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REVIEW

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Oleuropein: A natural antioxidant molecule in the treatment of metabolic syndrome

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Olive (*Olea europaea* Linn., Fam. Oleaceae) is commonly known as *Zaytoon* in Mediterranean region. Its fruits and oil are essential components of Mediterranean diets. Olive tree is a prevalent plant species and one of the important cultivated crops of Mediterranean region. Oleuropein is a phenolic constituents of olive, which, along with its related compounds, has been indicated to be majorly responsible for its beneficial effects. Oleuropein is a secoiridoid type of phenolic compound and consists of three structural subunits: hydroxytyrosol, elenolic acid, and a glucose molecule. It is also reported to be the chemotaxonomic marker of olive. The oleuropein is reported to possess a number of biological activities including action against dyslipidemia, antiobesity, antidiabetic, antioxidant, antiatherogenic, antihypertensive, antiinflammatory, and hepatoprotective actions. The scientific evidence supports the role of oleuropein as a potential agent against metabolic syndrome. The present review discusses chemistry of oleuropein along with potential role of oleuropein with reference to pathophysiology of metabolic syndrome.

KEYWORDS
diabetes, cardiovascular disease, chemistry, metabolic syndrome, obesity, *Olea europaea* L, oleuropein

1 | INTRODUCTION

Metabolic syndrome, formerly termed *Syndrome X*, is a disease of energy metabolism and storage. Its definition, as diversely described by various organizations, is criterial and metabolic indicators are utilized ordinarily. The most common metabolic factors considered in defining metabolic syndrome are hyperglycemia/impaired glucose tolerance, dyslipidemia, hypertension, and obesity (Parikh & Mohan, 2012). Epidemiologically, using a combination of presently employed descriptions, its worldwide prevalence in persons aged 18–30 years has been estimated to be 5.2% (Nolan, Carrick-Ranson, Stinear, Reading, & Dalleck, 2017). Prevalence studies have reported a positive correlation between age and incidence of metabolic syndrome. Further, the incidence is relatively higher in western countries such as America, with some estimates indicating it to be as high as 33–39% (O'Neill & O'Driscoll, 2015).

Olea europaea Linn. (Oleaceae) is commonly known as *Zaytoon* in Mediterranean region. Its fruits and oil are essential components of Mediterranean diets (MDs). Olive tree is a prevalent plant species and one of the important cultivated crops of Mediterranean region (Abaza, Taamalli, Nsir, & Zarrouk, 2015). The olive tree is particularly special to mankind due to its recurrent appearances throughout historical and religious texts and its incorporation into traditional herbal medicines (Kaniewski et al., 2012). The major phytoconstituents of olive belong to class of phenolics and lipids. The phenolic compounds of olives are classified on the basis of their chemical characteristics into mainly phenolic acids, phenolic alcohols, flavonoids, and secoiridoids (Esti, Cinquanta, & La Notte, 1998). Oleuropein is a phenolic constituents

of olive, which, along with its related compounds, has been indicated to be majorly responsible for its beneficial effects. It is also reported to be the chemotaxonomic marker of olive (Panza et al., 2004; Ryan et al., 1999). Recent preclinical and clinical studies have identified the beneficial effects of oleuropein against various human diseases. Oleuropein exhibits beneficial biological and pharmacological effects, such as antidiabetic (Al-Azzawie & Alhamdani, 2006; Hadrich, Garcia, et al., 2016), cardioprotective (I. Andreadou et al., 2007; Z. Janahmadi, Nekooeian, Moaref, & Emamghoreishi, 2015), hypolipidemic (F. Hadrich, Garcia, et al., 2016), and antiischaemic (I. Andreadou et al., 2006), antioxidant (Yoon, 2018), anticancer (De Marino et al., 2014), neuroprotective (Moosmann & Behl, 1999), and hepatoprotective actions (Barbaro et al., 2014).

2 | OCCURRENCE OF OLEUROPEIN

Oleuropein (80 mg g^{-1}) is abundantly present in olive (L. Cecchi, Migliorini, Cherubini, Innocenti, & Mulinacci, 2015). It is also found in other plants species like ***Jasminum polyanthum***, ***Fraxinus excelsior***, ***F. angustifolia***, ***F. chinensis***, ***F. mandshurica***, ***Syringa josikaea***, ***S. vulgaris***, ***Ligustrum ovalifolium***, ***L. vulgare***, ***Osmanthus asiaticus***, and ***Phillyrea latifolia*** (Soler-Rivas, Juan Carlos Espin, & Wichers, 2000).

2.1 | Mediterranean Diet

Olive oil is an essential component of the MD, which has, so far, proven to reduce the risk of many diseases and conditions. Benefits of the MD include a primary and secondary prevention of cardiac events and/or coronary heart disease (de Lorgeril et al., 1999; Dilis et al., 2012; Estruch et al., 2013). A reduction of oxidized low-density lipoproteins (LDLs; Fito et al., 2007), which data suggest, is associated with atherosclerotic cardiovascular disease (CVD) (Gao et al., 2007), protective effects on ischemic stroke development (Fung et al., 2009; Kastorini et al., 2011), a reduction in blood concentrations of inflammatory and coagulation markers (Chrysohoou, Panagiotakos, Pitsavos, Das, & Stefanadis, 2004), potentially decreasing risk of breast cancer (A. Trichopoulou, Bamia, Lagiou, & Trichopoulos, 2010; Hoffmann & Schwingshackl, 2016), colorectal cancer (Bamia et al., 2013), and it is also reported to reduce overall mortality (A. Trichopoulou, Costacou, Bamia, & Trichopoulos, 2003; Dilis et al., 2012; Mitrou et al., 2007; Toledo et al., 2015). It can also decrease inflammatory marker concentrations, decrease insulin resistance, increase endothelial function in patients with metabolic syndrome (Esposito et al., 2004), and even potentially prevent bone loss (Fernandez-Real et al., 2012).

Olive oil, as well as the fruit juice of olives, is and has been the subject of great interest in phytochemical and pharmacologic research. Intake of olive oil has been associated with a lower risk of colorectal cancer (Gimeno et al., 2007; Stoneham, Goldacre, Seagroatt, & Gill, 2000) and congenital heart disease (Buckland et al., 2012), potentially lower risk of osteoporosis (Saleh & Saleh, 2011), and development of type 2 diabetes (T2D) (Guasch-Ferre et al., 2015; Soriguer, Rojo-Martinez, Goday, Bosch-Comas, & Bordiu, 2013). Diabetic patients consuming the MD rich in olive oil are observed to have reduced postprandial lipidemia and cholesterol (Cao et al., 2018) and patients supplemented with extra-virgin olive oil experienced the same effect (R. Carnevale et al., 2017; Violi et al., 2015). In addition, reduced postprandial glycemic response in T2D (Bozzetto et al., 2016), glucose-induced neural damage, and suppressed diabetes-induced thermal hyperalgesia (Kaeidi et al., 2011). Olive oil increases high-density lipoprotein (HDL) levels (Covas et al., 2006; Hernaez et al., 2014) and lowers oxidative stress (R. Carnevale et al., 2014, 2018). Oleic acid, a monounsaturated fatty acid (MUFA), which constitutes up to 85% of olive oil, has been proven to reduce the risk of stroke (Samieri et al., 2011). MUFAs also reduce or prevent pancreatic β cells glucotoxicity, restore and promote β cell proliferation (Maedler, Oberholzer, Bucher, Spinas, & Donath, 2003), and also protect against cytokine and saturated fatty acid-induced apoptosis (Nemcova-Furstova, James, & Kovar, 2011; Welters, Tadayyon, Scarpello, Smith, & Morgan, 2004). Furthermore, a MUFA-rich diet can also improve insulin sensitivity (Vessby et al., 2001).

3 | CHEMISTRY, RELATED COMPOUNDS AND BIOSYNTHESIS OF OLEUROPEIN

3.1 | Chemistry of oleuropein

Oleuropein (1) is secoiridoid mainly obtained from unprocessed olive fruit and leaves of olive. Oleuropein is a complex molecule consisting of three structural subunits: a polyphenol (hydroxytyrosol), a secoiridoid (elenolic acid), and a glucose molecule (Figure 1). The major bioactive components of olive are oleuropein ligstroside, nuzhenide, nuzhenide oleoside, and demethyloleuropein (L. Cecchi, Migliorini, Zanoni, Breschi, & Mulinacci, 2018). The other minor components of olive are tyrosol, hydroxytyrosol, and related compounds. Oleuropein (1) was isolated and characterized as secoiridoid by Panizzi in 1960. The absolute configuration of chiral centers of the secoiridoid oleuropein was determined by Inouye, Yoshida, Tobita, Tanaka, and Nishioka (1970). The content of oleuropein in fruits vary with stages of development (L. Cecchi et al., 2015). The development of olive fruits is divided in to three phases; first is growth phase in which accumulation of oleuropein occurs; second phase is green maturation phase in which a reduction in oleuropein content occurs; and third is black maturation phase during which the oleuropein level are very low (A. Bianco & Uccella, 2000; Amiot, Fleuriet, & Macheix, 1989; Bastoni, Bianco, Piccioni, & Uccella, 2001; Donaire, Sanchez, Lopez-Gorge, & Recalde, 1975).

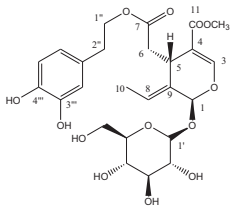

FIGURE 1 Chemical structure of oleuropein

3.2 | Biosynthesis of oleuropein

The biosynthesis of oleuropein in Oleaceae follow the mevalonic acid pathway. S. Damtoft, Franzyk, and Jensen (1992) proposed the biosynthesis of oleuropein in Oleaceae family. According to him, branching in the mevalonic acid pathway leads to biosynthesis of geraniol, 10-hydroxygeranoil, 10-hydroxynerol, and iridoidal. From iridoidal, loganin is biosynthesized, and later deoxyloganic acid, 7-epiloganic acid, and loganic acid are incorporated into ligustroside. Ligustroside is considered as a direct precursor of oleuropein, via 7-ketologanic acid as intermediate. A probable biosynthetic route from deoxyloganic acid, 7-epiloganic acid, 7-ketologanic acid, 8-epi-kingisidic acid, oleoside 11-methyl ester, 7-β-1-*D*-glucopyranosyl 11-methyl oleoside, and ligustroside to oleuropein was proposed by S. Damtoft et al. (1992); Figure 2):

3.3 | Oleuropein-related compounds in olive

Several minor compounds related to oleuropein (1) isolated from olive are summarized in Figure 3. Oleuropein is a methyl ester of demethyl-oleuropein (2) (A. Bianco & Uccella, 2000; Amiot et al., 1989; Bastoni et al., 2001; Donaire et al., 1975). Demethyloleuropein is a minor compound only in unripe olives, while, in some cultivar, in ripe olive, demethyloleuropein content became greater than oleuropein (L. Cecchi et al., 2015). Ligstroside (3), differ from oleuropein only for presence of a tyrosol unit instead of hydroxy-tyrosol (Asaka, Kamikawa, Kubota, & Sakamoto, 1972). Oleoside (4), is a dimethyl ester of oleuropein in which methyl alcohol replaces hydroxytyrosol in esterification of the carboxyl group at C-7 also. Oleuroside (5) differs from oleuropein in shifting of C-8/C-9 double bond to C-8/C-10 position in oleuroside (A. Bianco, 1990; Kuwajima, Uemura, Takais, & lnoue, K, Inouye, H., 1988). Compounds (6) and (7) are nonglucosidic iridoids that maybe arises from the hydrolysis of the glucosidic moiety of oleuropein with a subsequent rearrangement of aglycone (Gariboldi, Jommi, & Verotta, 1986). Two other nonglycosidic secoiridoids are elenolic acid (8) (Panizzi, Scarpati, & Oriente, 1960) and its methyl ester, which was first synthesized by MacKellar, Kelly, Van Tamelen, & Dorschel, 1973. The *o*-diphenolic compound 10 was obtained from ripe black olives by Scalzo and Scarpati (1993) and successively reisolated by Paiva-Martins and Gordon (2001).

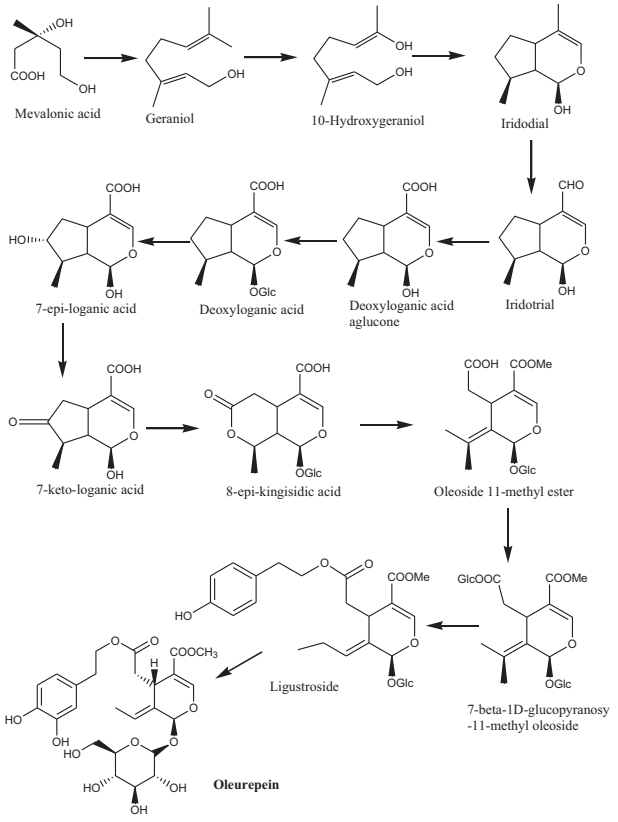

FIGURE 2 Biosynthesis of oleuropein (1) in Oleaceae

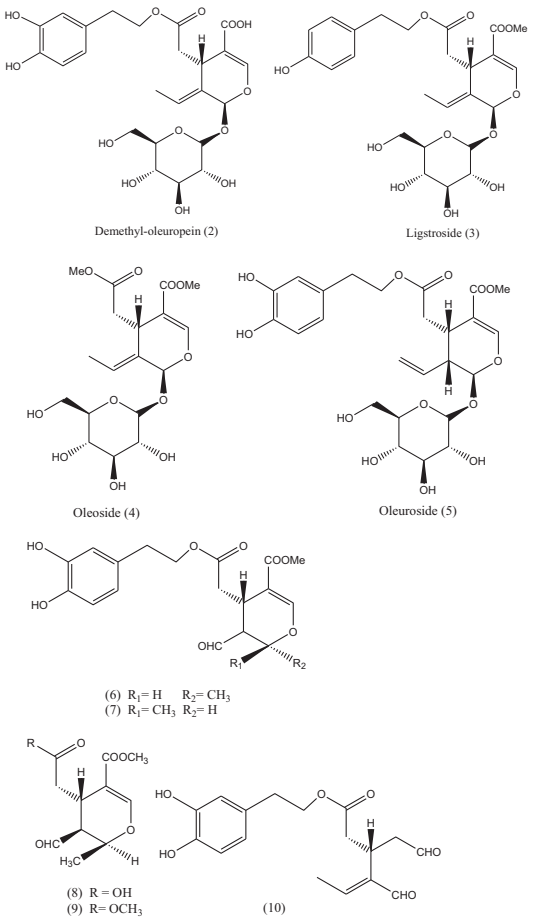

FIGURE 3 Oleuropein-related compounds in olive

4 | PATHOPHYSIOLOGY OF METABOLIC SYNDROME

Metabolic syndrome is not a distinct disease but a cluster of unfavorable metabolic factors and conditions the presence of which cumulatively elevate the probability of developing CVD and events associated with decreased life expectancy and expedite mortality. The variety of definitions also allow for the absence of one or more

disease indicators while still being considered inclusive. The most severe precipitation of metabolic syndrome is death, and, in most studies, examining complications, a consistent correlation between those with the syndrome and all-cause mortality has been observed. The presence and severity of risk factors also increase risk accordingly (Isomaa et al., 2001, Lakka et al., 2002, Katzmarzyk, Church, Janssen, Ross, & Blair, 2005, Ardern & Janssen, 2007, Liu et al., 2014). The pathophysiology of metabolic syndrome is diverse, resulting from numerous contributory factors. Considering it is not a distinct disease but a combination of contributories, the pathophysiology is dependent on the prevalence and progression of its individual components, namely, obesity, hyperglycemia/glucose intolerance, hypertension, and dyslipidemia. Risk factors associated with these diseases further compound development probability, but the commonly known appropriate lifestyle adjustments, such as diet adjustment and exercise, have potential to attenuate risk. Worsening of these elements invariably supports the presence of the syndrome and increases morbidity and mortality. The risk factors are highly interconnected and regularly exist as comorbidities. Up to 34.4% of the world population was overweight in 2008 (Stevens et al., 2012), and there is an increasing trend towards it. Obesity is essentially due to a poor diet, but genetic and epigenetic factors and environmental circumstances also contribute to its development. It is also estimated that currently 382 million suffer from diabetes and a further 316 million people are with impaired glucose tolerance (IDF, 2018). Pathogenesis of metabolic syndrome is multifaceted, and it includes a combination of multiple factors, such as sedentary lifestyle, unhealthy diet choice, and genetic factors. Metabolic syndrome is highly prevalent and adversely affects the general population by elevating risk of cardiovascular complications, obesity, and diabetes. Each individual factor exhibits its own mechanism for increasing cardiovascular risk, and changes to specific biomarkers occur in association with the disease and its severity. These include adipokines (leptin and adiponectin), neuropeptides (ghrelin), proinflammatory cytokines (IL-6 and TNF-α), antiinflammatory cytokines (IL-10), markers of antioxidant status (OxLDL, PON-1, and uric acid), and prothrombic factors (PAI-1; Srikanthan, Feyh, Visweshwar, Shapiro, & Komal Sodhi, 2016).

The pathogenesis of T2D has long been researched and is considered a complex mixture of developments within the body. Long-term obesity has long been recognized as a major predisposing factor to the emergence of a diabetic state (Jallut et al., 1990), but evidence exists that T2D involves a resistance to the action of insulin at effector sites, in particular, the muscles and liver, accompanied with a dysfunction of glucose storage. Furthermore, evidence also exists that steatosis is strongly related with the pathogenesis of T2D and generation of insulin resistance (Hu, Phan, Bourron, Ferre, & Foufelle, 2017). Excessive adipose tissue, as seen in obesity, causes inflammation and is strongly linked to the development of T2D as well (Kohlgruber & Lynch 2015). Initially, a state of impaired glucose tolerance develops at effector sites including the liver and muscles with simultaneous glucose storage dysfunction due to compensatory insulin hypersecretion followed by T2D (Jallut et al., 1990). Oral glucose tolerance and significant postprandial hyperglycemia also occurs. Diabetes is associated with higher risk of developing excessive lipid profiles, which itself can increase the risk of CVD. Usually, the majority of individuals with T2D are overweight, (Alqurashi, Aljabri, & Bokhari, 2011; Daousi et al., 2006; Thomas, Zimmet, & Shaw, 2006) and overweight or obese individuals without diabetes are already at a higher risk of developing a poor lipid profile and CVD (Daousi et al., 2006). In one study, the risk for myocardial infarction, ischemic heart disease, ischemic stroke, and all-cause mortality was respectively 5.1-fold, 3.2-fold, 3.2-fold, and 2.2-fold higher in individuals with very high levels of total triglycerides (TGs) and cholesterol (Nordestgaard, 2016). Furthermore, it has been found that up to 19% of T2D's have hypertension, hyperlipidemia, and obesity, and 51% of these have some combination of hypertension, hyperlipidemia, and obesity with another 5% having coronary artery disease plus hypertension and hyperlipidemia, either with or without obesity (P.J. Lin, Kent, Winn, Cohen, & Neumann, 2015).

5 | ROLE OF OLEUROPEIN IN TREATMENT OF METABOLIC SYNDROME

5.1 | Anti-Obesity effects of Oleuropein

Obesity is a major factor in the development of diabetes, and weight loss has been associated with better glycemic control (Knowler et al., 2002; Tuomilehto et al., 2001). Increased intraabdominal fat predisposes individuals to complications of insulin resistance and obesity (Ashwell, Cole, & Dixon, 1985; Carr & Brunzell, 2004; Enzi et al., 1986), and increased visceral fat has been associated with increased plasma TGs, decreased HDL, cholesterol and increased glucose levels, and risk of T2D (Despres et al., 1989; Fujioka, Matsuzawa, Tokunaga, & Tarui, 1987; Shuman et al., 1986). A reduction in obesity, slowing of weight gain, or cessation of further weight gain would be beneficial in T2D (Knowler et al., 2002; Tuomilehto et al., 2001). Oleuropein is reported to reduce bodyweight gain and abdominal adipose tissue level in animal models (Poudyal, Campbell, & Brown, 2010; F. Hadrich, Garcia, et al., 2016) by repressing mitochondrial activity during adipogenic differentiation and expression of the genes involved in adipogenesis. Santiago-Mora, Casado-Diaz, De Castro, and Quesada-Gomez (2011) found that oleuropein inhibited peroxisome proliferator-activated receptor gamma 2 (PPARγ2), the lipoprotein lipase (LPL), and the fatty acid-binding protein 4 (FABP-4) gene. PPAR-γ has been linked to adipocyte macrophage differentiation into their antiinflammatory M2 form (Odegaard et al., 2007), which has been linked to metabolic health and better insulin sensitivity (Sun, Kusminski, & Scherer, 2011; Glass & Olefsky, 2012). In a study by Drira, Chen, and Sakamoto (2011), on 3T3-L1 adipocytes, it was found that oleuropein inhibits differentiation. Inhibition of transcription factors PPAR-γ, C/EBPα, and SREBP-1c also occurred with oleuropein treatment. PPAR-γ and C/EBPα inhibited GLUT4 and CD36 during the differentiation process thus reducing cell multiplication. This study found that oleuropein-reduced intracellular fat accumulation by 40% and 70% at the dose levels of 200 and 300 μM, respectively. It also reduced adipocyte differentiation and reduced GPDH activity in a dose-dependent manner. Oxidative stress has also been linked to

increased adipocyte differentiation through accelerating cell cycle progression (H. Lee, Lee, Choi, Ko, & Kim, 2009) and SREBP-1c activation and consequential lipid accumulation has been attributed to oxidative stress (Sekiya, Hiraishi, Touyama, & Sakamoto, 2008). Oleuropein could counteract both these actions as it is a potent antioxidant. In another study, presence of PPARγ, SREBP-1c, and FAS as a result of a high cholesterol diet were significantly lower in oleuropein fed mice. This study also found that oleuropein increased adenosine monophosphate-activated protein kinase (AMPK) phosphorylation in epididymal adipose tissue (F. Hadrich, Garcia, et al., 2016). AMPK activation has been postulated to have a role of AMPK in fat metabolism. AMPK exists in fat cells where it regulates fat oxidation and lipogenesis. Leptin concentrations were also decreased with coadministration of oleuropein with a high-fat diet (Y. Oi-Kano et al., 2008; Y. Oi-Kano et al., 2017). It has also been found that an extra-virgin olive oil supplemented diet in mice increased content of uncoupling protein-1 in brown adipose tissue (Y. Oi-Kano et al., 2008, 2017), which have been associated with thermogenesis and catabolism of fats. In the same study, it was found that the supplementation also reduced fat gain in mice (Y. Oi-Kano et al., 2007). These facts were supported by another study that showed that oleuropein aglycone was 10 times stronger at inducing adrenaline and nor-adrenaline release (Y. Oi-Kano et al., 2008). In a more recent study, it was found that oleuropein and oleuropein aglycone also activate TRPA1 and TRPV1 receptors in HEK293 cells (Y. Oi-Kano et al., 2017). Transient receptor potential (TRP) receptors are widespread in many tissues and are implicated as a target for the development of drugs against obesity and diabetes medication (Andrea & Derbenev, 2016). TRP receptors have been implicated in adipogenesis in 3T3-L3 preadipocyte differentiation (Zhang et al., 2007), and another known TRPA1 ligand, capsaicin, has been shown to prevent diet-induced obesity. The effect was observed in TRPA1 knockout mice (Baskaran et al., 2017). In the study by Y. Oi-Kano et al. (2017), drawing on a previous studies finding that TRPA1 activation simulated adrenaline secretion (Iwasaki, Tanabe, Kobata, & Watanabe, 2008), it was found that oleuropein enhanced UCP1 expression in IBAT by stimulating noradrenaline secretion via the β2- and β3-adrenoceptors following TRPA1 and TRPV1 activation (Y. Oi-Kano et al., 2017).

5.2 | Antidiabetic effects of oleuropein

Olive leaves infusion and/or decoctions have traditionally been used to treat diabetes (Mootoosamy & Mahomoodally, 2014). In nicotinamide and streptozotocin induced codiabetic hypertensive rats, daily dose of oleuropein showed a significantly lower glucose levels in glucose tolerance test (Khalili, Nekooeian, & Khosravi, 2017) as well as reduced fasting blood glucose levels (Nekooeian et al., 2014a). Oleuropein administered alone improved glucose tolerance (Khalili et al., 2017; Poudyal et al., 2010) and reduced insulin resistance (S.W. Kim et al., 2014) or insulin sensitivity (Lepore et al., 2015) and, on C2C12 myoblast cells, promoted translocation of GLUT4 into the cell membrane via AMPK activation and MAPK's but not PI3 kinase (phosphatidylinositol 3-kinase)/protein kinase B (Akt; Fujiwara et al., 2017, Hadrich, Mahmoudi, et al., 2016). Oleuropein has been implicated to improve postprandial glycemic profile via hampering NOX_2-derived oxidative stress (R. Carnevale et al., 2018). These results were further consolidated ex vivo study (Alkhateeb, Al-Duais, & Qnais, 2018). Considering that T2D pathogenesis involves peripheral glucose uptake dysfunction, oleuropein may play a role in both treatment and prevention. F. Hadrich, Mahmoudi, et al. (2016) found that oleuropein and insulin coadministration led to an increase of phosphorylation of Akt and insulin receptor substrate, which increased GLUT4 presence on C2C12 myoblasts. This effect was not observed with oleuropein alone and only when insulin was present. This indicated that oleuropein increases insulin sensitivity.

Simultaneous daily intake of 51-mg oleuropein and 9.5-mg hydroxytyrosol for 12 weeks significantly improved insulin sensitivity and pancreatic β cell secretory capacity in overweight middle-aged men at risk of developing the metabolic syndrome (de Bock et al., 2013). In T2D mice fed with OPAICE diet, a phenolic extract containing 35% w/w oleuropein prevented weight gain and significantly reduced nonfasting blood glucose levels and hyperglycemia following glucose loading (Murotomi et al., 2015). Oleuropein also reduced fasting blood glucose in high-fat diet-fed mice (Fujiwara et al., 2017). Oleuropein has a local action on the intestinal wall where it was observed to inhibit intestinal maltase and sucrase enzymes. It also inhibited glucose transport across Caco-2 cell monolayers and GLUT-2 mediated transport in Xenopus oocytes (Kerimi et al., 2018). In that same study, it was also observed that only oleuropein in solution had an effect on postprandial hyperglycemia. Hydroxytyrosol and oleuropein shows α-glucosidase and α-amylase enzyme inhibitory activities (F. Hadrich, Bouallagui, Junkyu, Isoda, & Sayadi, 2015).

5.3 | Oleuropein effects on dyslipidemia

High levels of LDL, total cholesterol (TC), and low HDL are associated with increased cardiovascular risk and development of atherosclerotic CVDs and all-cause mortality (Nordestgaard, 2016; Goldbourt, Yaari, & Medalie, 1997; Assmann, Cullen, & Schulte, 1998). Improvement of the lipid profile can have a protective and preventative effect on risks associated with T2D. This fact is supported by the direct evidence of direct increased risk of T2D associated with deranged lipid profile (Daousi et al., 2006; Haffner, Lehto, Rönnemaa, Pyorala, & Laakso, 1998; Juutilainen, Lehto, Ronnemaa, Pyorala, & Laakso, 2005; Whiteley, Padmanabhan, Hole, & Isles, 2005), the detrimental effect high lipid concentrations have on β cell function (Kruit et al., 2010; Zheng et al., 2017). Further, antihyperlipidemic therapy in diabetics proves effective for reducing primary cardiovascular events (Jakob, Nordmann, Schandelmaier, Ferreira-González, & Briel, 2016; Rafel et al., 2018), and increased levels of HDL have been associated with a reduced risk of adverse events (Goldbourt et al., 1997). Oleuropein has been shown to reduce serum LDL (Jemai et al., 2009; A. Mahmoudi et al., 2018; Khalili et al., 2017; Lepore et al., 2015; F. Hadrich, Garcia, et al., 2016), TC (Jemai et al., 2009; A. Mahmoudi et al., 2018; Khalili et al., 2017; I. Andreadou et al., 2006; F. Hadrich, Garcia, et al., 2016; 246, Y. Oi-Kano et al., 2008), and serum

triglycerides (Jemai et al., 2009; A. Mahmoudi et al., 2018; Khalili et al., 2017; I. Andreadou et al., 2006; F. Hadrich, Garcia, et al., 2016; Y. Oi-Kano et al., 2008) while also increasing serum HDL (Jemai et al., 2009; A. Mahmoudi et al., 2018; Khalili et al., 2017; F. Hadrich, Garcia, et al., 2016). In wild-type mice, oleuropein caused reduction in serum TG and TC but not in PPAR-α null mice showing that effect was due to activation and upregulation of PPAR-α mRNA with an increase in multiple PPAR-α target genes (Malliou et al., 2018). Furthermore, an in silico study showed that oleuropein was a PPAR-α ligand that was corroborated with evidence of increased PPAR-α and retinoid X receptor homodimerization. This same study also found that oleuropein upregulated the LDL-R receptor in the liver and increased the expression of other genes involved in synthesis, uptake, transport, metabolism, and elimination of TGs (Malliou et al., 2018). This evidence suggests that oleuropein may have a similar mechanism of action for as of lipid-lowering drugs fibrates, though potentially with relatively lesser risk of associated adverse effects. It could be assumed that oleuropein would have a beneficial or protective effect by improving the lipid profile, preserving β cell function, and reducing the risk of adverse events, progression of T2D, its complications, and mortality related to it.

5.4 | Antioxidant effects of Oleuropein

A potent antioxidant effect has also been observed with olive oil (Rosillo et al., 2014) and olive oil extract. Its antioxidant effect was shown with its 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) and 2,2-diphenyl-1-picrylhydrazyl scavenging activity as well as with O_2^-, HOCL, and NO free radicals, which are a better representation of radicals existing in biological oxidative processes. This study also proved that the olive oil extract, of which oleuropein was the highest weight component, prevented morphological changes in erythrocytes caused by 2,2′-Azobis(2-amidinopropane) dihydrochloride, at a concentration of 25 μg/ml (Benavente-Garcia, Castillo, Lorente, Ortuno, & Del-Rio, 2000). It also reduced thiobarbituric acid reactive substance (TBARS) levels and oxidation of oxyhemoglobin. In another study, it reduced levels of reactive oxygen species (ROS) in pressure ulcers and also reduced amounts of nitrotyrosine, lipid hydroperoxides, and carbonylated proteins, but these effects were only detected after 7 days of treatment (Donato-Trancoso, Monte-Alto-Costa, & Romana-Souza, 2016). The treatment was found to possess promising wound healing property. Oleuropein was able to scavenge 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) radicals in trolox-equivalent antioxidant capacity test (Benavente-Garcia et al., 2000; Jemai et al., 2009; Ivanov et al., 2018) and was 50% more effective antioxidant than vitamin C in the ferric-reducing antioxidant power test (Ivanov et al., 2018). Oleuropein-reduced thiobarbituric acid reactive substances in tissues of the heart, liver, kidneys, aorta, and increased liver superoxide dismutase (SOD) and catalase (CAT) activity in mice (Jemai et al., 2009). In a study investigating oleuropein's cardioprotective antioxidant effects, it was found that oleuropein was an effective antioxidant, which reduced oxidative stress related cardiac reperfusion injuries in isolated rat hearts. This was characterized by a significant reduction in glutathione, oxidized glutathione, and TBARS (Manna et al., 2004). Oleuropein protected cells against hydrogen peroxide-induced stress in c2c12 myoblast cells (F. Hadrich, Garcia, et al., 2016), and it is believed that oleuropein's ability to reduce infarct size in in vivo models of cardiac ischemia and reperfusion is due to antioxidant effect. Somewhat increased state of oxidative stress has been shown to exist in patients with deep vein thrombosis (Ekim, Sekeroglu, Balahoroglu, Ozkol, & Ekim, 2014) and may also help in reperfusion in other parts of the cardiovascular system.

Oleuropein also reduced levels of ROS in platelets stimulated with arachidonic acid-induced NOX_2 activity (R. Carnevale et al., 2014). Oxidative stress also promotes the buildup of a compounds called asymmetric dimethyl L-arginine (ADMA), which reduces NO synthesis. This is because oxidative stress inhibits the action of dimethylarginine dimethylaminohydrolase, which promotes the breakdown of ADMA, thus leading to accumulation and a reduced synthesis of NO. Furthermore, ADMA itself increases oxidative stress (Cooke, 2004). NO has a major effect on endothelial function, and increased levels may provide a protective effect against cardiovascular risk.

The antioxidant effect of oleuropein has been observed in many tissues with various beneficial effects. It protected rat testes against ethanol induced oxidative stress and was measured as increased SOD, glutathione peroxidase (GPx) and total glutathione, and reduced TBARS. It also improved spermatozoa motility and membrane integrity (Alirezaei et al., 2012). It also showed protective effect against ethanol-induced ulcers to a greater extent than ranitidine, increased GPx, SOD, and CAT activity and reduced TBARS (Alirezaei et al., 2012). In cisplatin-induced oxidative stress it increased plasma antioxidant capacity (trolox-equivalent antioxidant capacity), significantly reduced total oxidant state and reduced 9-OH-dG, a marker of oxidative DNA damage (Geyikoglu et al., 2017). The same results were observed in rat kidneys (Geyikoglu et al., 2017b), in stomach and lungs (Geyikoglu et al., 2017c), and, most relevant to this article, in pancreas (Bakir, Geyikoglu, Koc, & Cerig, 2018). In bisphenol A-treated rats, oleuropein significantly reduced malondialdehyde levels and increased COD and TEAC in both livers and kidneys of rats (A. Mahmoudi et al., 2015). Another study using bisphenol A also corroborated this in liver tissue and found increased SOD and CAT levels and improved trolox capacity to a level close to the control (A. Mahmoudi et al., 2018). Furthermore, an extract, rich in oleuropein-related compounds, was found to protect against DNA damage from heterocyclic amines, which could occur due to development of oxidative stress (Fuccelli et al., 2018) and could help prevent carcinogenesis through this mechanism. Oleuropein also protected C_2C_{12} cells against H_2O_2-induced ROS production and reduced their occurrence significantly and also reduced TBARS (F. Hadrich, Garcia, et al., 2016). Studies confirm that ROS produced by vascular cells are plausible underlying cause in progression of CVDs such as ischemic heart disease, atherosclerosis, cardiac arrhythmia, hypertension, and diabetes (Singh, Devi, & Gollen, 2015). Evidence suggests a link between obesity, insulin resistance, and oxidative stress characterized by increased levels of malondialdehyde (Das, Biswas, Mukherjee, & Bandyopadhyay, 2016). Oleuropein's ability to reduce oxidative stress and improve oxidative

capacity in all tissue types may play a role in the risk reduction in the aforementioned conditions. In one study, addition of H_2O_2 to INS-1 cells decreased cell viability by increasing cell death, increased the ROS concentration and decreased glucose-dependent insulin secretion (Cumaoglu et al., 2011). Preincubation with oleuropein ameliorated all these effects although adding it after exposure had a lesser effect. This study directly links oleuropein antioxidant activity with a reduction in β cell toxicity and improved insulin secretion both of which would have a beneficial effect in diabetes. Previous studies have also suggested that oxidative stress plays a role in diabetes generation (Kaneto et al., 2007). Another study examined the effect of a cytokine cocktail on INS-1 cells. It found that the cytokines reduced cell viability and also reduced insulin secretion and it also found a large increase in ROS within the cells following its application. These effects were ameliorated by oleuropein (Cumaoglu et al., 2011). Furthermore, a study found that H_2O_2 stimulated the release of DPP-4 in a dose-dependent manner . DPP-4 cleaved incretins and could reduce pancreatic insulin secretion. Oleuropein prevented this effect and increased incretin levels with subsequent improved insulin secretion. In a trial of oleuropein and hydroxytyrosol in middle-aged men with oleuropein being the main compound of use at 51 mg daily, it was found that they cause a significant increase in β cell secretory capacity and insulin sensitivity (de Bock et al., 2013), and these effects could be in part attributed to oleuropein antioxidant activity.

5.5 | Anti-atherogenic effects of Oleuropein

Oleuropein is shown to be a potent antiinflammatory and has proven so in several studies. The inflammatory hypothesis of atherosclerosis has gained much backing evidence. A part of this process involves the release of proinflammatory signaling molecules in response of immunological activation. In new plaques, there is an initial activation of endothelial cells, which release chemoattractant molecules (Gu et al., 1998) and express adhesion molecules (Li, Cybulsky, Gimbrone, & Libby, 1993) attracting leukocytes. This happens in response to an inflammatory reaction within the cells. Leukocytes attach and then migrate intracellularly and transcellularly into the endothelium via these adhesion molecules (Cook-Mills, Marchese, & Abdala-Valencia, 2011). Oleuropein may inhibit or interfere with the release of cytokines and interrupt the cascade of leukocyte invasion and buildup of the plaque. Oxidative stress can also play a role in endothelial cell activation in atherosclerosis (Marui et al., 1993), and antioxidants have been shown to at least block activation from TNF-α. Furthermore, there is also evidence that oxidative stress and ROS are involved in cytokine activation of vascular cell adhesion molecule-1 (VCAM-1; Y.W. Lee, Kuhn, Hennig, Neish, & Toborek, 2001; Weber et al., 1994). The role of antioxidants in the expression and activity of VCAM-1 is highlighted in the review by Cook-Mills et al. (2011) and, with oleuropein being the potent antioxidant, could contribute to the inhibition or deceleration of atherosclerotic plaques formation through antioxidant reduction of leukocyte invasion. Oleuropein has also inhibited the induction of intracellular adhesion molecule 1 (ICAM-1; Y.H. Kim et al., 2018), another adhesion molecule responsible for leukocyte infiltration into tissues. ICAM-1 has also been implicated in the early stages of atherosclerosis (Fotis et al., 2012) with upregulation postulated to occur in sites of atherosclerotic plaque generation (Nakashima, Raines, Plump, Breslow, & Ross, 1998). Oleuropein has been shown to activate AMPK (F. Hadrich, Garcia, et al., 2016), and considering AMPK's activation has been strongly linked to a reduction of inflammatory cytokines (Salt & Palmer, 2012). TNF-α has also been shown to induce or potentiate ICAM-1 (Fingar et al., 1997; Javaid et al., 2003), which oleuropein can inhibit (Lee et al., 2018a; A. Mahmoudi et al., 2018). This may play a role in the prevention or attenuation of the inflammatory process involved in atherosclerotic plaque genesis.

A literature review by Gao et al. (2017), clearly represented the correlation between circulating oxidized LDL (oxLDL) and development of atherosclerotic CVD, despite some studies showing none. OxLDL is also associated with the development of diabetes (Stenvinkel et al., 2007). Fat-rich macrophages can then deposit on atherosclerotic plaques and contribute to further development. Oleuropein also inhibits oxLDL synthesis (Masella et al., 2004). Oxidative stress has been linked to oxidation of LDL (247). In the study by Masella et al. (2004), oleuropein almost completely prevented glutathione reduction in CD14 expressing J774 A.1 murine macrophage-like cells by preventing ROS accumulation through the improvement of the entire glutathione redox cycle. Macrophage oxLDL is said to contribute to the creation of the lipid-rich core as seen on plaques and thus a reduction in the creation of oxLDL could also help reduce plaque progression. OxLDL is also associated with the upregulation of a receptor called LOX-1. LOX-1 is an LDL receptor located primarily on endothelial cells but also on macrophages and smooth muscles and has been associated to the development of endothelial dysfunction, atherosclerosis, and myocardial ischemia (Hofmann, Brunssen, & Morawietz, 2018). LOX-1 activation reduces synthesis of NO and increases expression of ACE and its activation by oxLDL. It can also activate angiotensin 2 receptor type 1, induce ROS formation by activating NF-κB, increase VCAM-1 and ICAM-1 expression, and decrease endothelial nitric oxide synthase expression and SOD activities, whereas NF-κB and p38 MAPK phosphorylation are increased, and in LOX-1 knockout mice, there has been a reduction in monocyte adhesion and prevention of oxLDL-induced endothelial dysfunction, and blocking the LOX-1 receptor restored impaired NO-dependent relaxation and decrease superoxide anion radical formation (Hofmann et al., 2018).

Oleuropein activates PPAR-α, and PPAR-α/γ activation has been associated with a decrease in homocysteine, a known independent risk factor of CVD and atherosclerosis (VanEck et al., 2001), which downgrades expression of inducible nitric oxide synthase in foam cells derived from monocytes (Jiang, Zhang, & Xiong, 2007). Blockage led to increased inducible nitric oxide synthase expression, resulting in beneficial effect in atherosclerosis (Jiang et al., 2007) and as such presenting another pathway in which oleuropein may reduce or alleviate atherosclerosis. The adenosine 5′-triphosphate-binding cassette transporter, subfamily A, member 1 (Abca1) has been associated with

regulation of β cell cholesterol. A lack of AbCA1 induced a reduction in insulin secretion and β cell glucose tolerance (Kruit et al., 2010).

5.6 | Antihypertensive effects of Oleuropein

In a murine model of simultaneous hypertension and diabetes, daily dosage of oleuropein up to 60 mg day^{-1} produced a significant decrease in systolic blood pressure (Khalili et al., 2017), reduced renal hypertension (Khalili et al., 2017; Nekooeian et al., 2014b), improved oxidative stress in hypertensive rats (Ivanov et al., 2018), reduced blood pressure (A.A. Nekooeian, Khalili, & Khosravi, 2014a; A.A. Nekooeian, Khalili, & Khosravi, 2014b; Khalili et al., 2017), and mitigated the negative effects of angiotensin 2 on epithelial progenitor cells (Vougogiannopoulou et al., 2014). Angiotensin 2 is a known vasoconstrictor, and it also protected rat hearts from reperfusion injury, which is usually associated with oxidative stress (Bali et al., 2014; M. Esmailidehaj et al., 2012; M. Esmailidehaj et al., 2016; Manna et al., 2004). In rats with simultaneous hypertension and diabetes, left ventricular developed pressure and rate of rise and rate of decrease of ventricular pressure was also found to be lower with oleuropein treatment than with the control in one study (A.A. Nekooeian, Khalili, Khosravi, 2014b). A daily supplementation of ~30 mg was also found to reduce both systolic and diastolic blood pressure in women (Moreno-Luna et al., 2012). IL-6 levels have been associated with a high blood pressure (R. Carnevale et al., 2007), and oleuropein reduces IL-6 synthesis in macrophages and adipocytes levels via AMPK and IL-6 in macrophages (Salt & Palmer, 2012), and it has also been shown to reduce IL-6 in brain tissue (Lee et al., 2018b).

5.7 | Anti-inflammatory effects of oleuropein

A chronic inflammation related to adipose tissue, obesity, and activation of immune responses have been directly linked to the development and progression of diabetes (Kohlgruber & Lynch, 2015; Glass & Olefsky, 2012). Oleuropein is reported to inhibit leukotriene B4 via 5-lipooxygenase inhibition (de la Puerta, Ruiz Gutierrez, & Hoult, 1999; Lockyer, Corona, Yaqoob, Spencer, & Rowland, 2015; Vougogiannopoulou et al., 2014). It was shown to reduce COX-2 and prostaglandin E2 production, which had antiangiogenetic effect in cultured endothelial cells (Scoditti et al., 2012). It was also shown to reduce inflammation in IL-4 exposed epithelial cells by blocking IL-4 acting on a transcriptional level and also preventing eosinophil and macrophage infiltration, which prevented asthmatic fibrosis and alveolar emphysema (Y.H. Kim et al., 2018). A p38 signaling pathway blockage occurred in one study, reducing expression of TNF-α and NF-κB (A. Mahmoudi et al., 2018), and it reduced expression of NF-kB (A. Mahmoudi et al., 2018; Scoditti et al., 2012) with one study indicating inhibition of its p65 subunit translocation (Scoditti et al., 2012). Furthermore, oleuropein has been shown to activate AMPK (F. Hadrich, Garcia, et al., 2016), and AMPK activation has been linked to a reduction in secretion of IL-1β, IL-6, and TNF-α as it inhibits NF-kB activation in many cell types. AMPK activation has been demonstrated to inhibit TNF-α, IL-1β and IL-6 synthesis in macrophages and IL-6 and IL-8 synthesis in adipocytes (Salt & Palmer, 2012). One study on oleuropein's action on HCl/ethanol-induced gastric ulcers found that HCl/ethanol addition caused an increase in IL-1β, which then promoted neutrophil infiltration in the tissue. High-dose oleuropein blocked this effect, and IL-1β became comparable to the control (Al-Quraishy, Othman, Dkhil, & Abdel Moneim, 2017). In this same study, it was found oleuropein inhibited an increase in TNF-α release. TNF-α has been linked to insulin resistance (Kohlgruber & Lynch, 2015), and IL-1β has also been shown to be released in hyperglycemic states and promote apoptosis of β cells (Feve & Bastard, 2009), and one study found that oleuropein-reduced TNF-A and IL-1β significantly in the hippocampus of mice (B. Lee, Shim, Lee, & Hahm, 2018b) and it may do the same in β cells. Several types of interleukins have been associated with T2D with actions including impaired insulin action on the liver and adipose tissue, insulin signaling pathways by altering insulin receptor substrate phosphorylation, and decreasing the expression of several components of the insulin-regulated glucose transport and direct action on β cells (Feve & Bastard, 2009). Furthermore, one study found that daily olive polyphenol supplementation significantly reduced C-reactive protein levels indicating a powerful antiinflammatory effect (Moreno-Luna et al., 2012). Considering oleuropein's broad range of antiinflammatory mechanisms, it is plausible to assume that long-term use of oleuropein would provide some degree of protection against this mode of insulin resistance. A state of chronic subclinical inflammation has also been hypothesized to play a role in obesity (Glass & Olefsky, 2012), and oleuropein may reduce this inflammation and also protect against any risks induced from it. A dose of 52-mg oleuropein and 10-mg hydroxytyrosol was also found to improve vascular function and reduce inflammatory marker presence in healthy individuals (Lockyer et al., 2015).

5.8 | Oleuropein role in Oxidative Stress management

Evidence also exists suggesting a link between obesity, insulin resistance, and oxidative stress characterized by increased levels of malondialdehyde (Das et al., 2016). A study with induced diabetes and hypertension in a murine model showed increased concentrations of malondialdehyde and decreased erythrocyte SOD level (Khalili et al., 2017). Oleuropein has been shown to reduce malondialdehyde (I. Andreadou et al., 2015; Khalili et al., 2017; Z. Janahmadi, Nekooeian, Moaref, & Emamghoreishi, 2017), play a role in countering the pathogenesis, potentially protect the body against further rises in insulin resistance and, in a best-case scenario, even have a reversing effect. Oleuropein maintained or increased antioxidant erythrocyte SOD levels (A.A. Nekooeian, Khalili, Khosravi, 2014a; A.A. Nekooeian, Khalili, Khosravi, 2014b; Khalili et al., 2017; Z. Janahmadi et al., 2017). Furthermore, multiple studies have demonstrated the beneficial effects on antioxidants on the development of heart disease. As mentioned, oxLDL plays an important part in atherosclerosis (Gao et al., 2017). Oxidative stress has been shown to upregulate VCAM-1, and antioxidants can reduce this (Cook-Mills et al., 2011; Marui et al., 1993; Y.W. Lee et al., 2001) and have also been shown to reduce

inhibit monocyte adhesion (Weber et al., 1994). Oxidative stress has also been linked to the synthesis of more oxLDL (R. Carnevale et al., 2007), which has its own set of adverse effects and is linked to atherosclerosis (Gao et al., 2017). One study found that antioxidant enzyme gene expression exists at a lower concentration in pancreatic islets (Lenzen, Drinkgern, & Tiedge, 1996), which could lead them to being more prone to oxidative damage and cytotoxicity. This is undesirable especially when factoring in the damage due to glucotoxicity as part of T2D pathophysiology. Olive oil phenolics have been found to evidence a metabolic shift toward a "glucose saving/accumulation" strategy that could have a role in maintaining anorexigenic hormone secretion and could explain the reported appetite-suppressing effect of the administration of polyphenol-rich food (Di Nunzio, Picone, Pasini, & Caboni, 2018). Oleuropein has been studied in great detail, and its effects are broad and mostly beneficial.

5.9 | Oleuropein role in Autophagy

Autophagic dysfunction has been implicated in the generation of various diseases (Rubinsztein, Codogno, & Levine, 2012). Autophagy has also been implicated in the dysfunction of β cells in T2D as shown in β cell specific autophagy deficient mice having an increase in cell apoptosis and decrease in proliferation (Hur, Jung, & Lee, 2010). An improvement in the process of autophagy has also been witnessed in cardiomyocytes treated with oleuropein. This was characterized by activation and transcription of master autophagy control gene transcription factor EB and its target genes leading to greater autophagic flux (Miceli et al., 2018). In a study, it was found to protect cardiomyocytes from monoamine oxidase A-induced toxicity (Rubinsztein et al., 2012). This could indicate that taken long-term oleuropein could contribute to the maintenance of a healthy heart. Furthermore, mice with disruption of macrophage autophagy displayed significant increases in atherosclerosis (Liao et al., 2012; Ouimet et al., 2011; Razani et al., 2012). Oleuropein activated AMPK (F. Hadrich, Garcia, et al., 2016), the molecule implicated in the maintenance of mitochondrial autophagy by the upregulation of PGC-1α, a promoter of biogenesis of new mitochondria as well as expression of nuclear-encoded mitochondrial genes (Hardie, 2011). Oleuropein may also improve autophagy in these cells, but further research needs to be carried out to establish this effect. Oleuropein may also play a role in hepatic autophagy. A dysfunction of hepatic autophagy is associated with increased hepatocyte TG content and lipid droplet number and has even been implicated to play a part in the modulation of excessive cellular lipid accumulation that underlies the steatotic liver diseases of alcoholic and nonalcoholic fatty livers (Czaja et al., 2013). This was confirmed by a study that found that oleuropein indeed induced enhanced autophagy in hepatocytes in C57BL/6J mice through the activation of AMPK, which was previously found to be involved in autophagy (Porcu et al., 2018). Indeed, this study found a significant increase Beclin-1 and LC3B at transcriptional and posttranscriptional levels and found that oleuropein decreased intracellular hepatocyte fat levels. The study also found that oleuropein has no statistically significant effects on expression of caspase 3 or Bcl-2 on high-fat diet-fed mice.

5.10 | Oleuropein role in management of Hepatic Steatosis

Diabetics have also been shown to have up to 80% more fat in their liver than nondiabetics (Kotronen et al., 2008). Hepatic steatosis has been associated with an increase in the severity of risk factors contributing to incidence of Ischemic CVD, and these risk factors include hypertension, dyslipidemia, hyperglycemia, and being overweight (Y.C. Lin, Lo, & Chen, 2005) and also has been linked to the development and morbidity of T2D (Hu et al., 2017; Kotronen et al., 2008; Zaccardi, Webb, Yates, & Davies, 2016). Astonishingly, oleuropein has also been shown to act on HepG2 and FL83B liver cells and decrease the number and size of lipid droplets in free fatty acid-treated cells, reduce intracellular triglyceride accumulation (van der Stelt et al., 2015), prevent hepatic steatosis (F. Hadrich, Garcia, et al., 2016; Lepore et al., 2015; S.W. Kim et al., 2014), and prevent increase in liver weight in high-fat-fed mice (Jemai et al., 2009). Oleuropein also potentially protected against hepatocyte damage as shown by reduced levels of aspartate aminotransferase and alanine aminotransferase (F. Hadrich, Garcia, et al., 2016). In the study by it was concluded that oleuropein does not regulate lipid-droplet associated perilipin/ADRP/TIP47 family proteins including ADRP and AIP47. Furthermore, a study in which rats were fed with bisphenol A and oleuropein also reduced hepatic inflammation possibly through reducing the expression of p53 and COX-2 and enhancing Bcl-2 protein expression, improved oxidative stress through improving CAT and SOD activity (A. Mahmoudi et al., 2018).

The potential role of oleuropein in treatment of metabolic syndrome is summarized and shown in Table 1.

6 | CONCLUSIONS

The pathophysiology of metabolic syndrome has a complex mechanism involving elevated body fat distribution and insulin resistance. It has become a major public health concern that greatly increases the risk of cardiovascular complications and diabetes. The present review has discussed the potential therapeutic role of oleuropein against various complications leading to or associated with metabolic syndrome. The available evidence indicates the role of oleuropein in improving diabetic complications, reducing obesity, hypertension, dyslipidemia, and other complications of metabolic syndrome. However, the most of the reported studies have been carried out in various animal models and necessitate confirmation in humans. There are sufficient scientific reports to support the dietary intake of oleuropein in patients.

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TABLE 1 Oleuropein role in treatment of metabolic syndrome

Disease	Results/MOA	Reference
Anti-obesity effect		
	Inhibited PPARγ2, LPL, and FABP-4 gene	Santiago-Mora et al. (2011)
	Inhibited 3T3-L1 adipocytes and also	Drira et al. (2011)
	PPAR-γ, C/EBPα, SREBP-1c	
	Inhibited PPARγ, SREBP-1c and FAS	F. Hadrich, Garcia, et al. (2016)
	Increased AMPK phosphorylation in epididymal adipose tissue	
	Leptin concentration decreased	Van der Stelt et al. (2015)
	Activated TRPA1 and TRPV1 receptors in HEK293 cells	Y. Oi-Kano et al. (2017)
Antidiabetic effect		
	↓ insulin resistance	S.W. Kim et al. (2014)
	↓ fasting blood glucose levels	Nekooeian et al. (2014a)
		Fujiwara et al. (2017)
	Improved glucose tolerance	Khalili et al. (2017)
	Promotes translocation of GLUT4 into the cell membrane via AMPK activation	Fujiwara et al. (2017), F. Hadrich, Mahmoudi, et al. (2016)
	Improve PPHG via hampering NOX_2-derived oxidative stress	R. Carnevale et al., 2018
	Improved insulin sensitivity and pancreatic β cell secretory capacity	de Bock et al. (2013)
	Inhibits α-glucosidase and α-amylase enzyme	F. Hadrich et al. (2015)
	↓ insulin resistance	S.W. Kim et al. (2014)
Cardio-protective/miscellaneous effects of oleuropein		
	↓ in serum TG and TC due to activation and upregulation of PPAR-α	Malliou et al. (2018)
	Scavenge ABTS radicals	Jemai et al. (2009)
	↓ levels of ROS	R. Carnevale et al. (2014)
	Increased SOD and CAT levels and improved trolox capacity	A. Mahmoudi et al. (2018)
	Inhibit release of cytokines and interrupt the cascade of leukocyte invasion and buildup of the plaque	Marui et al. (1993)
	Inhibited the induction of ICAM-1 and formation of plaque	Y.H. Kim et al. (2018)
	Activate AMPK and it leads to reduction of inflammatory cytokines	Salt and Palmer (2012)
	Inhibits oxLDL synthesis and delays cardiovascular and diabetic complications	Masella et al. (2004)
	Activates PPAR-α and PPAR-α/γ leads decrease in homocysteine, thereby reduces the cardiovascular disease complications	VanEck et al. (2001)
	Activate AMPK and it leads to a reduction in secretion such as IL-1β, IL-6, and TNF-α as it inhibits NF-kB activation	F. Hadrich, Garcia, et al. (2016) Salt and Palmer (2012)

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; CAT, catalase; ICAM-1, intercellular adhesion molecule-1; LPL, lipoprotein lipase; oxLDL, oxidized low-density lipoprotein; PPAR, peroxisome proliferator-activated receptor; PPHG, postprandial hyperglycemia; ROS, reactive oxygen species; SOD, superoxide dismutase; TC, total cholesterol; TG, triglycerides.

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