

Leaves of *Olea europaea* L. as a source of oleuropein: characteristics and biological aspects

Folhas de *Olea europaea* L. como fonte de oleuropeína: características e aspectos biológicos

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Abstract

Olive fruits, leaves and derived virgin oils are known to be good sources of polyphenols and other antioxidants that have recently received increasing interest. In addition, its derivatives are responsible for the bitter and spicy taste of green olive fruits and virgin olive oils. In the physiology of the olive plant, the enzymatic biotransformation of oleuropein is related to fruit ripening and the tissue-specific defense mechanism. The oleuropein is one of the main phenolic compounds identified in fruits and olive leaves. It has several pharmacological properties, including antioxidant, cardioprotective, anti-heterogeneous, neuropathic, anti-cancer and other effects. Oleuropein is slightly absorbed after oral administration and reaches a maximum plasma concentration, being widely distributed in various organs and tissues, including the heart, liver and brain. In view of recent studies on the use oleuropein obtained from olive leaves in the treatment and prevention of diseases, this work was carried out with the aim of compiling the main information available in the literature through this review.

Keywords: Pharmacological properties; Olive leaves; Phenolic compounds; Oleuropein.

Resumo

Frutos, folhas e óleos virgens derivados de oliveiras são conhecidos por serem boas fontes de polifenóis e outros antioxidantes que recentemente têm recebido crescente interesse. Além disso, seus derivados são responsáveis pelo sabor amargo e picante das azeitonas verdes e dos azeites virgens. Na fisiologia da oliveira, a biotransformação enzimática da oleuropeína está relacionada com o amadurecimento dos frutos e com o mecanismo de defesa específico. A oleuropeína é um dos principais compostos fenólicos identificados em frutas e folhas de oliveira. Possui diversas propriedades farmacológicas, incluindo antioxidante, cardioprotetor, anti-heterogêneo, neuropático, anticancerígeno entre outros efeitos. A oleuropeína é ligeiramente absorvida após administração oral e atinge uma concentração plasmática máxima, sendo amplamente distribuída em vários órgãos e tecidos, incluindo o coração, o fígado e o cérebro. Tendo em vista os estudos recentes sobre a utilização da oleuropeína obtida da folha de oliveira no tratamento e prevenção de doenças, este trabalho foi realizado com o objetivo de compilar as principais informações disponíveis na literatura por meio desta revisão.

Palavras-chave: Propriedades farmacológicas; Folhas de oliveira; Compostos fenólicos; Oleuropeína.

Resumen

Se sabe que los frutos, hojas y aceites de aceitunas vírgenes son buenas fuentes de polifenoles y otros antioxidantes que recientemente han recibido un interés creciente. Además, sus derivados son los responsables del sabor amargo y picante de las aceitunas verdes y los aceites vírgenes. En fisiología del olivo, la biotransformación enzimática de la oleuropeína está relacionada con la maduración del fruto y con el mecanismo de defensa específico. La oleuropeína es uno de los principales compuestos fenólicos identificados en frutos y hojas de olivo. Posee varias propiedades farmacológicas, entre las que destacan antioxidante, cardioprotectora, antiheterogénea, neuropática, anticancerígena, entre otros efectos. La oleuropeína se absorbe ligeramente después de la administración oral y alcanza una concentración plasmática máxima, distribuyéndose ampliamente en varios órganos y tejidos, incluidos el corazón, el hígado y el cerebro. A la vista de estudios recientes sobre el uso de oleuropeína obtenida de la hoja de olivo en el tratamiento y prevención de enfermedades, este trabajo se llevó a cabo con el objetivo de recopilar la principal información disponible en la literatura a través de esta revisión.

Palabras clave: Propiedades farmacológicas; Hojas de olivera; Compuestos fenólicos; Oleuropeína.

1. Introduction

Oleuropein is a glycoside that represents the most prominent hydrophilic phenolic compound in olives and olive leaves. By enzymatic or chemical hydrolysis, oleuropein can degrade and produces several possible derivatives, such as aglyconic and hydroxytyrosol form, which can be found in olive oils (Romani et al., 2019).

Reports in the literature indicate that oleuropein has a high antioxidant power, anti-inflammatory property (Moa et al., 2019), hypotensive (Tsoumani et al., 2021), hypoglycemic (Cristiano et al., 2021), hypouricemic action (Wan et al., 2018), as well as health-beneficial pharmacological actions such as antimicrobial, antiviral and antitumor, in addition to inhibiting the increase in LDL ((Low Density) fraction Lipoprotein) in the blood (Ahamad et al., 2019).

In the face of several *in vivo* and *in vitro* studies that point out that oleuropein and its derivatives have this variety of beneficial properties, it has led researchers to become interested in these compounds, contributing to the identification and characterization of other biological activities of oleuropein with functional, pharmacological, biomedical potential. Thus, the present study aimed to provide information about the benefits of oleuropein.

2. Data Source and Search Strategy

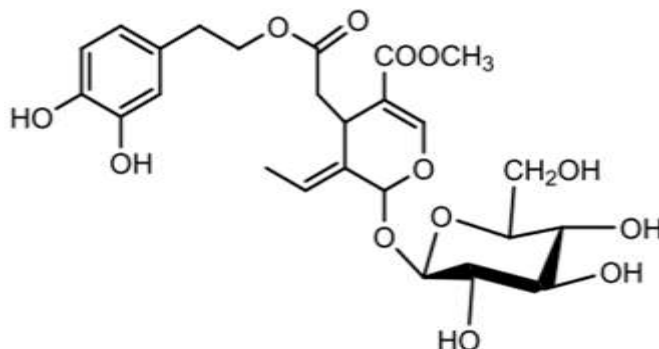
A comprehensive review was conducted by systematically searching in PubMed and Springer Link for all studies that developed an *a priori* OBS until May 2021. Subject headings related to OBSs (Oleuropein, phenolic compound, olive leaves) and other key terms (health, pharmacological, disease) were considered. Exclusion criteria were articles that did not meet the inclusion criteria mentioned above; For a writing of this review a total of 95 references were selected which presented the information and data of interest to the authors.

3. Structure Oleuropein

Oleuropein consists of a polyphenol belonging to a specific group of coumarin-like compounds, the secoiridoides. Secoiridoides are produced by the secondary metabolism of terpenes and formed from a phenylethyl alcohol (hydroxytyrosol and tyrosol), elenolic acid and, eventually, glucoside residues (Souilem et al., 2017).

Oleuropein (C₂₅H₃₂O₁₃) is an ester of hydroxytyrosol and glucoside of elenolic acid (an oleoside skeleton common to the glucosides of Oleaceae secoiridoides), it is a phenolic compound with a molecular mass of 540.54 g/mol. This molecule (Figure 1) is thermolabile, being able to degrade at 80°C, unstable in the presence of oxygen and light, has a high solubility in water and a low solubility in oil, has a crystalline appearance in its pure form and it is relatively odorless (Ansari et al., 2011).

Figure 1. Chemical structure of the oleuropein molecule.



Source: Authors.

This polyphenol is present in the specialized metabolism of plants of the *Olea* genus, being observed in plants of the Oleaceae family (olive tree), as well as in genera such as *Jasminum* and *Fraxinus* (Tanahashi et al., 1996). Oleuropein content varies according to the variety, climate, degree of ripeness of the olives at the time of harvest, as well as the processing system (Hassen et al., 2015). Oleuropein is the compound responsible for the bitter taste of the olives, leaves, pulps, and seeds of the olive plants. The oleuropein concentration can reach up to 140 mg. g⁻¹ dry matter in young olives and about 60 and 90 mg. g⁻¹ dry matter in the leaves (Tayoub et al., 2012).

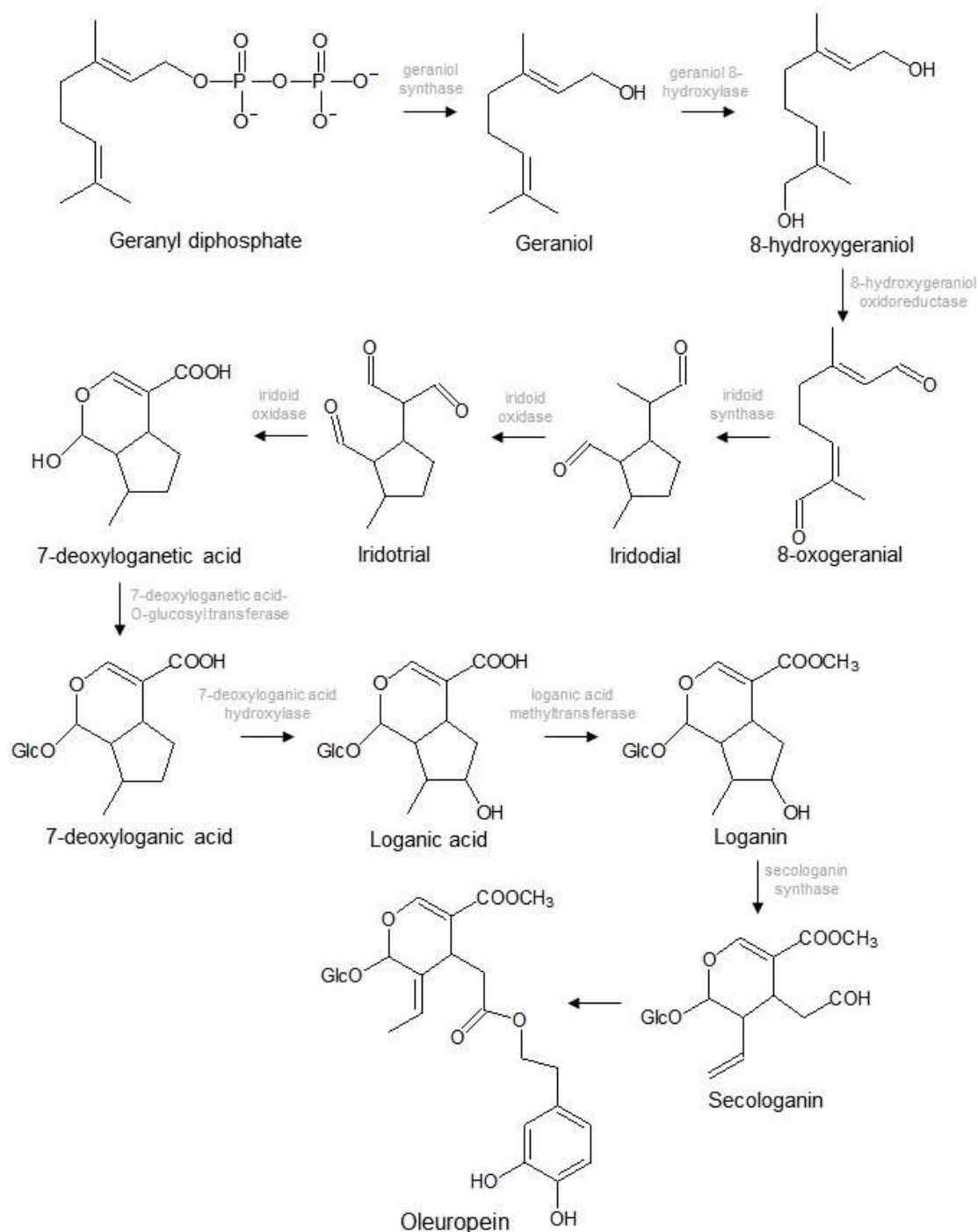
4. Biosynthesis and Degradation

The study on the synthesis of oleuropein began after it was first reported in 1960, and since then it is believed that in plants of the Oleaceae family, oleuropein is derived from mevalonic acid (MVA), which is converted by a series of reactions that include oxidations, reductions, glycosylations and methylations (Bonechi et al., 2019).

Oleuropein represents, in its synthesis, a meeting point between terpene synthesis and phenolic synthesis (Ryan et al., 2002). However, recent studies point out that many of the reactions for oleuropein synthesis are still unknown, which makes it inappropriate to exclude alternative routes of oleuropein biosynthesis (Alagna et al., 2012). Ryan et al. (2002) points out that the hydroxytyrosol fraction, that is, the phenolic fraction present in oleuropein derives from the hydroxylation of the aglycone ligstroside, with tyrosol (compound derived from tyrosine) being the main phenolic precursor of oleuropein, and not hydroxytyrosol. Damtoft et al., (1993) points out that the biosynthetic conversion is slow, probably due to the translocation of the precursors by the plant tissues. However, Alagna et al., (2016) report that ligstroside may be a derivative and not a precursor to oleuropein.

In addition, it is believed that the precursor molecule related to the synthesis of secairidoides (class to which oleuropein belongs) is geranyl-pyrophosphate (Miettinen et al., 2014). The conversion of this molecule to secologanin is related to approximately 9 enzymes (Miettinen et al., 2014; Mougiou et al., 2018; Guodong et al., 2019). However, as can be seen in Figure 2, the enzyme responsible for the transformation of secologanin into oleuropein is not yet known.

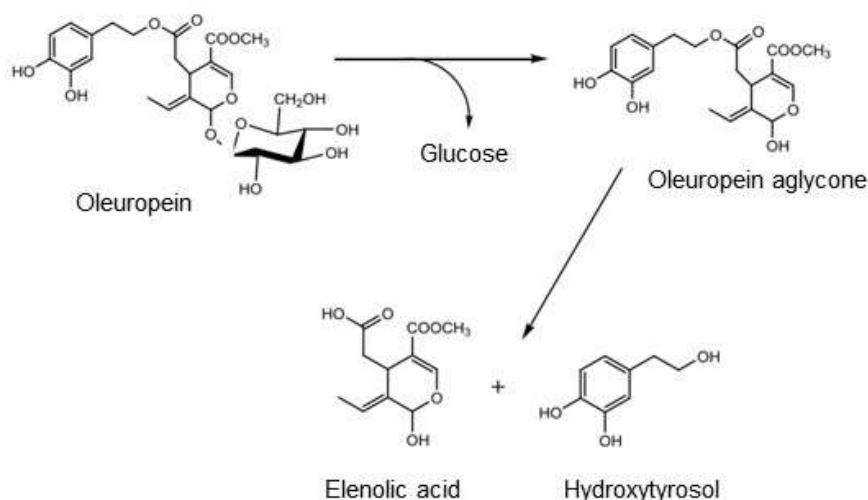
Figure 2. Metabolic route of synthesis of the oleuropein molecule from its geranyl diphosphate precursor and the enzymes responsible for biotransformation's



Source: Authors.

The degradation of oleuropein (Figure 3) can occur via enzymatic and / or chemical, culminating in the formation of compounds such as hydroxytyrosol, elenolic acid and dimethyl oleuropein, the latter resulting from the demethylation of oleuropein (Alagna et al., 2012).

Figure 3. Degradation of oleuropein into elenolic acid and hydroxytyrosol.



Source: Authors.

Oleuropein is an abundant compound in the early stages of olive fruit. During the growth and ripening of the olives there are three distinct phases, where in the first there is an accumulation of oleuropein (growth) and in the second and third there is a reduction in the levels of this compound (maturation). Recent studies report that during the maturation of olives in many olive cultivars, oleuropein is degraded into hydroxytyrosol, elenolic acid and dimethyl oleuropein (Yorulmaz et al., 2013). Ortega-Garcia et al. (2008) observed that during the fruit ripening process there was a decrease in the concentrations of oleuropein; however, in the leaves of the olive trees, during the same period, there was an increase in the concentration of the compound. The authors suggest that there may be an interaction between oleuropein and polyphenol oxidases (POP), converting oleuropein into compounds that act on the denaturation, cross-linking or alkylation of proteins, which may have protective effects against herbivores.

The degradation products of oleuropein may differ depending on the type of enzyme that acts on this compound. β -glycoside (EC 3.2.1.21) forms oleuropein aglycone or decarboxymethyl oleuropein aglycone, through the release of glucose; while esterase's produce glucosyl derivatives, such as hydroxytyrosol and elenolic acid, through the hydrolysis of ester bonds present in oleuropein (Wang et al., 2009). Oxidoreductases, peroxidases and polyphenol oxidases, promote browning through the oxidation of *o*-dihydroxy phenols to *o*-quinones (Segovia-Bravo et al., 2009). However, according to Ortega-Garcia et al. (2008) polyphenol oxidases are not related to the drop in the levels of oleuropein in fruits during maturation, with different times being observed in relation to the higher expression of the enzyme and high concentrations of the compound.

Studies by De Leonardis et al. (2015) revealed that the simultaneous presence of oleuropein and hydroxytyrosol causes the second compound to have an inhibitory effect on the action of polyphenol oxidases. According to Gutierrez-Rosales et al. (2010), the synthesis of oleuropein is related to enzymatic hydrolysis caused by β -glycosidase, an enzyme present in several stages and in the formation of compounds. Glycosyltransferases are said to be the catalysts for the formation of oleuropein through oleuropein aglycone (Alagna et al., 2012).

Currently researchers seek to identify the genes responsible for gene expression that increases the production of oleuropein, aiming at genetic improvement for increasing the concentrations of the compound and also for application in metabolic engineering in microbial hosts or plants (Alagna et al., 2016).

5. Biological Aspects

A number of studies have been carried out with leaf extracts and olive fruit for technological and functional purposes (Table 1), but few have been developed with pure oleuropein alone.

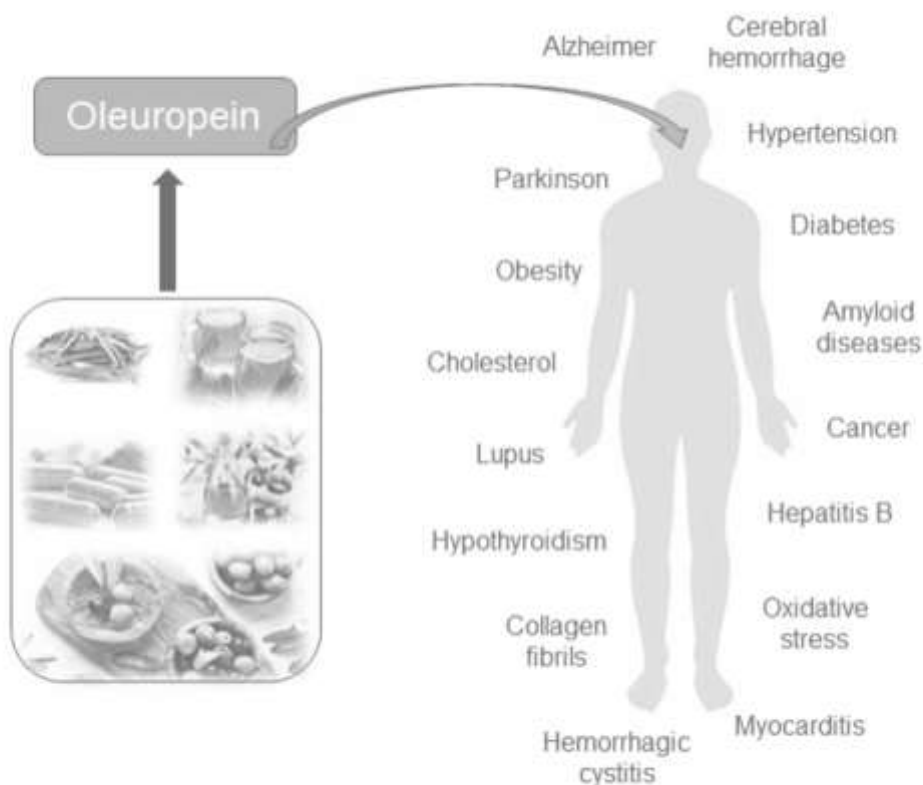
Table 1. Studies that evaluated the effects of using oleuropein on some diseases.

Diseases	References
Oxidative stress	Hassanzadeh et al., 2014; Ogun et al., 2016; Ji et al., 2018; Nasrallah et al., 2020.
Obesity	Hadrich et al., 2016; Oi-Kano et al., 2017; Malliou et al., 2018; Ahamad et al., 2019.
Diabetes	Liu et al., 2014; Sangi et al. 2015; Annunziata et al;2018; Benlarbi et al., 2020.
Cholesterol	Jemai et al., 2008; Malliou et al., 2018; Ahamad et al., 2019.
Cancer	Seçme et al., 2016; Capo et al., 2017; Sherif, Al-Gayyar, 2018; Ruzzolini e al., 2018; ; Nicolin et al., 2019; Torić et al., 2019; Przychodzen et al.,2019a; Przychodzen et al., 2019b; Castejón et al., 2020; Leto et al., 2020; Asgharzade et al., 2021; Hamed et al., 2021; Ramírez-Expósito et al., 2021.
Hypertension	Sun et al., 2017; Ahamad et al., 2019; Nediani et al., 2019.
Hepatitis B	Zhao et al., 2009.
Cerebral hemorrhage	Shi et al., 2017.
Myocarditis	Christia and Frangogiannis, 2013; Giner et al., 2013; Killen et al., 2014; Tiedje et al., 2014; Amoah et al., 2015; Liu et al., 2017; Zhang et al.,2017; Tsoumani et al., 2021;
Alzheimer's	Grossi et al., 2013; Cordero et al.,2018; Leri et al., 2019.
Parkinson	Pasban-Aliabadi et al., 2013; Sarbishegi et al., 2014; Di Rosa et al. 2018.
Collagen fibrils	Bharathy and Fathimau, 2017.
Hemorrhagic	Alupului, Calinescu and Lavric, 2012.
Cystitis	Boeira et al., 2011; Sinanoglu et al.,2012; Moraes et al., 2013; Sherif et al., 2016.
Lupus	Castejon et al., 2019
Amyloid diseases	Leri et al., 2018
Hypothyroidism	Mahmoudi et al., 2018

Source: Authors.

There are reports of the use of this compound in food preservation as a natural antioxidant, in sanitizing formulations and as a functional component in dairy products. The effects of the enzyme-linked immunosorbent assay on the treatment of diseases have also been investigated (Otero et al., 2020). Oleuropein and its derivatives have biological activities, containing antioxidant, anti-inflammatory, antimicrobial and antiproliferative properties and health protection effects in cardiovascular diseases, diabetes and neurological diseases (Yoon, 2018). Oleuropein is easily absorbed by the human body, and therefore, like other phenolic compounds present in the olive tree, much of the ingested oleuropein is absorbed (Vissers et al., 2002), which can participate in various functions in the body (Figure 4).

Figure 4. Biological effects on the human body related to the consumption of oleuropein.



Source: Authors.

Oxidative Stress

As a phenolic compound, oleuropein is recognized mainly for being an antioxidant, acting in the elimination of free radicals (Cicerale et al., 2012). This is mainly due to the presence of hydroxyl groups in their chemical structure, particularly that in the fraction 1,2-dihydroxybenzene. Hydroxyl groups can donate hydrogen to prevent oxidation of the molecule (Hassen et al., 2015).

Hassanzadeh et al. (2014) considered the antioxidant structure-activity relationship to study the radical elimination activity of oleuropein and its derivatives from the olive tree using the functional density theory (DFT). In the study, a unique radical position (C3) was identified in oleuropein, characterized by low enthalpy of dissociation of binding and rotation density, in addition to the ability to distribute electrons. According to the results, 2,2-diphenylpicrylhydrazyl (DPPH) cannot find the elimination site for nitric oxide (NO) and hydroxyl radical (OH). Thus, the authors concluded that the evaluation of antioxidant activity with DPPH may not be a determining test for all antioxidant comparisons.

Oral administration of extracts rich in polyphenols derived from the hydrolysis of olive leaves induced an increase in the antioxidant potential of serum lipid levels and in the hepatic activities of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) in rats fed a rich diet. in cholesterol (Jemai et al., 2008).

In a study to investigate the potential preventive effect of oleuropein on an experimental arsenic toxicity in mice, Ogun et al. (2016) found that oleuropein improved oxidative tissue damage by eliminating free radicals. In this study, the level of nitric oxide in the blood and tissues decreased, while the content of cerebral malondialdehyde increased, in rats treated with arsenic. In addition, immunoreactivity for inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS), increased with arsenic treatment, in addition to the immunohistochemical staining also demonstrated a reduction in the expression of iNOS and eNOS in the liver.

Many other studies have shown the antioxidant properties of oleuropein, such as reducing oxidative stress involved in intracerebral hemorrhage (Shi et al., 2017), relieving oxidative stress in acute colitis (Huguet-Casquero et al., 2020), the effect effective and promising antioxidant in hepatic steatosis (Santini et al., 2020), the ability to protect muscle cells against H₂O₂-induced stress in cells (Hadrich et al., 2016), inhibition of the production of reactive oxygen species in paraventricular nucleus (PVN) associated with hypertension (Sun et al., 2017), decreased oxidative stress caused by ischemic reperfusion injury in a rat kidney (Hana et al., 2020), and the effect on injury-induced oxidative stress of ischemic reperfusion in isolated rat heart (Esmailidehaj et al., 2016).

In a study carried out on the potential cytoprotective effect of oleuropein against oxidative stress and H₂O₂ induced autophagic cell death, where the viability of cells treated with oleuropein exposed to various levels of oxidative damage was evaluated. It has shown that the preparation of short-term cells using oleuropein can increase the therapeutic effect of mesenchymal stem cells (MSCs) against ischemic vascular diseases (Ji et al., 2018).

Obesity

Hadrich et al. (2016) aimed to evaluate the effect of oleuropein on the level of adiponectin in obesity induced by a hypercholesteremic diet in rats and the molecular mechanism underlying its activation, and observed that oleuropein induced a reduction in body weight, in the mass of adipose tissue, triglycerides and hepatic steatosis, and increased serum adiponectin concentration. As a result, it was suggested that oleuropein exerts an important anti-obesity effect in rats with a hypercholesteremic diet by activating protein kinase by adenosine monophosphate (AMPK), and by suppressing the expression of PPAR γ (peroxisome proliferator receptor γ) in adipose tissues.

In a study by Oi-Kano et al. (2017) oleuropein led to a reduction in the visceral fat content in obese rats, by activating the transient potential of the ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) receptors, which are associated with weight regulation, hormonal secretion, thermogenesis and neuronal function.

Malliou et al. (2018) carried out experiments on adult male mice, where oleuropein was applied daily for 6 weeks. It has been observed that oleuropein is poorly absorbed. Ahamad et al. (2019) in studies carried out on rats, found that oleuropein supplementation reduced intracellular fat gain by 40% and 70%.

Diabetes

Oxidative cell signaling linked to stress is strongly associated with abnormal glucose metabolism (Valko et al., 2007). Oleuropein has been diagnosed as a possible preventive component of diabetes and promotes the reduction of blood glucose concentration and can be used to treat hyperglycemic symptoms and to increase antioxidant activity (Wainstein et al., 2012). Sangi et al. (2015) introduced diabetes to rats by streptozotocin (STZ) and found that oleuropein intake significantly reduced

serum glucose levels in these animals. Liu et al. (2014) described that the intake of oleuropein increased insulin resistance in diabetes induced by a high-fat diet in rats, reducing the tumor necrosis factor alpha and interleukin-6, which is associated with the inflammatory process.

Annunziata et al. (2018) demonstrated that diabetic studies carried out in rodents indicated that rats induced with streptozotocin of 5 mg.kg⁻¹ of oleuropein considerably reduced glucose. Benlarbi et al. (2020) analyzed diabetes in rodents where the corrective effect of the aqueous extract of olive leaf was superior to that of oleuropein, it was also found that the addition of oleuropein and the aqueous extract restores the damage caused by glucose cell viability.

Cholesterol

Rabbits on a hypercholesterolemic diet, after treatment for six weeks with oleuropein (10 or 20 mg / (kg x d)), showed a reduction in total cholesterol and triglyceride concentrations (Andreadou et al., 2006). Jemai et al. (2008) tested the effect in rats fed a high cholesterol diet, and found that the hyperlipidemia induced by this diet resulted in an increase in total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C). The administration of olive leaf extracts, rich in oleuropein and polyphenols significantly reduced the serum levels of TC, TG and LDL-C and increased the serum level of high-density lipoprotein cholesterol (HDL-C).

Malliou et al. (2018) in an evaluation of oleuropein with PPAR α in mice decreased serum TG levels and hepatic TG content. It can also be observed that the total cholesterol concentration decreased and that oleuropein had no effect on the relative weight of the liver.

Ahamad et al. (2019) detected the presence of PPAR γ in a cholesterol-rich diet were considerably lower in oleuropein administered to fed rats, oleuropein confirmed a decrease in serum LDL, at the same time as an increase in serum HDL. In another study conducted with wild-type mice, it was found that the use of oleuropein enabled the reduction of total cholesterol (TC) and triglycerides (TG).

Cancer

Neuroblastoma is one of the most common types of pediatric tumors that can spread quickly to neuronal tissues. Studies evaluating the therapeutic effect of oleuropein on cell proliferation, invasion, colony formation, cell cycle and apoptotic mechanisms in the SH-SY5Y neuroblastoma cell line in in vitro conditions, have shown that oleuropein can be a therapeutic agent in the treatment neuroblastoma. It was observed that oleuropein caused the cell cycle to be trapped by negative regulation of CylinD1, CylinD2, CyclinD3, CDK4, CDK6; up-regulation of p53 and CDKN2A, CDKN2B, CDKN1A gene expressions; induction of apoptosis by inhibition of Bcl-2; activation of Bax, caspase-9 and caspase-3 gene expressions; reduction of invasion in SH-SY5Y cells; and suppression of the number of colonies (Seçme et al., 2016).

Cisplatin-based chemotherapy is responsible for a large number of kidney failures, and is still associated with high mortality rates. Studies with oleuropein ingestion have indicated protection against cisplatin-induced nephrotoxicity in rats, in addition to significant cytoprotective activity (Geyikoglu et al., 2017).

According to Przychodzen et al. (2019b) recent studies have shown that non-receptor tyrosine phosphatase 1 (PTP1B) plays a key role in the pathophysiology and development of breast cancer. Przychodzen et al. (2019b) concluded that oleuropein inhibited PTP1B activity in an MCF-7 breast cancer model.

Hypertension

In spite of advancements in breast cancer therapy, this disease is still one of the significant causes of fatalities

globally. Dysregulation of miRNA plays a pivotal role in the initiation and progression of cancer. Therefore, the administration of herbal compounds with anticancer effects through controlling microRNA expression can be considered as a promising therapy for cancer (Asgharzade et al., 2021).

A study examined the effect of oleuropein on two breast cancer cell lines (MCF7 and MDA-MB-231). The findings revealed that oleuropein significantly decreased cell viability in a dose- and time-dependent manner, while it increased the apoptosis in MCF7 and MDA-MB-231 cells. In the presence of oleuropein, the expression levels of miR-125b, miR-16, miR-34a, p53, p21, and TNFRS10B increased, while that of bcl-2, mcl1, miR-221, miR-29a and miR-21 decreased. The findings pointed out that oleuropein may induce apoptosis via not only increasing the expression of pro-apoptotic genes and tumor suppressor miRNAs, but also decreasing the expression of anti-apoptotic genes. Oleuropein can be regarded as a suitable herbal medication for cancer therapy (Asgharzade et al., 2021)

Studies have revealed that oleuropein exerts its anticancer function through impacting the expression of genes involved in the cancer progression and apoptosis induction. However, the molecular mechanisms underlying the function of oleuropein in the inhibition of cancer have not been well-identified. Considering that one of main approaches in cancer treatment is the induction of apoptosis in cancer cells, the function of this compound in boosting or attenuating apoptosis pathways has been examined in the literature (Ahmad Farooqi et al., 2017)

Oleuropein showed positive effects in several pathological conditions that affect humans. In particular, recent preclinical and observational surveys release evidence that this compound exhibits chemo-preventive effects in several tumors. Studies have indicated that this phenol can prevent several crucial stages of malignant progression, including tumor, angiogenesis, survival, cell proliferation, metastasis and also invasion by modulating the expression and activity of various growth factors, cytokines, adhesion molecules and enzymes involved. in the process. In addition, it is highlighted that the signaling molecules showed to be involved in targeting and growing cancer cells spread in bones. These findings are indicative of a potential therapeutic role for oleuropein in the prevention and treatment of cancer (Leto et al., 2021).

In a study by Hamed et al. (2021), an oleuropein controlled the miR-194 / XIST / PD-L1 loop without triple negative breast cancer, representing a new nutriepigenetic in immunoncology.

Sherif and Al-Gayyar (2018) reported that oleuropein potentiates the antitumor activity of cisplatin and can improve the side effect of its use by reducing the dose required to treat hepatocellular carcinoma (HCC), one of the most common tumors in the world and the leading cause of death from cancer.

An oleuropein has a protective action against cancer or neurodegeneration, in a study carried out it can be demonstrated that an oleuropein forms a complex with copper transition metal. The relationship between oleuropein and copper has been investigated in human neuroblastoma cells SH-SY5Y, demonstrating harmful effects in cultured SH-SY5Y cells, with an aglycone oleuropein that is less toxic to these cells (Capo et al., 2017).

Many studies provide evidence on the effectiveness of oleuropein in preventing and treating various pathologies associated with bone loss (Leto et al., 2020). In which these effects are related to the activity of oleuropein in modulating several common signaling molecules contained in the pathogenesis of malignant and non-malignant bone diseases. Thus, oleuropein would be a compound with potential use in preventing the growth and spread of cancer cells in the bones (Przychodzen et al., 2019a; Nicolin et al., 2019).

Hypertension is associated with increased production of reactive oxygen species (ROS) in the paraventricular nucleus (PVN) of the hypothalamus. In spontaneously hypertensive rats, eight weeks of 60 mg / kg / day of oleuropein were administered, and in response, an increase in the antioxidant defense system in the PVN in the rats was observed (Su et al., 2017).

Ahamad et al. (2019) observed the antihypertensive effects of oleuropein, daily dosages of oleuropein up to 60 mg.Kg.day⁻¹ causing a decrease in blood pressure and reduced hypertension in rats with simultaneous hypertension and diabetes. Supplementation was also performed daily dose of 30 mg, where a reduction in systolic and diastolic blood pressure was observed in women.

Nediani et al. (2019) conducted a randomized controlled clinical trial in pre-hypertensive volunteers, who after an ingestion consumption of olive leaf extract enriched with oleuropein for six weeks (136 mg oleuropein; 6 mg HT), presented blood pressure (BP) considerably lower. Trials in patients with stage 1 hypertension revealed that a daily dose of 2,500 mg of olive leaf extract (with 16-24% oleuropein) for four weeks, decreased systolic and diastolic BP with an effect similar to that exerted by a dose effective (12.5-25 mg twice daily) of Captopril (the standard therapy for stage 1 hypertension).

Hepatitis B

Jasminum officinale L. of the *Grandiflorum* variety (JOG) is a plant of the Oleaceae family, which in folk medicine is used for the treatment of hepatitis in southern China. Studies have shown that oleuropein obtained from JOG flowers effectively blocks the secretion of hepatitis B surface antigen (HBsAg) in HepG2 2.2.15 cells in a dose-dependent manner. It was also observed that the intraperitoneal application of 80 mg.kg⁻¹ of oleuropein, applied twice a day, reduced viremia in ducks infected with hepatitis B virus in the absence of any signs of toxicity (Zhao et al., 2009).

Cerebral hemorrhage

Shi et al. (2017) evaluated the intake of oleuropein in an animal model of intracerebral hemorrhage in Sprague-Dawley rats, from general symptoms to detailed molecular mechanism. From the treatment with oleuropein, there was a relief of oxidative stress in the neurological deficit associated with intracerebral hemorrhage and cerebral edema in a dose-dependent manner. In this way, the structure of the hematocephalic barrier can be preserved and the oxidative stress can be smoothed out, therefore, it can be used as a promising therapeutic agent for intracerebral hemorrhage.

Myocarditis

Myocarditis is a common cardiovascular disease and one of the main causes of dilated cardiomyopathy. In the study by Zhang et al. (2017) myocarditis was induced in rats and the intake of oleuropein was applied. The results suggest that oleuropein effectively prevents the development of myocarditis by inhibiting the inflammatory responses mediated by mitogen-activated protein kinases (MAPKs) and the nuclear factor kappa-B (NF-κB). With myocarditis, cytokines secreted from activated immunocytes destroy the functionality of cardiomyocytes and inflammatory cells magnify the cardiac inflammatory reaction (Amoah et al., 2015; Christia and Frangogiannis, 2013). The nuclear factor kappa-B (NF-κ B) is one of the cross-talk points of multiple inflammatory signal pathways that play key roles in regulating cytokine expression (Liu et al., 2017), as it controls the production of countless pro-inflammatory mediators (Giner et al., 2013; Killeen et al., 2014). Mitogen-activated protein kinases (MAPK) act on immunity in altering the levels of translation and expression of various pro-inflammatory cytokine (Tiedje et al., 2014).

Alzheimer's

Fragments of Amyloid-β (Aβ), aggregates of oligomeric Aβ and pyro glutamylated-Aβ peptides, epigenetic engines and autophagy dysfunction, research in different ways for Alzheimer's disease (Luccarini et al., 2015). Grossi et al. (2013) observed a beneficial effect of oleuropein disease in reducing neurodegeneration associated with Alzheimer's. The authors

demonstrated that dietary supplementation of oleuropein aglycone strongly improves cognitive performance in young and middle-aged TgCRND8 transgenic mice, reduces levels of A β 40 and A β 42, in addition to reducing the size and compactness of A β amyloid plaques. An improvement in non-spatial episodic memory and functional memory was also highlighted, together with the improvement of cortical neuropathological aspects and an indication of autophagy that protects neurons from A β -induced cytotoxicity.

Cordero et al. (2018) observed in *in vitro* and *in vivo* models that oleuropein prevents and reduces symptoms associated with Alzheimer's disease. The results in human cells establish that the use of oleuropein may be useful to delay cognitive impairment in humans. Another recent study reported the positive effect of using European countries in the face of Alzheimer's disease, interfering with the pathway of amyloid aggregation (Leri et al., 2019).

Parkinson

Parkinson's disease consists of a progressive neurodegenerative disorder characterized by the progressive death of dopaminergic neurons in the midbrain. Pasban-Aliabadi et al. (2013) using an *in vitro* model of Parkinson's disease, which consists of 6-hydroxidopamine-induced toxicity in the adrenal pheochromocytoma of rats, reported that oleuropein reduced intracellular ROS, activated caspase 3, the Bax / ratio Bcl-2 and DNA fragmentation in cells treated with oleuropein. The protective effects of oleuropein are related to its anti-oxidative and anti-apoptotic properties and suggest its therapeutic potential in the treatment of Parkinson's disease.

Sarbishegi et al. (2014) observed that the treatment of elderly rats with oleuropein for 6 months decreases the oxidative damage in dopaminergic neurons of the substantia nigra pars compacta (SNc) by increasing the activity of antioxidant enzymes. Thus, it is observed that the consumption of oleuropein in the daily diet can be useful to reduce the damage of oxidative stress and eliminate free radicals, increasing the activities of antioxidant enzymes.

A study by Di Rosa et al. (2018) showed the protective effect against Parkinson's disease of polyphenols in olive oil, hydroxytyrosol and oleuropein, in a model system of Parkinson's disease.

Collagen fibrils

Collagen fibrils can accumulate in excessive amounts and impair the normal functioning of the organs, and this accumulation is a hallmark of cardiac fibrosis, keloids and systemic scleroderma. In cardiac fibrosis, the accumulation of collagen fibrils in blood vessels leads to thickening of the arteries and changes in cardiac architecture and function (Krenning et al., 2010). Bharathy and Fathimau (2017) investigated the inhibitory effect of oleuropein on the formation of collagen fibrils, and found a substantial reduction in the formation of fibrils, suggesting the effect of oleuropein on collagen self-assembly; and they also observed that the formation of collagen fibrils was increasingly inhibited due to the increased concentration of oleuropein.

Hemorrhagic Cystitis

Hemorrhagic cystitis is a devastating complication seen in patients after conventional chemotherapy treatments that include oxazaphosphorine alkylating agents, such as ifosfamide and cyclophosphamide (CYP) (Alupului et al., 2012; Sinanoglu et al., 2012). Studies have shown that CYP induced urinary inflammation in the mucosa and submucosal connective tissue of the bladder, inducing vascular damage, subsequent bleeding, ulceration and erosion of the mucosa (Boeira et al., 2011; Moraes et al., 2013). It was observed that oleuropein neutralized the harmful effects of cyclophosphamide on the bladder, possibly due to its antioxidant and anti-inflammatory activities, exerting a definitive uroprotective effect against

cyclophosphamide-induced hemorrhagic cystitis in rats (Sherif et al., 2016).

Castejon et al. (2019), pointed out the use of oleuropein may be an alternative in the preventive / palliative treatment of nephritis in the management of systemic lupus erythematosus (SLE). Without a safe and effective treatment, SLE can affect several active systems, being a chronic and autoimmune inflammatory disease.

Leri et al. (2018) conducted a study on the relationships between the effects of the oleic form of oleuropein on aggregation and cellular interactions of the D76N β 2-microglobulin (D76N b2m) variant associated with a familial form of systemic amyloidosis with progressive intestinal dysfunction and extensive visceral amyloid deposits. Where, they observed that this polyphenol has a protective effect against the cytotoxicity of D76N b2m, since it remodels D76N b2m aggregates and the cell membrane, interfering with the association of protein folded cell membranes, which triggers amyloid-mediated cytotoxicity.

Mahmoudi et al. (2018) when evaluating the protective effect of phenolic compounds in olive leaves against bisphenol A-induced thyroid dysfunction (BPA) and growth disturbance in young rats during lactation, observed that oleuropein supplements and olive leaf extract with hydroxytyrosol in mothers treated with BPA they protect the thyroid gland and improve bone growth in young rats. BPA has the ability to bind to various hormone receptors, such as estrogen and thyroid receptors, and can negatively interfere with the endocrine system. The binding of BPA to thyroid hormone receptors (HRT) affects the hormonal balance, which is essential for fetal and newborn development.

6. Others Pharmacological Effects of Oleuropein

Oleuropein has several pharmacological properties with scientific proof, among which we can mention: antioxidant, antimicrobial and antiviral activities, in addition to anti-atherogenic and anti-inflammatory potential. The vasodilation, antiplatelet, hypotensive, antirheumatic, diuretic, antipyretic (Mao et al., 2019) and protective effects on male reproductive (Lozano-Castellón et al., 2021; Rostamzadeh et al., 2020) are related to oleuropein Ethnopharmacological studies demonstrated that oleuropein have therapeutic potential for gastric ulcers (Koc et al., 2020).

In the field of cosmetics, this glycoside is of great interest since it has effect skin protectant (Masre, 2021) and anti-aging activation of proteasome, reduction of DNA oxidative damage and lipid peroxidation were also demonstrated. Many reports suggested that oleuropein had hepatoprotective and gastroprotective effects, in addition oleuropein has been studied to combat depression. This compound demonstrated anti-ischemic and hypolipidemic activities as well as analgesic and sedative effects (Rabiei et al., 2018; Zare et al., 2012). Owing to its significant functionality, the incorporation of oleuropein and/or oleuropein-rich extracts into food-based products is likely to be a promising practice for development of functional foods and nutraceuticals (Hassen et al., 2015).

7. Prospectives

Olive leaves (*Olea europaea* L.) present in their composition, several compounds of interest such as simple phenols and others with more complex structures. Among the simple phenols, the following are highlighted: hydroxytyrosol, tyrosol and caffeic and vanillic acids, while among the dry pyridoids the highlight is oleuropein (very complex phenol), which has a structure chemical with larger size and greater abundance, having a bitter taste. The pharmacological properties of olive oil, the olive fruit and its leaves have been recognized as important components of medicine and a healthy diet because of their phenolic content. It acts in the prevention of heart disease, a natural antioxidant, has anti-inflammatory and antimicrobial properties, besides, together with hydroxytyrosol, they have a synergistic effect with vitamins E and C. According to the information about oleuropein presented, it can be verifying that this compound has several properties beneficial to health and

that is why it has been shown to be an important subject for research in the most diverse areas (drugs, food and cosmetics). There are already studies about the different properties attributed to oleuropein but there are still several gaps which become of interest in the most diverse areas.

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