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APPLICATIONS OF OLEUROPEIN

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ABSTRACT

One of the most prevalent phenolic compounds found in olive leaves is oleuropein. Numerous studies have demonstrated the biologically significant effects of this compound, including anti-inflammatory, anti-atherogenic, anticancer, antimicrobial, and antiviral effects, which has led to its increased attention in the scientific community. Oleuropein can be recovered and purified (mostly by chromatographic techniques) from a variety of sources using both conventional and non-conventional methods. It can then be applied in a number of contexts.

Because of its numerous pharmacological properties, oleuropein is commercially obtainable as a food enhancement in Mediterranean countries. Numerous scientific and clinical investigations have demonstrated their efficacious significance.

KEYWORDS: Olea europaea L., oleuropein, phenolic compound, antioxidant, anti-obesity, antimicrobial.

INTRODUCTION

In the Mediterranean region, Olea europaea Linn. (Oleaceae) is frequently referred to as Zaytoon. Its fruits and oil are the only foods that the Mediterranean foods allow. Olive trees are a common plant species and a significant crop in the Mediterranean region *(Abaza et al., 2015)*.

The phenolic and lipid groups contain the majority of the phytochemicals found in olives.

The primary phenolic component of oil leaves is oleuropein, which accounts for up to 14% of the dry weight of olive oil and fruit *(Olea europaea L.) (Bonechi et al., 2019)*. Oleuropein (OLE), a coumarin molecule found primarily in the leaves and belonging to the secoiridoid family, is primarily responsible for the bitter taste of the different parts of the fruit. *(Barbaro et al., 2014)*.

The oleuropein family is produced from oleuropein through a process that starts with mevalonic acid and produces iridoidal, 10-hydroxygeraniol, geraniol, and 10-hydroxynerol. After iridoidal is synthesized into loganic acid and deoxyloganic acid, ligustrosides are formed from seven epiloganic acids. Oleuropein is produced directly by ligustries, with 7-ketologanic acid acting as a bridge. Oleuropein, oleoside, deoxyloganic acid, 7-ketologanic acid, 7-epiluganic acid, and 8-epicingisidiic acid are likely formed through a variety of metabolic processes. 11-methyl ester, 7b1d-glucopyranosyl, 11-methyloleoside, and ligustrosides *(Ahmed et al., 2019)*.

Bioavailability of oleuropein

Virgin olive oils are high in phenolic components and Vissers et al. reported that 55–60% of ligstroside-glycones, tyrosol, hydroxytyrosol and oleuropein-glycones given to human volunteers were absorbed (Vissers et al., 2002). Furthermore, they suggested that a critical step in the metabolism of ligstroside-glycones and oleuropein in general is the conversion of oleuropein-glycoside, an olive oil phenol, to tyrosol or hydroxytyrosol (Vissers et al., 2002). 15% of healthy human volunteers who received an oleuropein-glycoside supplement had urine free of tyrosol and hydroxytyrosol. (Vissers et al., 2002).

Two more investigations have confirmed this theory by demonstrating that oleuropein is quickly absorbed when given orally, peaking in plasma levels two hours after administration. Hydrotyrosol constituted one of its principal byproducts. Both medications are quickly diluted and primarily eliminated in urine as glucoronides or in extremely small amounts as free forms, according to Tan et al. (2003) and Boccio et al. (2003). Additionally, the process by which the phenolics in olive oil are absorbed is still unknown.

APPLICATIONS OF OLEUROPEIN

1. As Antioxidant and food preservative agent:

The notable antioxidant activity of oleuropein, especially in its capacity as a free radical scavenger, is one of its most remarkable properties *(Cicerale et al., 2012)*.

Oxidative reactions cause food to degrade and lose quality. In an investigation employing oleuropein extracts, it was discovered that Tabaq-Maz, a popular fried rib dish in India, had better storage quality and lipid oxidative stability *(Dua et al., 2015)*.

Research conducted by Coni et al. (2000) on laboratory rabbits fed specific diets including oleuropein and olive oil demonstrated results. These findings show that oleuropein reduces plasma levels of total, free, and esterified cholesterol and increases LDL's resistance to oxidation.

In isolated rat hearts, oleuropein's potential protective qualities have also been investigated by (Manna et al., 2004). Before being reperfused, the hearts experienced global ischemia for 30 minutes with no flow. At different intervals, the activity of reduced and oxidized glutathione, as well as creatine kinase, was measured in the coronary cardiac effluent. The amount of thiobarbituric acid-reactive material in the muscle was used to calculate the degree of lipid peroxidation.

According to De la Puerta et al. (1999), the main phenolic components in the polar fraction of olive oil that demonstrated anti-eicosanoid and antioxidant actions on leukocytes were oleuropein, tyrosol, hydroxytyrosol, and caffeic acid.

Moreover, Visioli et al. (2000) showed that supplemented volunteers had a dose-dependent decrease in 8-iso PGF2 excretion in urine due to treatment with catecholic phenolic from olive oil (oleuropein), indicating a reduction in in vivo lipid peroxidation.

Because of its antibacterial, antioxidant, hypoglycemic, and anti-inflammatory properties, oleuropein is a bioactive that is good for human health *(Fernández-Bolaos et al., 2006; Guinda, 2006)*.

Dominciano et al. *(2016)* supplemented milk and yogurt with oleuropein since these foods are suitable matrices for the production of a variety of functional foods and well-liked dairy products with high nutritional content.

Both the proliferation of these microorganisms and the breakdown of oleuropein by lactic acid bacteria were unaffected.

Yogurt and milk with oleuropein added showed respectable flavor, color, and texture that was similar to conventional in a study by Zoidou et al. *(2017)*.

2. In the management of diseases:

Researches have demonstrated the beneficial medicinal effects of oleuropein, including its role as an antioxidant *(Shi et al., 2017; Sun et al., 2017; Fki et al., 2020)*, reductions in body weight, triglycerides, and total cholesterol, as well as possible diabetes *(Dele Ben et al., 2019; Wainstein et al., 2012)*, hypertension (Sun et al., 2017), interstitial hemorrhage (CVA), hepatitis B, and cancer therapy (Seçme et al., 2016; Shi et al., 2017; Zhao et al., 2009; Barzegar et al., 2019; Nassir et al., 2019; Zhang & Zhang 2019), as well as nonalcoholic fatty liver illness *(Santini et al., 2020)*. An essential factor to consider is the fact that the human body absorbs a significant amount of the oleuropein that is consumed *(Vissers et al., 2002)*.

It has been discovered that a variety of tiny elements of olive oil are effective inhibitors of the initiation, propagation and advancement of multiphase cancer development.

Oleeuropein, according to research by Hamdi and Castellon *(2005)*, suppresses the development of tumor cell lines obtained from advanced-grade human malignancies in Swiss albino mice suffering from soft tissue sarcoma. These tumor cell lines include LoVo, which is a colorectal adenocarcinoma cell, RPMI-7951, malignant melanoma of the skin with lymph node metastases, and infiltrating ductal carcinoma of the breast pleural effusion.

Menendez et al. *(2007)* reported that oleuropein aglycone was nearly five times more efficient in lowering the sustainability of breast cancer cells in HER2 oncogene-amplified SKBR3 cells compared to HER2-negative MCF-7 cells.

Secondly, in 2008, Menendez et al. showed that significant levels of apoptosis are preferentially induced in HER2-overexpressing breast cancers by the secoiridoids deacetoxyoleuropein aglycone, ligstroside aglycone, and oleuropein aglycone. In a dose- and time-dependent manner, these agents significantly reduced HER2 tyrosine autophosphorylation and HER2 protein levels. *(Menendez et al., 2008)*. A research by Han et al. *(2009)* found that by delaying cell development and inducing apoptosis, 200 lg/mL of oleuropein dramatically impacts MCF-7 cell viability and reduces the number of MCF-7 cells. According to Han et al. *(2009)*, Oleuropein also showed a statistically significant decrease in the proportion of cells in the G0/G1 phase, preventing the transition of G1 phase to S phase.

Low micromolar dosages of basic extracts and phytochemicals, of which oleuropein is the primary constituent, were found to be effective against cell lines in reducing growth, as demonstrated by Goulas et al. *(2009)*. These extracts have the ability to reduce the growth of human bladder cancer (T-24), human breast adenocarcinoma (MCF-7), and bovine brain capillary endothelial (BBCE) cells.

Visioli and Galli have found that oleuropein has an anti-atherogenic effect *(Visioli & Galli, 2001)*. According to a 2003 study by Carluccio MA et al., oleuropein decreases the adherence of monocytoid cells to activated endothelium as well as the mRNA and protein of vascular cell adhesion molecule-1 (VCAM-1). In ischemic hearts that received initial treatment with oleuropein, the release of oxidized glutathione was significantly inhibited, leading to a reduction in membrane lipid peroxidation, which is thought to be a key factor in the development of atherosclerosis *(Manna et al., 2004)*. Upon restoration of blood flow, a rapid release of oxidized glutathione was observed in these hearts.

According to Visioli et al. (1998), oleuropein enhances nitric oxide (NO) production in macrophages when exposed to lipopolysaccharide, by stimulating the inducible version of nitric oxide synthase, which improves the performance of these immune cells. Oleuropein is known to reduce leukotriene B4 formation and lipoxygenase activity, both of which contribute to reduced inflammation *(De la Puerta et al., 1999)*.

Other reports suggest that oleuropein inhibits leukotriene B4 by inhibiting 5-lipooxygenase *(De la Puerta et al., 1999; Lockyer et al., 2015; Vougogiannopoulou et al., 2014)*. In addition, studies have shown that it has an antiangiogenic effect, reducing the production of COX-2 and prostaglandin E2 in endothelial cells *(Scoditti et al., 2012)*. It has also been shown to reduce inflammation in epithelial cells when exposed to IL-4, by reducing the infiltration of eosinophils and macrophages, and reducing the production of IL-4, which prevents the occurrence of fibrosis and emphysema *(Kim et al., 2018)*.

In vitro experiments have shown that oleuropein has a significant effect in reducing fatty liver. Fatty liver has been linked to increased risk factors for ischemic cardiovascular disease, such as obesity, dyslipidemia, hypertension, and hyperglycemia, according to Lin et al. *(2005)*. Oleuropein acts on hepatocytes such as HepG2 and FL83B, reducing triglyceride accumulation and the size and density of lipid droplets when cells are exposed to free fatty acids, thus preventing the development of fatty liver *(Hadrić et al., 2016; Lepori et al., 2015)*. It also prevents liver weight gain in mice fed a high-fat diet *(Gemae et al., 2009)*. According to Hadrić et al. *(2016)*, oleuropein also contributes to the protection of hepatocytes from damage, by reducing the levels of the enzyme's aspartate aminotransferase and alanine aminotransferase.

3. Antimicrobial activity

According to earlier research, oleuropein significantly lowers the incidence of Listeria monocytogenes, Escherichia coli, and Staphylococcus aureus (91 and 49%, respectively) in multi-species biofilms that are formed on polystyrene microplate surfaces. Dominiciano et al. *(2016)* reported that this enhanced the efficacy of peracetic acid, a widely used disinfectant, in eliminating biofilms of Listeria monocytogenes on surfaces made of stainless steel. Oleuropein, at doses ranging from 20 to 320 mg L-1, inhibited the growth of Mycoplasma hominis, Mycoplasma fermentans, Mycoplasma pneumonia, and Mycoplasma pirum in a study conducted by Furneri et al. *(2002)*.

Following their slaughter, the hens treated with olive leaves revealed more microbiological stability in their thighs and drumsticks than the control group. Specifically, the growth of Staphylococcus aureus,

psychrotrophic and mesophilic aerobes, was inhibited by 5 g/kg of olive leaves, while Enterococcus spp., lactic acid bacteria, thermotolerant and total coliforms were prevented by 10 g/kg of the leaves. PS The results indicate that a potential strategy for enhancing the microbiological quality of chicken meat is the addition of olive leaves to diet. The presence of oleuropein and polyphenols added to the benefits of using olive leaves *(Marangoni et al., 2015)*.

Strong antibacterial activity of oleuropein has been revealed against both Gram-positive and Gram-negative bacteria, as well as mycoplasma *(Furneri et al., 2002; Bisignano et al., 1999)*. Phenolic substances resembling oleuropein seem to work against bacteria by breaking down peptidoglycans in bacterial cells and/or damaging the bacterial membrane. The exact mechanism underlying oleuropein's antimicrobial activity has not yet been fully established, despite some authors' suggestions to the contrary *(Bisignano et al., 1999)*. Oleuropein and membrane lipids have been studied by various authors using biophysical assays *(Caturla et al., 2005)*.

According to Saija and Uccella's *(Saija and uccella, 2001)* theory, an agent's ability to cross a cell membrane and get to its target site is influenced by the glycoside group. It has also been suggested to successfully obstruct the pathways by which certain amino acids necessary for a given microbe's development are generated.

The direct stimulus of phagocytosis, the immune system's reaction to all types of bacteria, is another method that has been proposed. Salmonella enteritidis growth, Staphylococcus aureus production of enterotoxin B and the growth of Bacillus cereus spores can all be inhibited by oleuropein and its hydrolysis products *(Furneri et al., 2002; Caturla et al., 2005; Saija et al., 2001)* The growth of Escherichia coli, B. cereus, and Klebsiella pneumoniae is entirely inhibited by oleeuropein and other phenolic compounds (p-hydroxybenzoic, vanillic, and p-coumaric acids) *(Aziz et al., 1998)*.

Commercial Olea europaea (olive) leaf extracts, which contain high levels of oleuropein, have been shown to be effective against methicillin-resistant Staphylococcus aureus (MRSA), Helicobacter pylori, and Campylobacter jejuni in recent research by Sudjana et al. *(2009)*. The scientists also shown that these extracts had an effect on the structure of the gut flora by notably inhibition the amounts of H. pylori and C. jejuni.

In addition to the strong antiviral properties claimed for it in a U.S. protection for the hepatitis virus and herpes mononucleosis, rotavirus, bovine rhinovirus, canine parvovirus, and feline leukemia virus, Research has indicated that oleuropein demonstrates noteworthy antiviral efficacy against para-influenza type 3 virus and respiratory syncytial virus *(Fredrickson et al., 2000)*.

Furthermore, one study (Walker, 1996) found that olive leaf extracts increased the efficacy of the HIVRT inhibitor 3TC. Olive leaf extracts were tested for their antiviral properties contrary to HIV-1 infection and replication, viral hemorrhagic septicemia virus (VHSV), and salmonid rhabdoviruses *(Micol et al., 2005)*. In vitro experiments showed that HIV replication was inhibited, and at EC50s of 0.2 g/ml, HIV cell-to-cell transmission was decreased in a dose-dependent manner *(Lee-Huang et al., 2003)*.

HIV-1 gp41 (surface glycoprotein subunit), which is in charge of HIV entrance into healthy cells (mostly oleuropein), is believed to be the focus of olive leaf extract activity. Lee-Huang et al. *(2007)* report that an integrated theoretical and experimental effort has been made to determine the HIV protein targets of olive leaf extract and its molecularly-level inhibitory effect.

4. Skin protection and as antiaging compound

Ancora et al. *(2004)* demonstrated the direct antioxidant impact of olive oil's phenolic components, especially oleuropein, which functions at the skin's surface as a free radical scavenger.

In a recent study, Kimura and Sumiyoshi *(2009)* proposed that the protective effects of oleuropein and olive leaf extracts against chronic UVB-induced skin damage, carcinogenesis, and tumor formation may be attributed to the inhibition of VEGF, MMP-2, MMP-9, and MMP-13 expression, facilitated by a reduction in COX-2 levels.In healthy human fibroblasts, replicative senescence is brought on by both genetic and environmental factors. Age-related declines in the function of the proteasome, a multicatalytic nonlysosomal protease, are observed in human fibroblasts, despite its enhanced expression slowing senescence in these cells. Katsiki et al. *(2007)* showed that oleuropein, as opposed to other well-known chemical activators, more effectively increases the proteasome's activity in vitro, potentially by changing the proteasome's conformation.

Additionally, oleuropein decreases intracellular reactive oxygen species (ROS) levels, preserves proteasome activity throughout replicative senescence, and decreases the quantity of oxidized proteins by accelerating proteasome-mediated degradation rates in human embryonic fibroblasts in the early stage. Notably, cultures treated with oleuropein exhibit a 15% longer life span and a delay in the start of senescence morphology *(Katsiki et al., 2007)*.

Perugini et al. *(2008)* developed an oleuropein-containing emulsion and emulsifier to estimate their cosmetic effects against UVB (Ultra Violet Radiation)-induced erythema. These chemicals were subjected to willing participants both pre- and post-UVB-induced erythema in order to assess their lenitive and protective effects. The findings revealed that preparations containing oleuropein have less UV damage and lenitive efficacy.

5. Anti-Obesity and antidiabetic effects of Oleuropein:

Obesity is the primary cause of diabetes, and research has shown that decreasing weight improves glycemic control *(Knowler et al., 2002; Tuomilehto et al., 2001)*. By inhibiting mitochondrial activity during adipogenic differentiation and the expression of genes associated to adipogenesis, oleeuropein has been demonstrated in animal models to reduce body weight gain and the quantity of abdominal adipose tissue *(Poudyal et al., 2010; Hadrich et al., 2016)*. Oleuropein decreased the genes for lipoprotein lipase (LPL), fatty acid-binding protein 4 (FABP-4) and peroxisome proliferator-activated receptor gamma 2 (PPARγ2). These findings were reported by Santiago-Mora et al. *(2011)*. Odegaard et al. *(2007)* state that PPAR-γ is linked to the anti-inflammatory M2 type of adipocyte macrophage differentiation, which is linked to enhanced insulin sensitivity and metabolic health. *(Sun et al., 2011; Glass)*.

Drera et al. *(2011)* found that oleuropein inhibited the differentiation process in 3T3-L1 adipocytes, as its administration suppressed the transcription factors C/EBPα, SREBP-1c, and PPAR-γ. During the differentiation phase, PPAR-γ and C/EBPα were observed to reduce the levels of GLUT4 and CD36, which contributed to the reduction of cell proliferation. The research also showed that oleuropein reduced intracellular lipid accumulation by 40% and 70% at concentrations of 200 and 300 μM, respectively, and reduced differentiation and GPDH activity in a dose-dependent mechanism. Oxidative stress is also associated with accelerating cell differentiation and increasing lipid accumulation through the activation of SREBP-1c (Li et al., 2009; Sekia et al., 2008). Studies have shown that brown adipose tissue in mice fed extra virgin olive oil has higher levels of unconjugated protein-1, which is associated with lipolysis and thermogenesis *(Oi-Kano et al., 2008)*. The same study also showed that

supplementation prevented weight gain in mice *(Oi-Kano et al., 2007)*. Subsequent findings confirmed that oleuropein aglycone increases the secretion of norepinephrine and epinephrine by tenfold. A 2017 study showed that oleuropein and oleuropein aglycone activate TRPA1 and TRPV1 receptors in HEK293 cells, receptors that are widely found in various organs and are potential targets for pharmacological interventions to treat diabetes and obesity *(Oi-Kano et al., 2017; Andrea and Derbenev, 2016)*. Studies have shown that oleuropein reduces blood LDL levels *(Mahmoodi et al., 2018)*, in addition to reducing triglycerides *(Jemai et al., 2009; Mahmoodi et al., 2018; Khalili et al., 2017; Andreadou et al., 2006; Hadrić et al., 2016; Oi-Kano et al., 2008)* and total cholesterol *(Jemai et al., 2009; Khalili et al., 2017; Hadrić et al., 2016)*. It also increases blood levels of high-density lipoprotein (HDL) (Jemai et al., 2009; Mahmoodi et al., 2018; Khalili et al., 2017; Hadrić et al., 2016). Historically, olive leaf decoctions have been used to treat diabetes, according to a study by Mootoosamy & Mahomoodally *(2014)*.

When administered alone, oleuropein increased insulin sensitivity *(Lepore et al., 2015)* and reduced insulin resistance *(Kim et al., 2014)*. The movement of GLUT4 into the cell membrane of C2C12 myoblast cells occurs through AMPK activation and MAPKs, excluding the involvement of PI3 kinase/protein kinase B *(Fujiwara et al., 2017; Hadrich et al., 2016)*. Hadrich et al. *(2016)* discovered that when oleuropein and insulin were administered together, Akt and insulin receptor substrate phosphorylation increased, increasing the amount of GLUT4 on C2C12 myoblasts. Only in the presence of insulin was this effect seen; oleuropein by itself was not. It was suggested by this that oleuropein improves insulin sensitivity.

Oleuropein has been shown to inhibit intestinal maltase and sucrase enzymes locally on the intestinal wall. Additionally, it prevented GLUT2-mediated transport in Xenopus oocytes and the transport of glucose across Caco-2 cell monolayers (Kerimi et al., 2018). It was also noted in that same study that the only treatment that affected postprandial hyperglycemia was oleuropein in solution. According to Hadrich et al. *(2015)*, α-glucosidase and α-amylase enzyme inhibitory actions are demonstrated by hydroxytyrosol and oleuropein.

CONCLUSIONS

The current study reviewed the applications of oleuropein in treating many cases of diseases, such as diabetes, obesity, hyperlipidemia, inti-inflammatory effects and atherosclerosis, and its role in protecting the skin and aging conditions. It is also used in food preservation and is considered a good antioxidant, as well as have an anti-bacterial and anti-viral effect. All of these conclusions were based on studies conducted on laboratory animals in addition to clinical studies, and this is scientific evidence that supports giving oleuropein to patients.

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