLE and D	Activation of Nfr2-related pathways and downregulation of inflammation related genes (*e.g.*, iNOS, COX-2).	(Aparicio-soto et al., 2017; Feng et al., 2017; Hassen et al., 2015; Janahmadi et al., 2017; Sherif, 2018; Yin et al., 2019)
Antitumor	HT	Inhibition of proliferation, induction of cell cycle arrest. Induction of pro-apoptotic pathways (*e.g.,* PI3K/Akt/FOXO3a, PI3K/Akt/mTOR, caspase cascade)	(Calahorra et al., 2020; Goldsmith et al., 2018; Imran et al., 2018; KarkovićMarković et al., 2019; Robles-Almazan et al., 2018)
	OLE	Alteration of pro/anti-apoptotic Bcl-2 family proteins ratio. Downregulation of anti-apoptotic factors, oxidative stress and inflammation.	(Asgharzade et al., 2020; Boss et al., 2016; Goldsmith et al., 2018; Imran et al., 2018; Shamshoum et al., 2017)
Anti-obesity, anti-diabetic	OLE and D	Enhancement of GPBAR1, better insulin secretion. Reduction of glycaemia. Activation of ERK/MAPK signaling pathway.	(Sato et al., 2007; Ling Wu et al., 2017)
Cardioprotective effect	HT, tyrosol, OLE and D	Reduction of systolic blood pressure, cardiac hypertrophy, and plasma levels of total cholesterol and angiotensin II. Downregulation of oxidative stress and inflammation.	(Bendini et al., 2007; Covas et al., 2006; Gómez-Caravaca et al., 2015; Janahmadi et al., 2015; Soler-Rivas et al., 2000; Tuck & Hayball, 2002; Vazquez et al., 2019; Lixing Wu et al., 2018)

D: derivatives; Nrf2: nuclear factor (erythroid-derived 2)-like 2; ROS: reactive oxygen species; RNS: reactive nitrogen species, HO-1: heme oxygenase 1; NO: nitric oxide; PGE2: prostaglandin E_2; TNF-α: tumor necrosis factor-alpha; NF-κB: nuclear factor kappa B; iNOS: inducible nitric oxide synthase; COX-2: cyclo-oxygenase-2.

4.1. Antioxidant effect

Numerous studies have reported the antioxidant properties of olive-related by-products (OP, OMWW, olive leaf) by the free radical scavenging (ABTS assay), ferric reducing ability of plasma (FRAP assay), the Trolox-Equivalent antioxidant capacity (TEAC) assays, the 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging and oxygen radical absorbance capacity (ORAC) assays (Cedola, Cardinali, D'Antuono, Conte, & Del Nobile, 2020; Moudache, Colon, Nerín, & Zaidi, 2016; Posadino et al., 2021; Tamasi et al., 2019). In general, phenolic compounds, such as HT, OLE, OLE aglycone, and derivatives are significantly related with the antioxidant effects of the olive by-products. The antioxidant properties of HT result from its *o*-diphenolic structure, responsible for the free radical scavenging and metal chelating properties (Araújo, Pimentel, Alves, & Oliveira, 2015; KarkovićMarković, Torić, Barbarić, & JakobušićBrala, 2019). Antioxidant effects have not only been reported by DPPH and ABTS assays (Kouka et al., 2017; Pannucci et al., 2019), but also in cell cultures and *in vivo* models (Granados-Principal et al., 2014; Kouka et al., 2017; Ricelli et al., 2020). Similar effects have been also observed with HT derivatives found in by-products, such as HT oleate (Benincasa, La Torre et al., 2019) and homovanillic alcohol (Ricelli et al., 2020).Several mechanisms of action have been proposed for HT, including the activation of the nuclear factor (erythroid-derived-2)-like 2 (Nrf2), a transcription factor that plays a crucial regulator role on the antioxidant response element (ARE) or the activation of NK-p62/SQSTM1 pathway, both involved in the cellular response against oxidative stress (Kouka et al., 2017; Robles-Almazan et al., 2018). HT has been also reported to stimulate mitochondrial biogenesis and function by peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PPARGC1α) activation (Granados-Principal et al., 2014). A schematic representation of these mechanisms has been presented in Fig. 4.

Like HT, OLE also presents a *o*-diphenolic structure, responsible for its antioxidant properties (Araújo et al., 2015), acting as a ROS and reactive nitrogen species (RNS) scavenger, specially nitric oxide (NO) (Czerwin et al., 2012). In addition, both *in vitro* and *in vivo* studies showed that OLE reduces ROS, RNS, and oxidative markers production, inhibits lipid peroxidation and also improves the antioxidant defense systems, increasing the levels and activity of antioxidant enzymes (Czerwin et al., 2012; Janahmadi, Nekooeian, Moaref, & Emamghoreishi, 2017; Jemai, Bouaziz, Fki, El, & Sayadi, 2008) (Fig. 4). As expected, OLE derivatives present in olive and OO by-products, like OLE-aglycone or oleacin have shown analogous effects (Czerwin et al., 2012; Nardi et al., 2017).

4.2. Anti-inflammatory effect

Olive and OO by-products also exert anti-inflammatory effects, although they were reported by less studies compared with those focused on antioxidant activity. Recently, phenolic extracts from OMWW and OP have been shown to reduce NO production in lipopolysaccharide (LPS)-stimulated RAW-264.7 macrophages (Plastina et al., 2019) and inhibit the production of the interleukin-8 (IL-8) pro-inflammatory cytokine in human colorectal adenocarcinoma Caco-2 cells (Di Nunzio et al., 2018), respectively. Anti-inflammatory effects have been also observed *in vivo*. For example, in rats, OO by-products promoted an inflammation reduction associated with gastrointestinal disorders (Parisio, Lucarini, Micheli, Toti, Bellumori, Cecchi, Calosi, Bani, Di, et al., 2020). In general, these properties of by-products have been attributed to the presence of compounds such as HT, OLE and their derivatives, as anti-inflammatory activity is usually linked to antioxidant activity.

HT and types of derivatives, such as HT oleate or HT stearate, have shown anti-inflammatory properties *in vitro* and *in vivo*. Several cellular studies have reported that these compounds inhibited NO, prostaglandin E2 (PGE2) and pro-inflammatory cytokines production, tumor necrosis factor-alpha (TNF-α) secretion and expression, and repressed inflammatory-related genes expression, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), matrix metallopeptidase-9 (MMP-9), among others (Bigagli et al., 2017; Plastina et al., 2019; Robles-Almazan et al., 2018). In addition, HT and their derivatives have been reported to activate the nuclear factor (erythroid-derived 2)-like 2 (Nfr2) transcription factor, leading to an inhibition of pro-inflammatory mediators, and also modulates microRNA-146a expression, a post-transcriptional regulator of the inflammatory response (Bigagli et al., 2017). These effects and mechanisms have been also observed in animal models, such as liver-injured rats or systemic lupus erythematous mice models (Aparicio-soto et al., 2017; Fki et al., 2020). In Fig. 4, a

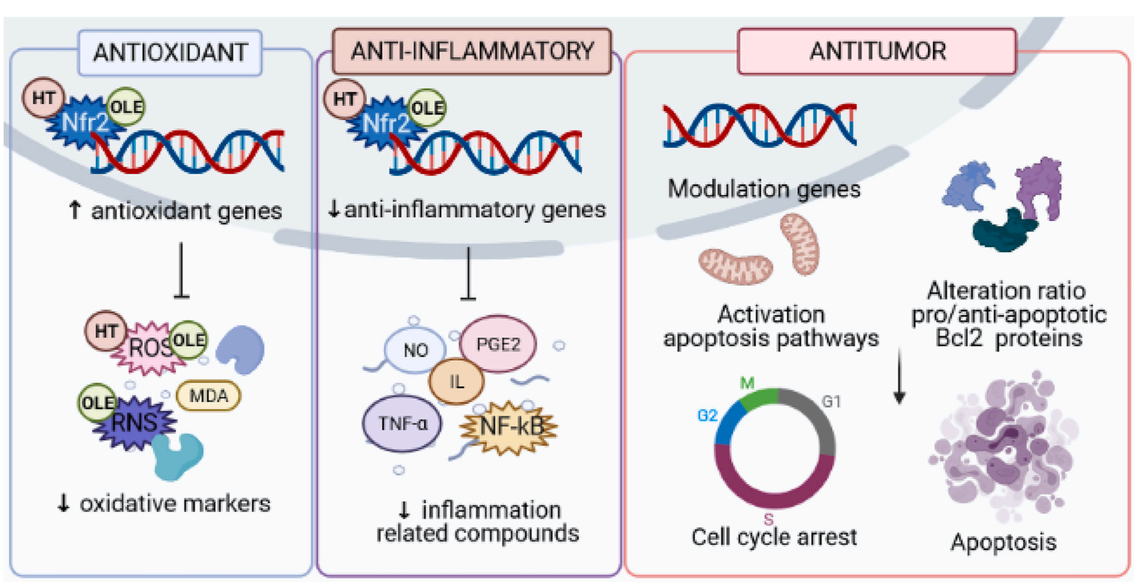

Fig. 4. Schematic mechanisms of antioxidant, anti-inflammatory and antitumor properties of HT and OLE.

schematic representation of anti-inflammatory mechanisms is presented.

Regarding OLE and derivatives, such as oleacin or oleocanthal, similar anti-inflammatory effects and mechanisms have been observed in cell cultures, including the inhibition of the nuclear factor κ-B (NF-κB) and its translocation into the nucleus and the production of pro-inflammatory cytokines (such as NO, PGE2, interleukins, etc.) and also the downregulation of genes like COX-2 and iNOS (Aparicio-soto et al., 2017; Hassen, Casabianca, & Hosni, 2015; Janahmadi et al., 2017) (Fig. 4). It has been reported that OLE also inhibits the activation of NF-κB and mitogen-activated protein kinase (MAPK) pathways, being both important regulators of the inflammatory process (Feng et al., 2017). This anti-inflammatory activity has been also corroborated on animal models, where OLE reduced the levels and the expression of pro-inflammatory mediators and genes, which has been attributed to the activation of Nrf2/heme-oxygenase-1 (HO-1) signaling pathway (Sherif, 2018; Yin et al., 2019).

4.3. Antitumor effect

The antitumor properties of olive by-products have been also described in the literature. To cite some of the most recent studies, phenolic extracts from olive leaf and OP exerted inhibitory effects against mouse sarcoma S180, HeLa, Caco-2 and HCT116 cell lines (Lanza et al., 2020; Wang et al., 2019) and the antitumor properties have been mainly correlated to HT and OLE (Imran et al., 2018; Robles-Almazan et al., 2018).

Regarding HT, it has been demonstrated to inhibit the proliferation and growth and induce apoptosis in different cancer cell lines and *in vivo* models, by promoting cell cycle arrest in the G0/G1 phase and also by modulating the expression of different pathways and genes involved in tumor progression, as it has been extensively covered by previous reviews (KarkovićMarković et al., 2019; Robles-Almazan et al., 2018) (Fig. 4). For example, HT has been shown to activate PI3K/Akt/FOXO3a pathway and caspase signaling, which play a fundamental role in cell apoptosis, and also downregulates the expression of Bcl-2, an anti-apoptotic protein (Imran et al., 2018). Recently, HT exerted cytotoxic effects against pancreatic cancer cells, MIA PaCa-2, and HPDE cells, inducing cell cycle arrest. In MIA PaCa-2, HT induced activation of caspase 3/7 and the subsequent apoptosis and altered the ratio of pro/anti-apoptotic Bcl2 family proteins. Further analysis showed that HT increased the gene expression and the protein content of c-Jun and c-Fos, involved in proliferation, cellular differentiation, and also apoptosis (Goldsmith et al., 2018).

OLE has shown also antitumor effects in different cancers, reducing viability and inducing cell cycle arrest and apoptosis (Boss, Bishop, Marlow, Barnett, & Ferguson, 2016; Imran et al., 2018). Like HT, it has been observed that OLE exerts antitumor properties affecting many different pathways, such as caspase pathway, PI3K/Akt/mTOR pathway, or extracellular signal-regulated protein kinases 1 and 2 (ERK-1 and ERK-2), and also downregulating inflammatory and oxidative factors (Shamshoum, Vlavcheski, & Tsiani, 2017) (Fig. 4). In a previous cited study, OLE induced apoptosis in MIA PaCa-2 cells trough activation of caspase 3/7, increased pro/anti-apoptotic Bcl2 proteins ratio and augmented the expression of c-Jun and c-Fos (Goldsmith et al., 2018). Recently, this compound has shown to decrease cell viability and induce apoptosis in breast cancer cell lines MCF7 and MDA-MB-231 through the downregulation and upregulation of anti and pro-apoptotic genes, respectively, and also modulating microRNA expression (Asgharzade et al., 2020). Other compounds to which antitumor properties are attributed are luteolin or apigenin, due to their ability to reduce oxidative damage and also modulate the inflammatory response mediated by NF-κB, and also tumor progression-related pathways (Boss et al., 2016).

4.4. Anti-obesity and antidiabetic effect

Obesity is known to be associated with a series of metabolic diseases, including insulin resistance, which can lead to type II diabetes (Rabe, Lehrke, Parhofer, & Broedl, 2008). Phenolic acids, flavonoids and their derivatives seem to be responsible for the greatest antidiabetic activities of olive and its by-products (Vlavcheski, Young, & Tsiani, 2019), since phenolic compounds are inhibitors of α-glucosidase and α-amylase enzymes, which are therapeutic targets of anti-diabetic drugs (Kamiyama et al., 2010). Among the by-products of the food industry, olive leaves, skin and pomace are the main components with antidiabetic and anti-obesity properties (P. Gullón, Gullón, Astray, et al., 2020), as evaluated in several works (Abunab, Dator, & Hawamdeh, 2017; de Bock et al., 2013; Guex et al., 2019; Liu, Jung, Park, & Kim, 2014).

These biological activities are mainly attributed to phenolic compounds, in particular to OLE and some derivatives (Kaeidi et al., 2011; Sato et al., 2007). For instance, it has been reported that OLE and oleanolic acid enhance the role of G-protein-coupled bile acid receptor 1 agonists, improving metabolic disorders with greater peripheral use of glucose and better insulin secretion (Sato et al., 2007). More recently, OLE has shown to reduce glycemia and enhance glucose tolerance in several animal models. This compound stimulates the insulin secretion promoted by glucose in pancreatic β-cells with a dose-dependent effect, activating the ERK/MAPK signaling pathway (Ling Wu, Velander, Liu, & Xu, 2017).

4.5. Cardioprotective effect

Nowadays, there are many studies that support the cardioprotective properties of olive by-products, such as antiarrhythmic and vasodilator effects (Covas et al., 2006), linked to their antioxidant and anti-inflammatory properties, being HT, tyrosol, OLE, and their derivatives the major responsible of the cardioprotective effect (Bendini et al., 2007; Gómez-Caravaca, Lozano-Sánchez, Contreras Gámez, Carretero, & Taamalli, 2015; Soler-Rivas, Espiń, & Wichers, 2000; Tuck & Hayball, 2002). To cite some examples evaluating by-products and bioactive compounds, a study assessed the effect of EVOO enriched with phenolic compounds obtained from its by-products in rats. The results showed that the group supplied with enriched EVOO presented decreased systolic blood pressure, cardiac hypertrophy, and reduced plasma levels of total cholesterol and angiotensin II (Vazquez et al., 2019). In agreement, other authors reported that olive leaf extract, and also its main component HT, can protect rat cardiovascular H9c2 cells against apoptosis induced through the endoplasmic reticulum pathway, exerting a cardioprotective effect (Lixing Wu, Xu, Yang, & Feng, 2018). In other study, OLE displayed cardioprotective effects in rats with acute myocardial infarction because it prevents cardiac deterioration by reducing oxidative stress and decreasing the release of pro-inflammatory cytokines (Janahmadi, Nekooeian, Moaref, & Emamghoreishi, 2015). Regarding the antihypertensive effect, a study reported that the consumption of 500 mg twice a day of olive leaf extract for 8 weeks was able to lower blood pressure in a similar extent than the group treated with captopril, and also the olive leaf extract was able to lower triglyceride levels (Susalit et al., 2011).

5. Innovative applications on food, pharmaceutical and cosmetic industries

The high content of active principles in most of the OO by-products allows their use for therapeutic, dietary, and gastronomic purposes. Thus, notable efforts have been made to recover bioactive compounds, mostly phenolics, from different OO by-products to use them as functional additives or for their application in pharmaceutical and cosmetic products (Araújo et al., 2015). Table 4 shows some examples. To obtain the maximum benefit from the by-products, it is necessary to extract and purify their active components, which is usually performed in the form

Table 4
Innovative applications from olive by-products in the food, pharmaceutical and cosmetic industries.

Matrix	Analyte	Innovative Application	Benefit	Ref.
Applications in the food industry				
OO by-products	HT, OLE	Incorporation in sunflower oil	Improve their antioxidant properties.	Araújo et al. (2015)
Alperujo	HT	HT-rich oil.	Increase the antioxidant activity of the oil	Tirado, Fuente, and Calvo (2019)
Olive cake	PC	VOO enriched with PC.	Increase antioxidant capacity without the drawback of a higher calorie intake.	Suárez et al. (2010)
OMWW	PC	PC incorporated in milk (before pasteurization)	Off-flavor compounds formation inhibition (Maillard Reaction) during the heat treatment. Nutritional and sensorial properties improvement.	Troise et al. (2014)
OP	PC	Incorporated to milk	Improve its health properties	Aliakbarian et al. (2015)
OP	PROT, S, LIG	Sugars for bioEtOH production (yield: 25%)	Sustainable biorefinery approach	Kazan et al. (2015)
Olive vegetation water	PC	Fresh pork sausage enriched with PC	Food-borne pathogens (*Listeria monocytogenes, Staphylococcus aureus*) inhibition growth.	Fasolato et al. (2016)
OMWW	DF	Additive for fat replacement in low fat meatballs	Oil uptake restriction giving rise to meatballs with reduced fat content. Culinary properties improvement.	Galanakis et al. (2010b)
Applications in the pharmaceutical industry				
OP	PC	Intestinal diseases new treatment	Metabolic change towards a glucose saving strategy (appetite-suppressing effect). Decrease of the secretion of the pro-inflammatory cytokine, IL-8.	Di et al. (2018)
OP skin (New by-product)	TA	Therapeutic agent based on the skin of olive fruit	Antidiabetic effect. Improves insulin action.	Romero et al. (2018)
OMWW and dry OP	PC	Agent against visceral pain	Reduce the pain perception, the macroscopic intestinal damage, the inflammatory infiltrate, and the fibrosis.	Parisio, Lucarini, Micheli, Toti, Bellumori, Cecchi, Calosi, Bani, Di Cesare Mannelli et al. (2020)
Applications in the skin care industry				
OO by-products	Minerals	Ingredients for cosmetic	Hydration finality.	Rodrigues et al. (2015)
Leaves, Stems, Flowers, OMWW, Fruit Pulp, Seeds.	OLE, PC.	Skin care industry.	Antioxidant, anti-inflammatory, anti-atherogenic, anti-cancer activities, antimicrobial, antiviral activities	Kishikawa et al. (2015)
OP	SQ	Biological skin barrier against solar rays	Antioxidant properties at the cutaneous level	Rodríguez-Gutiérrez et al. (2014)
OO by-products	MUFA	Ingredient for cosmetics and products	Improve epidermis and sebaceous glands functions (permeability barrier and promote the stratum corneum acidification).	Lin and Khnykin (2014)

DF: dietary fiber; EtOH: Ethanol; LIG: Lignin; HT: Hydroxytyrosol; MUFA: monounsaturated fatty acids; OLE: Oleuropein; OMWW: Olive mill wastewater; OP: Olive pomace; OO: olive oil; PC: Phenolic content; PROT: Protein; S: Sugars; SQ: Squalene; TA: triterpene acids; VOO: virgin olive oil.

of an extract. For purification, it is usually employed liquid-liquid extraction methods in counter-current adsorbent resins with supercritical fluid with a column operating in the counter-current mode or ultrafiltration and adsorption in non-ionic resins (Fernández-Bolaños, Rodríguez, Rodríguez, Guillén, & Jiménez, 2006). However, to achieve high purity chromatographic methodologies with silica gel or sephadex LH-20 columns are required (D. M. Otero, Oliveira, et al., 2020). In addition, Fernandez-Bolanos and co-workers have been developed an industrial purification system which allows to obtain HT from any liquid source of olive by-product in two stages of purity. The first form at 50% of purity, is obtained by passing the liquid source of HT through an ion-exchange resin to trap the antioxidant and further elution with water. The second form of HT in a 99.6% of purity is obtained by a procedure consisting in using a XAD-type adsorbent non-ionic resin and washed it with a mixture of methanol or ethanol and water (30–33%) (Fernández-Bolaños et al., 2006).

5.1. Food industry

Once the compound is purified it can be incorporated into other foods to improve its functional properties or stability. In this line of research, some studies show the incorporation of phenolic fractions (HT, OLE) from by-product into oils to improve their antioxidant properties (Araújo et al., 2015). For examples, an *in vivo* assay shows the effects of HT-enriched sunflower oil in twenty-two healthy volunteers who participated in a cross-over study involving two 3-week periods in which they consumed 10–15 g/day of either HT-enriched sunflower oil (45–50 mg/day of HT) or non-enriched sunflower oil. (Vázquez-Velasco et al., 2011). Results showed the product functioned as a functional food by increasing arylesterase activity and reducing oxidized LDL and sVCAM-1 level. In another research, hydroethanolic extracts rich in phenolic compounds from olive cake were included in OO to improve their antioxidant capacity (up to 73%) without increasing the caloric intake (Suárez, Romero, & Motilva, 2010). In animal feed supplementation, the possible use of olive leaves as a food supplement in chicken feed has been studied, obtaining eggs enriched with long-chain omega-3 fatty acids (P. Gullón, Gullón, Astray, et al., 2020). Alternative uses of OMW phenolic extracts are represented by their application as feed, to improve the quality of meat and animal products. Concentrations as little as 1.5% of crude phenolic extract, corresponding to approximately 300 mg/kg total phenolic compounds, for swine were applied (Caporaso, Formisano, & Genovese, 2018).

Besides, olive by-products were also employed in milk, winemaking and meat industries supplying some innovative applications. HT has been used as a substitute for sulfur dioxide in the winemaking process due to its antimicrobial properties (P. Gullón, Gullón, Astray, et al., 2020). In dairy products, the possible protective effect of phenolics from olive by-products in the Maillard Reaction was investigated. For this purpose, Troise incorporated phenolic powder content from OMWW in raw milk before ultra-pasteurization, resulting in the inhibition of off-flavor compounds formation during the heat treatment, improving both the nutritional and sensorial properties (Troise et al., 2014). In addition, a phenolic extract from OP was incorporated into milk as a new functional ingredient to improve its health properties (Aliakbarian et al., 2015). Regarding meat products, obtaining phenolics from agricultural by-products was used as an eco-friendly strategy for food conservation (Fasolato et al., 2016). Indeed, the purified phenolic extract from olive vegetation water was added to fresh Italian sausages, showing a clear inhibition of food-borne pathogens growth, like *Listeria monocytogenes* and *Staphylococcus aureus*. Thus, it was demonstrated that phenolic extracts from olive vegetation water constitute a promising source of ingredients to improve food safety and quality of fresh sausages (Fasolato et al., 2016). A fraction of dietary fiber from OMWW can be also used as additive for fat replacement in low-fat meatballs, improving their culinary properties, by restricting the oil uptake and, therefore, reducing the overall fat content of meatballs (Galanakis, Tornberg, & Gekas, 2010b). It has also been reported the use of OLE extracts from leaves and olive fruits in sanitizing formulations and mannitol recovered from olive residues (pruning, leaves and aqueous residues) has been used as a thickener (P. Gullón, Gullón, Astray, et al., 2020; D. M. Otero, Oliveira, et al., 2020). In addition, vitamin E and monounsaturated fatty acids have been isolated from olive by-products and applied as natural ingredients due to their oxidative stability and antioxidant activity.

To summarize, different phenolic compounds (HT, OLE, *etc*.) and dietary fiber, have important biological properties (especially antioxidant activity), scientifically proved to be used as food additives and preservatives in a wide range of food products, including dairy, oil, and meat industries. Companies are already using phenolics as a natural preservative to increase the shelf life of products. However, it has been shown once added to food, HT has advantages over other phenolic compounds as it remains active much longer while the concentration of other phenolic compounds decreases (P. Gullón, Gullón, Astray, et al., 2020).

5.2. Pharmaceutical industry

In 2011, the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies released an opinion about the effects of olive polyphenols in the body after their consumption (Panel & Nda, 2011). These compounds can balance blood high-density lipoprotein (HDL)-cholesterol levels, preserve the low-density lipoproteins (LDL) particles from oxidative damage, and keep a normal blood pressure. In addition, they can assist in the correct gastrointestinal and respiratory functions, promote anti-inflammatory properties and, in general, contribute to body defense response against external agents. This scientific evidence, together with European circular economy policies, have boost the research on olive by-products revalorization in the last decade, not only in the food industry, but also in the pharmaceutical sector. One of the potential applications is the use of polyphenols from by-products in the treatment of intestinal diseases (Di et al., 2018). In this sense, the anti-inflammatory properties and the effect on cell metabolome of an aqueous extract of OP were studied in human intestinal Caco-2 cells. Such supplementation reduced the main pro-inflammatory cytokine, IL-8, secretion, showing the therapeutic potential of polyphenols from olive pomace in intestinal illness. Additionally, the effects on cell metabolome revealed a metabolic change towards a glucose saving strategy that explain the appetite-suppressing effect observed upon polyphenols-rich foods uptake (Di et al., 2018). In addition, the evaluation of polar lipids (from OP and OP production by-products) showed the inhibition of platelet activating factor involved in inflammatory pathologies, such as atherosclerosis (P. Gullón, Gullón, Astray, et al., 2020).

In parallel, Romero and co-workers concluded that OP skin is rich in triterpenoid acids, discovering a new bioactive-rich by-product from the OO mill processing (Romero et al., 2018). It is worthy to highlight that triterpenoid acids improve insulin action and, thus provide an antidiabetic effect (Tan et al., 2008). The olive by-products are also implicated in the relief of the abdominal pain, which is still considered a health problem in the current society. In a recent *in vivo* study, EVOO, OMWW, and dry OP were orally administered (dose of 0.3 g/kg) to colitis-induced rat models, providing evidence about the effectiveness of by-products in reducing not only pain perception, but also macroscopic intestinal damage, as well as fibrosis (Parisio et al., 2020). Finally, the effect of two olive by-products having phenols and polysaccharides in the modulation of the human microbiota was studied, showing an increase in Lactobacillaceae and Bifidobacteriaceae populations after nine-day administration of an olive pâté (obtained from the EVOO production) in the proximal tract. The polyphenol profiling showed the formation of tyrosol in the distal tract, while two ellagic acid metabolites derived from gut microbes (urolithins C and A) were induced from another by-product which was obtained from olive pomegranate mesocarp.

To sum up, the latest studies about the olive by-products employment in the development of new pharmaceutical products point out their positive use in gastrointestinal disorders, as appetite-suppressant agents, antinociceptives, and as modulators of human microbiota, among others, most due to the high contents in phenolic compounds, triterpenoid acids and polysaccharides.

5.3. Cosmetic industry

OO by-products have the potential to be further developed and used in the skin care industry. The previously mentioned compound OLE, present in olive leaves, stems and flowers is widely considered for nutraceutical applications due to its antioxidant, anti-inflammatory, anti-atherogenic, anticancer, antimicrobial and antiviral activities, together with its hypolipidemic and hypoglycemic effects (Omar, 2010). One study has proved that OO by-products containing OLE are good candidates for applications in skin treatment, since leaf ethanolic extracts containing this compound inhibited *Staphylococcus aureus* growth and reduced melanin biosynthesis in B16 melanoma cells. Also, the OMWW extract inhibited granule release from RBL-2H3 cells (Kishikawa et al., 2015).

The potential use of OMWW as a source for the recovery of phenols and their application as UV booster in cosmetics was also investigated with satisfactory results (Galanakis, Tsatalas, & Galanakis, 2018). The absorption of physical and chemical UV filters increased as a function of olive phenols concentration (in both UVB and UVA regions). Although UVA rays penetrate deeper into the skin and can cause cancer, both radiations lead to free radicals, toxic elements for skin cells and provoke skin ageing. Olive by-products are also rich in minerals, which were proposed as ingredients for cosmetic products with a hydration finality. Minerals are one of the main components of the natural moisturizing factor, which is significantly correlated with the state of hydration, stiffness, and pH, in the stratum corneum (Rodrigues et al., 2015). OP is also a good reservoir of squalene, which shows antioxidant properties at the cutaneous level against solar rays, acting as an active biological skin barrier (Rodríguez-Gutiérrez, Rubio-Senent, Lama-Muñoz, García, & Fernández-Bolaños, 2014). Besides, squalene may also have moisturizing properties, being eventually used as an ingredient in dermo-protective creams and other cosmetic formulations as emollient agent (Rodríguez-Gutiérrez et al., 2014). Squalene daily dose from food has been related to many health benefits and there are on the market several squalene formulations as nutraceuticals. However, cosmetics is the largest end-use industry of squalene due to its increasing usage in skincare products manufacturing. The demand for natural cosmetics with good quality has been the main driver for the growth of the market, especially in countries like France, Germany, Italy and Spain. Finally, olive by-products have also been proposed as promising ingredients for cosmetical products due to the high content of monounsaturated fatty acids (MUFAs), which are crucial in the structural function of cell membranes (Lin & Khnykin, 2014), playing an essential role in the proper functions of epidermis and sebaceous glands, including permeability barrier and promoting the acidification of the stratum corneum. Summarizing, olive by-products have interesting molecules (OLE, squalene, minerals, FAs) with biological activities (antioxidant, anticancer, antimicrobial, hydration) which can be of interest for product design in the cosmetic industry.

6. Future perspectives

Nowadays, the consumer habits are evolving towards more selective products with highly functional compounds, obtained by environmentally friendly and sustainable methodologies. As shown before, the production of OO, especially in the Mediterranean countries, is an important sector that requires the establishment of new applications in the use of its by-products in the food, pharmaceutical and cosmetic industries (Donner & Radi, 2021). However, the innovation processes to obtain precious products from olive by-products need the planification of a business model (bioeconomy strategy) that determines the viability of the extraction and their use in these industries. Up to now, the most widely-adopted choices in the OO sector in most countries with bioeconomy strategies support bioenergy and biofuels production (Berbel & Posadillo, 2018). In the case of OP in Spanish cultures, it is removed by authorized managers to whom the agro-industries pay for it. Subsequently, the manager can revalue these by-products, with the extraction of OP oil and the sale of biomass (olive pit). Also, they can be intended for feed, showing low economic benefits for the industry (Berbel & Posadillo, 2018). Thus, the development of high-value and innovative products from olive by-products is an urgent objective in many agri-food strategies, but when it comes to commercial application, the implementation of the policies is mainly focused on the application of biomass or materials to bioenergy.

Another issue to consider is that the recovery of by-products in the food industries may require the incorporation of new procedures and equipment, which can be unacceptable for small industries. Among extraction techniques, EAE is becoming an extended procedure to improve the extraction performance of various compounds in OO by-products (Kazan, Soner, Sargin, & Yesil-celiktas, 2015). It is based on the earlier treatment of the matrix with the corresponding enzyme, followed by a solvent extraction process. The hydrolytic enzymes can catalyze the degradation reactions of cell walls and membranes (composed of large and complex polymeric structures, such as cellulose, hemicellulose, lignin, and pectin), increasing the permeability of bioactive compounds and enabling target compounds release. For example, Kazan used OP to obtain added-value products, such as proteins, fermentable sugars, ethanol and lignin after a high pressure extraction and hydrolysis processes (Kazan et al., 2015). The use of this technology and the previously ones described (PLE and SCFE) needs qualified personnel and new investments which are difficult to support in small olive industries. To solve this issue, be the creation of plants for the use of by-products at the regional level, either in the form of companies or cooperatives, depending on the concentration of the raw material and the volumes that would need to be processed, constitutes one promising strategy to be developed (Sdino, Rosasco, & Lombardini, 2020). One plant could serve to different stakeholders and the investment by agribusiness is low, so their profitability can be increased. In this context, the recovery of some by-products from OO could be an opportunity for family-owned OO mills (D'Adamo, FalconeGastaldi, & Morone, 2019). Nevertheless, it seems necessary to promote an inter-sectorial dialogue and create collaborations to increase the amounts and applications of by-products in different fields.

7. Conclusions

The scientific evidence supporting the healthy benefits associated with the consumption of olives, takes an advantage to open new markets that meet the consumers requirements about their health. The information collected in this review shows that the by-products derived from the *Olea europaea* L. processing industry are secondary but valuable products, from which different biologically active molecules can be recovered by green extraction technologies (PLE, SFE, *etc.*) and reused for food, pharmaceutical and cosmetic purposes following the circular economy policies. One of the main advantages on recovering valuable molecules from olive by-products is their incorporation to functional foods. A direct effect was proven between the use of olive by-products in human consumption and the heath claims. In this context, different food industries have used the phenolic fraction of olive by-products, holding mostly HT and OLE, as food additives and as preserving agents due to their antioxidant properties.

In this review, we also described the progress in the biomedical field about the use of olive by-products to treat intestinal disorders and as appetite-suppressing agents, pain reducers, and modulators of human microbiota. These activities are attributed to phenols, triterpenoid acids and polysaccharides present in OO, olive fruit, OMWW, olive extracts, and leaf. In addition, olive by-products have other value molecules like squalene, minerals and FAs, so that they are precious products to be used for the skin care. To summarize, the exploitation of olive by-products to formulate new food and nutraceutical products constitute an innovative strategy that meets current and future expectations of consumers about environmental impact, ethical issues, human health, and safety.

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