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OLIVE AND ITS ANTIOXIDANT MOLECULE OLEUROPEIN FOR MANAGEMENT OF OBESITY AND DIABETES: A REVIEW

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ABSTRACT

Obesity is a major risk factor for the development of various metabolic disorders including diabetes and cardiovascular complications. *Olea europaea* Linn. (Olive) has been used widely in folk medicine in Mediterranean countries. Oleuropein is the main phenolic compound in olives and is responsible for the bitter taste of immature and unprocessed olives. Chemically, oleuropein is the ester of elenolic acid and 3,4-dihydroxyphenyl ethanol, which possesses beneficial effects on human health. Oleuropein has shown several pharmacological actions including anti-cancer, neuroprotective, antiobesity, antidiabetic and cardioprotective activities. In this review paper we collected authentic literature on oleuropein from different databases such as Science direct, PubMed, Scopus, Springer and Google scholar etc. The present review paper aims to collect information about olive and oleuropein, in the attempt to provide evidence for the health benefits of Olive consumption and scientifically support the widespread adoption of traditional Mediterranean diet as a model of healthy eating.

INTRODUCTION

The prevalence of obesity is increased worldwide resulting in an association with major health problems such as diabetes, ischemic heart diseases, stroke and cancer.[1] Type 2 diabetes (T2D) is a chronic metabolic disorder that has a significant impact on the health, quality of life, and life expectancy of patients, as well as on the health care system.[2] This dreadful disease is found in all parts of the world and is becoming a serious threat to mankind health.[3] Herbal remedies and natural products derived from plants and plant products that have been traditionally used to treat various chronic conditions including diabetes and obesity.[4] *Olea europaea* Linn. belongs to Oleaceae family, and it is primarily cultivated in Mediterranean countries such as Turkey, Iraq, Spain, Greece, Morocco, Tunisia and Italy. The fruits, oil, and leaves derived from the olive tree are commonly used in Mediterranean diets. Olive tree is a globally prevalent plant species and has been described as one of the most important cultivated crops.[5] 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.[6] Olive contains mainly two groups of compounds: phenols and related substances and lipids. Phenolic compounds in olives are primarily classified as phenolic acids, phenolic alcohols, flavonoids, and secoiridoids based on their chemical characteristics.[7] Oleuropein, demethyloleuropein, and ligstroside are the most abundant secoiridoids in olives.[8]

Olives pharmacological properties mainly attributed by its phenolic constituents *viz.* oleuropein and related compounds. Oleuropein consists of three structural subunits, including hydroxytyrosol, elenolic acid, and a glucose molecule. It has been a recognised chemo-taxonomic marker of Olive.[9] The bitter taste of unprocessed olives is due to the presence of oleuropein. The concentration of oleuropein in different sources was reported as 93-134 mg/g in olive leaves,[10]0.4–21.7 mg/g in olive fruits[11] and 0.0-11.2 mg/g (dry weight) in virgin olive oil.[12] Recent epidemiological and experimental studies described the beneficial effects of oleuropein derived from olive trees on various human diseases. Oleuropein exhibits beneficial biological and pharmacological effects, such as antidiabetic,[13, 14] cardioprotective[15], hypolipidemic[16] and antiischemic[17], antioxidant[18], anticancer[19], neuroprotective[20], and hepatoprotective properties.[21] This review paper summarizes the health benefits of Olive and oleuropein and its antiobesity, antidiabetic effects.

METHODOLOGY: The information on the Olive and oleuropein protective role in obesity and diabetes were collected from several databases such as Science direct, PubMed, NCBI, Springer and Google scholar etc., from 1960 to 2019. The keywords used for the searching, such as Olive benefits, and oleuropein and obesity, oleuropein and diabetes mellitus, oleuropein and chemistry.

DISTRIBUTION OF OLIVE TREE

Olive is believed to have begun in Syria and Crete 5000 years' ago and this particular species is not known to exist in the wild and is considered a cultigen. Despite this, there are wild forms of the Olive tree spread across Africa, Macaronesia and Asia. Olive trees are cultivated for their fruit, olives, and for the production of olive oil which totalled more than 30,000,00 tons worldwide.[22]

PHYTOCHEMISTRY OF OLIVE

Oleuropein is the major bioactive compound of *O. europaea*, widely known as the olive tree and present in high amount in unprocessed olive fruit and leaves. The oleuropein molecule consists of three structural subunits: a polyphenol, namely 4-(2-hydroxyethyl) benzene-1,2-diol which is also known as hydroxytyrosol, a secoiridoid called elenolic acid and a glucose molecule (Figure 1). Oleuropein, tyrosol, hydroxytyrosol and related compounds represent the main characteristic phenolic fraction of *O. europaea* and are considered as bioactive components. Oleuropein is the first secoiridoid that structure was recognized in 1958-1965, but only several years later it was classified as secoiridoid, when this class of mono-terpenoids was constituted. Oleuropein structure was determined by Panizzi et al.[23] Only the absolute configurations of C-l and C-5 remained undetermined, as the *cis/trans* configuration of C-8/C-9 double bond. Inouye et al.[24] determined some years later[9],the absolute configuration of chiral centres of the secoiridoid oleuropein. In the development of the olive fruit, three phases are usually distinguished: a growth phase during which accumulation of oleuropein occurs; a green maturation phase coinciding with a reduction in the levels of chlorophyll and oleuropein; and a black maturation phase characterised by the appearance of anthocyanins and during which the oleuropein level continues to fall.[25] Therefore, oleuropein is very abundant in the early stages: in young fruits it could reach 14% of dry matter.

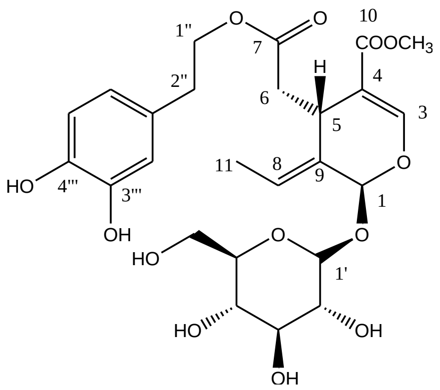

Figure1. Chemical structure of oleuropein

PATHOPHYSIOLOGY OF DIABETES AND OBESITY

Diabetes mellitus is a metabolic disorder characterized by persistently high blood glucose concentrations.[26] Type 1 diabetes is due to an autoimmune destruction of β-cells in the pancreas resulting in a total insulin deficiency, while type 2 diabetes (T2D) is a chronic metabolic disorder with both numerous genetic predispositions and lifestyle factors contributing to its development, emergence and morbidity. In 'at-risk' individuals, initially, insulin resistance is compensated by β-cell hypersecretion and hyperinsulinaemia but following an extended period of time, the β-cell reserve capacity is exceeded and exhausted resulting in a hypoinsulinaemic, and consequentially, a hyperglycaemic state.[27] 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 pre-disposing factor to the emergence of a diabetic state[28], 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.[29] Furthermore, evidence also exists that steatosis is strongly related with the pathogenesis of T2D and generation of Insulin resistance.[30] Excessive adipose tissue, as seen in obesity, causes inflammation and is strongly linked to the development of T2D.[31]

Initially a state of impaired glucose tolerance develops at effect or sites including the liver and muscles with simultaneous glucose storage due to compensatory insulin hypersecretion[29] followed by T2D[28] and these conditions leads development of oral glucose tolerance and significant post-prandial hyperglycemia. This consistent hyperglycaemia is the principle cause of both microvascular and macrovascular complications. Usually, the majority of individuals with T2D are overweight[32] and overweight or obese individuals without diabetes are already at a higher risk of developing a poor lipid profile and cardiovascular complications.[33]

ANTIOBESITY EFFECTS OF OLIVE AND OLEUROPEIN

Obesity is a major factor in the development of diabetes and weight loss has been associated with better glycemic control.[34, 35] Increased intra-abdominal fat predisposes individuals to complications of insulin resistance and obesity[36-38] and increased visceral fat has been associated with increased plasma triglycerides (TG), decreased HDL, cholesterol and increased glucose levels, and risk of T2D.[39-41] A reduction in obesity, slowing of weight gain or cessation of further weight gain would be beneficial in T2D.[34, 35] Bodyweight and abdominal adipose tissue gain have been prevented by Oleuropein in animal models.[42-44] This occurs potentially by oleuropein repressing mitochondrial activity during adipogenic differentiation and expression of the genes involved in adipogenesis. Santiago-Mora et al.[45] found that oleuropein inhibited 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 anti-inflammatory M2 form[46] which has been linked to metabolic health and better insulin sensitivity[47, 48]In a study by Drira et al.[49] on 3T3-L1 adipocytes, it was found that Oleuropein inhibits differentiation. Inhibition of transcription factors PPAR-γ, C/EBPα, SREBP-1c occurred after the addition of Oleuropein. SREBP-1c inhibition reduced FASN. PPAR-γ and C/EBPα inhibited GLUT4 and CD36 during the differentiation process thus reducing cell multiplication. This study found that it reduced intracellular fat accumulation by 40% and 70% at 200 and 300 μM respectively, 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[50] and SREBP-1c activation and consequential lipid accumulation has been attributed to oxidative stress.[51] Oleuropein could counteract both these actions as it is a potent anti-oxidant. 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 sane study also found that Oleuropein increased AMPK phosphorylation in epidydimal adipose tissue.[16] 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 concentration were also decreased with co-administration of oleuropein with a high fat diet.[44]

ANTIDIABETIC EFFECTS OF OLIVE AND OLEUROPEIN

Olive leaves infusion and/or decoctions have traditionally been used to treat diabetes.[52] The proof of the anti-diabetic effect of olive (leaf or mill waste) extracts or its main phenolic oleuropein was established in *in-vitro* and *in-vivo* experiments.In nicotinamide and streptozotocin induced co-diabetic hypertensive rats, daily dose of oleuropein showed a significantly lower glucose levels in a glucose tolerance test,[53] reduced fasting blood glucose levels.[54] Oleuropein administered alone improved glucose tolerance,[53, 43] and reduced insulin resistance[55] or insulin sensitivity[42] 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).[56, 14] Oleuropein has been implicated to improve postprandial glycaemic profile via hampering Nox2-derived oxidative stress.[57]These results were further consolidated *ex-vivo* study.[58] Considering T2D pathogenesis involved a peripheral glucose uptake dysfunction, oleuropein may play a role in both treatment and prevention. The study,[14] found that oleuropein and insulin co-administered led to an increase of phosphorylation of Akt and IRS 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.

Oleuropein 51mg daily with hydroxytyrosol 9.5 mg daily 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.[59] In T2D mice fed a OPAICE diet, a phenolic extract containing 35%w/w oleuropein prevented some weight gain but more importantly, significantly reduced non-fasting blood glucose levels and hyperglycaemia following glucose loading.[60] Oleuropein also reduced fasting blood glucose in high fat diet mice.[56] Oleuropein has a local action on the intestinal wall where it was observed to inhibit intestinal maltase and sucrase but not α-amylase. It also inhibited glucose transport across Caco-2 cell monolayers and GLUT-2 mediated transport in Xenopus Oocytes.[61] In that same study it was also observed that only oleuropein in solution had an effect on post-prandial hyperglycaemia.

Table 1. Olive and oleuropein role in management of obesity and diabetes

Disease	Results/ MOA	Reference
Anti-obesity effect		
Anti-obesity effect	Inhibited PPARγ2, LPL), and FABP-4 gene	[45]
	Inhibited 3T3-L1 adipocytes and alsoPPAR-γ, C/EBPα, SREBP-1c	[49]
	Inhibited PPARγ, SREBP-1c and FAS Increased AMPK phosphorylation in epidydimal adipose tissue	[14]
	Leptin concentration decreased	[46]
Antidiabetic effect		
Antidiabetic effect	↓ insulin resistance	[55]
	↓ fasting blood glucose levels	[54, 56]
	Improved glucose tolerance	[53]
	Promotes translocation of GLUT4 into the cell membrane via AMPK activation	[56, 16]
	Improve PPHG via hampering Nox2-derived oxidative stress	[57]
	Improved insulin sensitivity and pancreatic β-cell secretory capacity	[59]
	Inhibits α-glucosidase and α-amylase enzyme	[16]

CONCLUSION

The traditional Mediterranean diet contains, unlike the Northern European and American diet, a considerable proportion of vegetables, cereals, fruit, fish, milk and olive oil. The beneficial effects of olive oil are attributed due to presence of phenolic compounds especially because of oleuropein. Olive oil and leaves has been used in the human diet as extracts, herbal teas, and powder and contain several potentially bioactive compounds that may have antioxidant, antihypertensive, anti-atherogenic, anti-inflammatory, hypoglycemic, and hypocholesterolemic properties. In conclusion, the oleuropein shows its antiobesity effects by modulating lipids metabolism by down-regulating the expression of PPAR-γ, increasing adiponectin levels in serum and activating AMPK in white adipose tissue. There are a number of researches documented on the antiobesity and antidiabetic role of Olive tree and oleuropein and their possible therapeutic role for the treatment of obesity and diabetes.

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Conflict of Interest:

The authors declare that there have no conflicts of interest.

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