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A Review

Oleuropein and oleic acid: A novel emerging dietary target for human chronic diseases

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The human chronic metabolic disease is predominantly associated with the disturbance in the lipid, proteins and nucleic acid biological balance due to the attack of free radicals generated from oxidative stress. Currently, the available synthetic antioxidants are synthesized by food industries are very effective and inexpensive but as chronic use, it exhibits many toxicological health effects like synthetic drugs. Hence, plant origin antioxidants gained increasing attention all over the world. In this regards, Olive tree (*Olea europaea* L.) belongs to *Oleaceae* family and its by-products such as olive leaves and olive oil are highly focused by many researcher due to its potential therapeutic effects in a reversal of various chronic diseases without any side effects. Oleuropein and Oleic acid are the major components in the olive by products and attributes olive as a holly natural remedy and also olive oil considered as a potential food ingredient in the Mediterranean diet. The fat content in olive fruits is higher than olive leaves. Whereas, the protein ratio is higher in olive leaves and more abundance of Oleuropein, which contributes major health benefits as compared to olive oil. Oleic acid with high MUFA ratio contributes to the major health benefits of olive oil to several human chronic diseases.

Keywords: Dietary antioxidants, Mediterranean diet, *Olea europaea* L., Oleic acid, Oleuropein

Introduction

The olive tree (*Olea europaea* L.) belongs to the *Oleaceae* family. Byproducts (olive oil and olive leaves) from the olive tree had gained important attention in the Mediterranean Basin. As per the reports, 98% of the total olive crop is only from the Mediterranean region apart from the rest of the world[1]. Hence, it is considered as highly value added ingredient in the Mediterranean diet offers various dietetic, ceremonial and medicinal benefits to these region peoples[2]. The application of Olive products in the diet was expanded from Mediterranean basin to other rest of the world such as, European Mediterranean Island, Arab peninsula and Asian counties[3] especially in the applications as traditional remedies in the treatment of several health illnesses. Currently, the harvested products such as Olive oil (from Olive fruit) and olive leaves harvested form olive trees has grabbed the attention of many researchers for their potential therapeutic applications in the treatments of different systemic disorders arising with the modernization of food habits in several developing countries. Earlier studies showed the novel applications of compounds derived from olive leaves and olive oil and their mode of actions in the treatment of several human disease conditions. *In vivo* and *in vitro* studies on these olive products confirmed as natural remedies and it overcomes the adverse affect which in contrast to the current use of synthetic drugs in the medical sciences.

Olive leaf: An emerging natural remedy

The application of *Olea europaea* L. in folk medicine has been practiced from the ancient time[2] as an effective natural remedy for malarial fever treatment[4,5]. Olive leaves were introduced recently into the Pharmacopoea PhEur 5 as potential natural remedies[6]because of the presence of oleuropein (a polyphenolic iridoid glycoside) and its derivatives such as hydroxytyrosol and tyrosol[7], and its pharmacological benefits[8]. Olive leaves were characterized as one of the most powerful antioxidants containing herbs as compared to other many natural herbs[9,10]. It was reported that, oleuropein

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present in olive leaves possess highest levels of antioxidant and free radical scavenging capacity (1-14%) as compared to the olive oil content of oleuropein (0.005-0.12%) among various parts of olive tree[11,12]. Many factors effects the chemical composition of olive leaves primarily by soil moisture content, soil pollution and atmospheric conditions. Whereas, the origin, branches proportion and storage conditions also affect its chemical properties. In addition, the nitrogen and carbohydrates content of olive leaves also influenced by different climatic conditions[13-15]. Phenolic compounds present in crude olive leaf extracts and their chemical structures are shown in (Tables 1 & 2).

Oleuropein: A novel target for synthetic drugs adverse effects

The major abundant phytochemcial in olive leaves is oleuropein, which is expressed significantly higher in olive leaves than olive oil[16,17]. Oleuropein is a predominant secoiridoid with bitter in nature and can be hydrolyzed to hydroxytyrosol, elenolic acid, oleuropeinaglycone, and glucose[16,18]. It was discovered by Bourquelot and Vintilesco in 1908[19]. Hydroxytyrosol acts as a precursor of oleuropein. The total polyphenol content and the total flavonoid content of olive tree leaves were determined to be 2058 mg GAE (gallic acid equivalent) per 100g[1]. It is hypothesized that, due to its planar configuration and large size oleuropein is poorly absorbed. Whereas, oleuropein is glycoside in nature can potentially enter into epithelial cells of the small intestine *via* sodium-dependent glucose transporter (SGLT1). The bioactive oleuropein possesses calcium antagonistic activity[20] and responsible for its hypotensive, antiarrythmic, hypoglycemic and vasodilatory effects.

Table 1 — Chemical Structures of Olive tree by-products such as Oleuropein and Oleic Acid

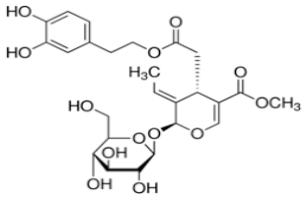
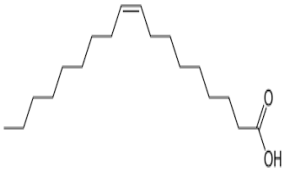
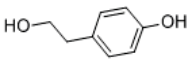
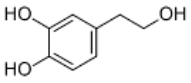
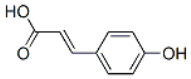
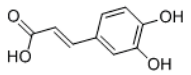
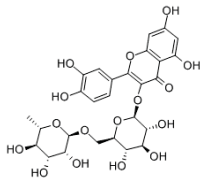
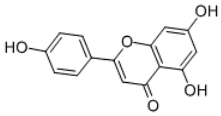
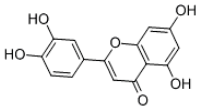
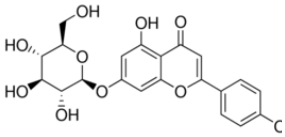
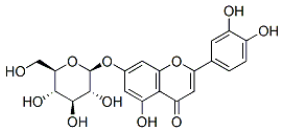
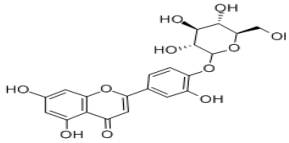
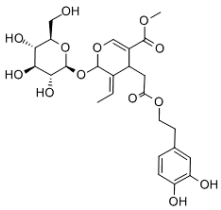
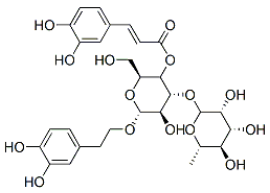
Olive tree Byproducts	Major constituent	Chemical Structure
Olive leaf	Oleuropein	
Olive oil	Oleic acid	

Table 2 — Phenolic Compounds Present In Crude Olive Leaf Extracts and Their Chemical Structures

Class	Compound	Chemical Structure
Phenylalcohol	Tyrosol	
	Hydroxytyrosol	
Phenylacid	P-coumaricacid	
	Caffeicacid	
Flavonoids	Rutin	
	Apigenin	
	Luteolin	
	Apigenin -7-O-gluocoside	
	Luteolin -7-O-glucoside	
	Luteolin -4-O-glucoside	
Secoiridoids	Oleuropein	
	Verbascoside	

Oleuropein provides cardioprotection with its antioxidative, anti-ischemic, antiatherogenesis and hypolipidemic effects. One study reported that, *in vivo* the McCoy cells proliferation derived from the synovial fluid is inhibited by Oleurpein also gives protection against arthritis[21].

Oleuropein plays an important role in the inhibition of 5 and 12 lipoxygenases, eicosanoid production and platelet aggregation, whereas, it enhance the mouse macrophages nitric oxide production and coronary arteries blood flow. It was reported that, oleuropein decreases the infract size and plasma markers of oxidative stress (such as SOD, catalase and peroxidase). Sudjana *et al.* (2009) revealed that, the antimicrobial activity of Oleuropein present in olive leaves inhibited *in vitro* the growth of *Staphylococcus aureus*, *Helicobacter pylori* and *Campylobacter* and *Campylobacter jejuni*[22]. A preliminary clinical study from Khayyal *et al.* (2002) on 20 monozygotic adult twin pairs with mild hypertension in Germany reveled the significant reduction in blood pressure with the oral administration of EFLA® 943 (1000 mg/day), a stable Olive leaf extract which is standardized to oleuropein. This study also showed the significant effect of EFLA® 943 (1000 mg/day) on LDL-cholesterol level reduction[23]. Existing literature revealed that, the therapeutic effect of oleuropein in lowering the serum creatinine, uric acid, lipids, glucose and liver enzymes in streptozotocin-induced diabetic animal model as a potential antidiabetic remedy[24-26].

Olive oil as a natural metabolic enhancing diet ingredient

Olive oil is an extract of olive fruit (*Olea europaea* L.), the main diet ingredient in the Mediterranean region which plan an important role inthe low incidence of many metabolic chronic diseases in these Arabian basin also the rest of the world where it is in abundantly using as diet[27]. Many studies revealed that, these potential effects are due to the presence of high content of monounsaturated fat (MUFA) and oleic acid like major phenolic compound (Table 3) along with other its phenolic content[28]. There is a direct relationship between a higher proportions of MUFA with the low risk of chronic disease. Some comparative studies showed that, the consumption of olive oil reduced the risk of several vascular and carcinogenic health problems and aid in the improvement of the individual reduced health conditions[29,30]. It is reported that, about 10-20 mg of phenolic compounds are supplied through the olive oil rich Mediterranean diet[31].

Olive oil obtained from the mechanical extraction of Olive fruit, is mainly composed of antioxidatve phenolic compounds such as oleic acid as major. The other phenolic compounds in olive oil include palmitic acid, tyrosol and hydroxytyrosol, caffeic acids and some complex compounds (lignans, ligstroside and asoleuropein) along with traces of sterols (phytosterol and tocosterols) and squalene. The phenolic compounds in the olive oil are hydrophilic in nature. The fat content in olive fruits is higher than olive leaves (Table 4) is earlier studies reported that, several MUFA rich seed oils were ineffective as compared to Olive oil in the amelioration the chronic diseases[32,33]. After the ingestion of olive oil the simple or conjugate forms of phenolic compounds such as Tyrosol and hydroxytyrosol are rise to early absorption[34].

Oleic acid: A potential solution for chronic diseases

Oleic acid with high MUFA ratio, contributes the major health benefits of olive oil to several human chronic diseases (Table 1)[35]. The derivates of oleic acid such as tyrosol and hydroxytyrosol acts as strong effective antioxidants which are transported and absorbed via passive diffusion after the ingestion in dose dependent manner *in vitro*[36,37].

A study for Machowetz *et al.* reported that, the oxidation of DNA was reduced with 25 mL of olive oil per day[38]. Another study from Menendez *et al.* revealed the anti-cancer activity of olive oil in both *in vitro* and *in vivo*. In this study they showed, oleic acid is effectively suppressess the human epidermal growth factor receptor 2′ (HER2) oncogene over-expression that involved in the etiology of

Table 3— Total fatty acid composition (%) of Olive Oil

Fatty acids	Range
Palmitic (C16:0)	6.99-11.05
Palmitolic acid (C16:1)	0.49-1.11
Stearic acid (C18:0)	2.61-4.43
Oleic acid (C18:1)	76.52-82.49
Linoleic acid (C18:2)	3.07-6.62
Linolenic acid (C18:3)	0.48-0.95

Table 4 — The average chemical composition of olive fruits and leaves

Composition (g/100 fresh weight)	Moisture	Protein	Lipid	Ash (minerals)	Carbohydrates
Olive leaf	49.8	7.6	1.1	4.5	37.1
Olive fruit	50.0	1.6	22.0	1.5	24.9

several types of human cancers metastasis[39]. This may be due to the antioxidative property of oleic acid which prevent the continuously free radical attack to DNA that leads to the mutation followed by the formation of neoplasm[10,40,41]. Some earlier studies stated that, olive oil significantly inhibited cell proliferation and complete cease of cell growth in human promyelocytic HL60 leukemia cells, human amelanotic melanoma (C32 cell line) and human osteosarcoma cell lines (MG-63 and Saos2)[42-44]. The lower levels oxidative damage of DNA reported in MUFA rich olive oil as compared to PUFA rich oil[38]. The low incidence of coronary heart disease was reported with olive oil rich Mediterranean diet. Escrish *et al*. revealed, the non-fatal myocardial re-infarction was 70% lower in the Mediterranean group with olive oil than in the control group. This study showed the potential effect of olive oil in coronary heart diseases prevention for high risk population[40].

The consumption of olive oil leads to the lower LDL levels. Previous studies revealed, supplementation of virgin olive oil leads to the significant reduction in LDL levels, whereas, the HDL levels were improved[27,45]. This lipid modulating the effect of olive oil mainly due to the presence of phenolic compounds and this hypolipidemic effect may also be lead to the low incidence of several cardiovascular diseases among Mediterranean populations. Perez-Jimmenez *et al.*, stated that, regular supplementation of 40 mL virgin olive oil for 7 weeks showed the reduction in platelets aggregation. The aggregation of platelets in blood also plays an etiological role in the development of cardiovascular diseases[46]. In recent years, various researches have shown several other therapeutic effects of olive oil such as antibacterial[47,48], antiviral[49], antidepressant[50], hypoglycemic[51] and antiatherogenic[52] were mainly due to the presence of polyphenols, or seciridoids, present olive oil[2,49,53,54].

Conclusion

Oleuropein and Oleic acid are contributed the major antioxidative properties to olive leaves as well as olive oil as compared to other plant originated natural remedies. Many researchers reported that the low incidence of cardiovascular diseases in a population where olive oil is one the main ingredient in it. Recently, the isolation of TGR5 like derivative form olive leaves become the effective therapeutic target for chronic human diseases. So far, many studies on human population revealed the effectiveness of Olive oil in the significant health recovery from many metabolic disorders, whereas, very few studies reported the use of olive leaf extract on humans. The current research on olive by products is targeting the isolation of novel bioactive compounds its molecular level applications in many human diseases.

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