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The Effect of Olive Leaf Extract on Systolic and Diastolic Blood Pressure in Adults: A Systemic Review and Meta-Analysis

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Abstract

Hypertension (HTN) is one of the most common disorders and increases the risk of cardiovascular diseases (CVD), which are one of the main causes of death in the world. The Mediterranean diet has the efficacy to modulate CVD risk factors such as HTN, mainly because of olive tree products, which are the most pivotal ingredients in this diet. Among the olive tree products, olive leaf consists of many sorts of phenolic compounds and has several beneficial effects on human body, such as antioxidant, anti-atherosclerotic, anti-inflammatory and especially anti-hypertensive effects. So, we conducted a new systematic review and meta-analysis on anti-hypertensive effect of OLE in adults. The meta-analysis showed a significant reduction effect of OLE on systolic blood pressure. The anti-hypertensive effect of OLE is mainly considered due to its principal phenolic compound known as oleuropein (OL), which reduces blood pressure by a number of particular mechanisms associated with its specific chemical characteristics.

Keywords: olive leaf, oleuropein, anti-hypertensive, phenolic compound, blood pressure

1. Introduction

CVD is one of the most common causes of death in the world [1]. Some disorders such as HTN, type 2 diabetes mellitus (DM2), hypercholesterolemia, atherosclerosis and inflammatory disorders can increase the risk of CVD [2]. Among these disorders, HTN is one of the most common diseases imposed by modern lifestyle in terms of decreased physical activity and unbalanced lipid-rich diet [3].

It is estimated that around 30% of the world population will get involved with HTN by 2025 [4]. HTN gradually develops without notice, hence possibly aggravating such fatal diseases as CVD and chronic heart failure (CHF) [3]. There are several risk factors for HTN, such as family history, genetic and environmental factors [4]. The prevalence in females is dependent on age. In other words, prevalence of HTN in women >50 years old strongly increases. For instance, high blood pressure ratio

in women compared with men increments from 0.6 to 0.7 at the age of 30 years old, reaching 1.1 to 1.2 at the age of 65 years old [5]. CVD risks augment throughout the blood pressure range, which begins at 115/75 mmHg. The blood pressure which is higher than 140/90 mmHg needs intervention [3].

Drugs decreasing blood pressure including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), α -blockers and diuretics dwindle the complications of HTN [6]. However, most patients suffer from enhanced adverse drug reactions even in common doses and medication costs because of needing ≥ 2 drugs to attain blood pressure goals ($< 140/90$ mmHg or $< 130/80$ mmHg in DM or chronic kidney disease) [6]. Whilst chemical drugs are necessary for treating and dominating the cardiovascular risk factors mentioned in the previous lines, diet also plays an important role in modulating them.

The Mediterranean diet is one of the most supreme in the world in terms of preventing chronic illnesses, such as CVD [2, 7, 8]. The bulk of the Mediterranean diet originates from plant sources of which olive tree products are the quintessential ingredient [9].

Olive tree (*Olea europaea*) belongs to genus *Olea* of the Oleaceae family [10]. The parts used in olive tree are leaf, fruit and skin. In ancient times, people applied olive tree, particularly olive leaves to treat fever, gout, wounds, diabetes, atherosclerosis and HTN [3, 11]. As a matter of fact, the leaf of the olive tree has several beneficial effects on human health attributed, in part, to hypocholesterolemic, antioxidant, antimicrobial, hypoglycaemic, anti-inflammatory, anti-atherosclerotic, and especially anti-hypertensive effects [1, 7, 12]. The uses of olive leaf for humans are abundant. However, our aim is to focus on the anti-hypertensive yield.

2. Anti-hypertensive effect of olive leaf extract

There are lots of animals and human trials conducted to inquire about the anti-hypertensive effect of OLE. The animal studies are mostly conducted on rats. In 2002, Khayyal et al. performed an 8-week investigation into the effects of oral administration of OLE at different levels (25, 50 or 100 mg/kg/day) on blood pressure in rats rendered hypertensive by oral doses of 4-week L-NAME (NG-nitro-L-arginine methyl ester, 50 mg/kg/day). They reported a dose-dependent prophylactic influence against the ascent in blood pressure induced by L-NAME and the greatest effect was related to the 100 mg/kg of the extract [13]. Besides these observations, the effect of OLE has also been researched in 2016 by Romero et al. In this study, a 5-week investigation on OLE (15% w/w OL) in spontaneously hypertensive rats at 30 mg/kg body weight reported a significant reduction of systolic blood pressure (-21.6 ± 5.5 mmHg) [14]. Although there are many other animal studies in this field, we intend to talk more about human clinical trials. Here, we collected a systematic review on a number of human randomised controlled trials (RCTs), which have been conducted to investigate the effect of OLE compared to placebo on systolic and diastolic blood pressure as primary or secondary outcomes in adults.

In 2008, an open, controlled, parallel-group, co-twin trial was carried out for 8 weeks on the anti-hypertensive effect of OLE in 40-borderline hypertensive monozygotic twins (age: 16–60) by Perrinjaquet-Moccetti et al. There were two parallel experiments, the first being the effect of a 500 mg OLE tablet (equivalent to 104 mg OL) once daily compared with no medication. The second experiment involved a 500 mg OLE tablet once daily compared with that of 1000 mg (equivalent to 208 mg OL) divided

into two distinct doses. As a result, they revealed a significant dose-dependent decrease in blood pressure within pairs, with mean systolic differences of ≤ 6 mmHg (500 mg vs control) and ≤ 13 mmHg (1000 vs 500 mg), and diastolic differences of ≤ 5 mmHg. Also, mean blood pressure had significantly decreased just for the high dose group [3].

Elsewhere, in 2008, Saberi et al. verified the anti-hypertensive effect of OLE in another way. They enrolled 64 mild to moderate hypertensive patients with normal treatment resistance. They randomised the patients into two distinct groups ($n=32$ intervention & $n=32$ placebo). In the intervention group, each person received a 1000 mg OLE capsule divided into three doses daily. Consequently, the study demonstrated a significant decrease in mean systolic blood pressure. They found no remarkable effect on diastolic blood pressure and mean arterial pressure in the intervention group compared to before OLE treatment, despite the fact that there was meaningful diastolic blood pressure reduction in the OLE group compared to the placebo group [5].

In contrast, De Bock et al. who performed a 12-week randomized, placebo-controlled, crossover trial in 2013, demonstrated a different result. They assessed the effect of an OLE capsule (51.1 mg oleuropein; 9.7 mg hydroxytyrosol) daily on cardiovascular risk factors and insulin action in middle-aged overweight men. 46 participants (aged 35–55 years; BMI 25–30 kg/m²) randomly consumed OLE or placebo for 12 weeks with crossing over to the alternate arm after a 6-week washout. As a result, there were no remarkable changes in ambulatory (24-hour) blood pressure [15].

Further, in 2017, Lockyer et al. performed a randomised, double-blind, controlled, crossover trial to investigate the influence of a liquid-form OLE (136mg oleuropein; 6mg hydroxytyrosol) on blood pressure in prehypertensive patients. They used ambulatory blood pressure as the primary endpoint. The participants were 60 male subjects aged 45.3 ± 12.7 , and body mass index (BMI) 27.0 ± 3.4 kg/m². They received either OLE or placebo for 6 weeks before switching to the other treatment after a 4-week washout. After tracking down the 24-hour and daytime blood pressure in patients, they represented a marked daytime and 24-hour systolic and diastolic blood pressure reduction (about 3 mmHg) compared to the control group (placebo) [7].

In 2020, Yaghoobzadeh et al. performed a 12-week investigation into the effect of OLE on cardiometabolic profiles in patients (aged 30–60) with essential HTN. The trial participants were randomly selected regarding intervention and control groups. ($n= 30$ intervention & $n=30$ placebo). As a result, a 250 mg OLE capsule, twice daily, could decrease systolic blood pressure significantly. However, it did not show a meaningful effect on the diastolic part [4].

As you notice, all of these studies show the anti-hypertensive effect of OLE, except the experiment conducted by De Bock et al. [15]. The most important differences between this study and other studies might be related to the study design, type of disease, nature of OLE, duration of extract in-take, patients' compliance and inclusion/exclusion criteria [4]. There is a systemic review and meta-analysis conducted by Muhammad Asyraf Ismail et al. in 2021 to show the effect of OLE on cardiometabolic profile in prehypertensive and hypertensive adults [1]. However, with all due respect to the authors of this study, there were a number of cases that encouraged us to make some updates with more accurate results. To clarify, the previous meta-analysis included 5 trials. Among these trials, in 2019, Javadi et al. did not investigate the effect of OLE on blood pressure [16]. Wong et al., studied a combined extract [17]. So, this study is not able to show us the pure effect of OLE. Susalit et al., compared OLE effect with a very strong anti-hypertensive drug (captopril) [6]. These three trials made the previous meta-analysis non-accurate, and they also excluded three useful RCTs for

different reasons. De Bock et al. [15] were deleted because of not involving prehypertensive or hypertensive group in the study. Saberi et al. [5], was also deleted due to being a non-English RCT in addition to Lockyer et al. [7], who could not retrieve data after contacting the author [1]. Ultimately, the previous meta-analysis could not demonstrate the accurate effect of OLE on blood pressure. Hence, to determine the OLE effect on systolic and diastolic blood pressure, we aimed to perform a meta-analysis of these 5 human trials (**Figures 1 and 2**).

Our meta-analysis shows that OLE has a significant effect on the reduction of systolic blood pressure. But, its effect on diastolic blood pressure is not meaningful. The anti-hypertensive property of the olive leaf is due to its phenolic compounds.

2.1 Phenolic compounds

Phenolic compounds are assorted as secondary metabolites that have a restricted distribution without any explicit function in general metabolism [10]. On the other hand, primary metabolites including nucleic acid, carbohydrate, protein, lipid and cofactors, are involved in the synthesis of substances that are pivotal for the growth of all organisms [18]. Olive tree polyphenols are present in the plant to combat pathogens inducing bacterial infections and to react to pests and insect injuries [19, 20]. There are a wide variety of phenolic compounds in *Olea europaea* and its by-products with much more concentration in olive leaves (comparison, 145 mg total phenolics/100 g fresh leaf compared to 110 mg/100 g olive fruit and 23 mg/100 ml extra virgin olive oil) [1, 7, 15]. Another comparison confirms the much more concentration of total polyphenols in olive leaves is relative to the olive oil and fruit; 1350 mg/kg fresh olive leaf versus 232 ± 15 mg/kg of extra virgin olive oil [21, 22]. High content of phenolic compounds in olive leaf excited the interest of many scholars to continue the investigations with animals and humans, and that resulted in realizing the beneficial health effects such as anti-hypertensive effects [23]. Major phenolic compounds extracted from olive leaf are categorised in the following.

Figure 1. The meta-analysis of OLE compared to placebo or no treatment. Outcome: diastolic blood pressure (mmHg).

Figure 2.
The met-analysis of OLE compared to placebo or no treatment. Outcome: systolic blood pressure (mmHg).

2.1.1 Olive leaf phenolic compounds categorisation

Some researchers categorised the phenolic compounds of olive tree in 5 groups: flavones (apigenin-7-glucoside, diosmetin, diosmetin-7-glucoside, luteolin and luteolin-7-glucoside); flavonols (rutin); flavan-3-ols; oleuropeosides (verbascoside and OL) and substituted phenols (vanillin, vanillic acid, caffeic acid, tyrosol and hydroxytyrosol) [24]. Also, some researchers categorised the phenolic compounds of olive leaves into three distinct groups: (1) phenolic acids like vanillic acid, syringic acid, salicylic acid, vanillin, etc. (2) Flavonoids like luteolin, rutin, and apigenin-7-o-glucoside, luteolin-7-o-glucoside, etc. (3) Hydroxycinnamates and structurally related compounds like verbascoside, oleoside, ligasterol, oleuropein, etc. [25]. The most abundant phenolic compound identified in olive leaves is oleuropein, followed by hydroxytyrosol, luteolin-7-glucosides, verbascoside, and apigenin-7-glucosides [23]. It has been demonstrated that there are some factors that affect the chemical composition variability of olive leaves, like origin, storage conditions, proportion of branches existing in the extract, weather conditions, moisture content and degree of soil contamination [26, 27]. On the other hand, some processes such as drying and extraction enable us to change nutritional composition of the OLE [28]. Oleuropein, the principal phenolic compound in olive leaf has a significant impact on the reduction of blood pressure due to the potential mechanisms of action with its specific chemical characteristics [2].

2.1.1.1 Oleuropein

Oleuropein (OL) is a glycosylated secoiridoid that uniquely exists in plants of the Oleaceae family, presented in olive leaves at higher concentrations, and representing 1–14% of olive leaf weight, includes oleuropein in contrast with 0.005–0.12 % of olive oil weight [25, 29, 30]. OL is also known as a coumarine-like compound presented in olive trees [8]. It is an elenolic ester of hydroxytyrosol (HT), in addition to an oleosidic skeleton possessed in common to the secoiridoid glucosides of Oleaceae

[11]. In fact, HT, known as 2-(3,4-Di-hydroxyphenyl)-ethanol is the precursor of OL and the major phenolic compound in extra virgin olive oil [25, 31]. The chemical formula of one oleuropein molecule is $C_{25}H_{32}O_{13}$ with molar mass equals to $540.518 \text{ g.mol}^{-1}$ in its standard state (at 25°C [77°F], 100 kPa) (**Figure 3**) [32]. OL has been distinguished in olive flesh, leaf, seed and peel of green (unripe) olive and is an active substance of olive leaves. Its concentration declines during maturation phase happening in olive fruits because of undergoing hydrolysis yielding different products, such as HT [8, 33, 34]. It creates the bitter taste of olive that must be removed by immersion in lye, hence generating an edible olive, known as table olive [29]. OL content in olive leaves varies depending on the cultivar, production area and leaf tissue conditions (frozen, dried or fresh) [11]. There is the possibility of extracting OL molecules by some special methods explained in the following.

2.1.1.2 Extracting methods

There are various extracting methods of phenolic compounds from olive leaves (after drying and milling), including solid-liquid extraction by maceration and soxhlet extraction utilizing water-methanol blends or hexane to yield OLE [1, 35, 36]. For more explanation on one of the most common techniques, mixing the specific quantity of dried olive leaf powder with an aqueous alcohol solution, incubating there to produce an alcohol extract. after a draining process, the crude extract will be dried again and treated with alcohol and water solution at least two more times. Then, by distilling the mixed extract under vacuum, the OLE will be produced [6, 12]. OL can be chemically decomposed into two different products, including hydroxytyrosol (HT) and elenolic acid by distinct factors such as high temperature, acid, base, light,

Figure 3. Oleuropein chemical structure. Source: pubChem. URL: <https://pubchem.ncbi.nlm.nih.gov/compound/5281544>. Description: data deposited in or computed by pubChem.

metal ions, etc. [37]. This process assembles the enzymatic hydrolysis of this phenolic compound that occurs in human body. However, the studies conducted to exactly specify what happens to this phenolic compound extracted from olive leaves during absorption from small intestine and colon to the blood circulation, have mentioned scattered findings. Therefore, we go directly to the mechanism of its action in the body.

2.1.1.3 Mechanisms of action

The studies performed in human models to show the mechanisms of action for anti-hypertensive property of OL are scarce and have been conducted much more in vitro. This mysterious compound is endowed with anti-hypertensive property which is thought to be due to its influence on membrane receptors and/or enzymes involved in cell signalling, including ACE, L-type Ca^{2+} channels, nitric oxide (NO) and reactive oxygen species (ROS), or to clarify, the metabolite of OL inhibits ACE. Another mechanism is that a degraded product of OL (3,4-dihydroxy-phenyl-ethanol) directly affects L-type Ca^{2+} channels as an antagonist resulting in blocking the channels [29, 38, 39]. In fact, OL has synergic effects with other active substances in OLE to present ACEI and CCB activity in the body. Also, the Vasodilator effect of OLE justifies its anti-hypertensive activity [1, 29]. This phenolic compound performs a particular task to increase NO bioavailability and expression of the inducible form of endothelial NO synthase (e NOS) studied in animal subjects [9, 25, 29, 40]. As a matter of fact, OL reacts with NO and its noxious derivative peroxynitrite ($-\text{OONO}$). There is a possibility that OL increases NO production via modifying two specific enzymes: nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) and NO synthase [41]. These mechanisms modulate NO bioavailability, thus improving vascular function and ultimately reducing blood pressure [25]. The last one influences ROS. ROS play a significant role in the development of oxidative stress, which also encompasses the principal role in the pathology of HTN. ROS are produced permanently in the human body. They are indispensable for several mechanisms happening in the cells, such as chemical signalling, immune performance and energy production [24]. When the balance between ROS and antioxidants upsets, meaning ROS level more than the other, the cell makes oxidative stress [2, 9]. Indeed, an excess in the production of ROS which could be controlled by a number of enzymes, including glutathione peroxidase, catalase (CAT) and superoxide dismutase (SOD), enable to damage lipids, proteins and DNA in the cells particularly cardiovascular cells, are even able to ruin the vascular function and structure [2, 42, 43]. So oxidative injury increases the risk of CVD. In this regard, the OL molecule consists of some active components that have determined scavenging functions [44]. So, there is a potential antioxidant property that is suggested to be related to the H-atom donation from the OL phenolic groups [8, 33, 45]. In other words, OL preserves paraventricular nucleus (PVN) of the hypothalamus from oxidative stress. OL activates the Nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated signalling pathway and finally, it improves mitochondrial function. Thus provides an exquisite way to treat HTN [1, 8, 46]. Hence, antioxidant property of OLE enhances its antihypertensive yield.

2.2 OLE safety

In spite of the beneficial health properties of OLE in human body, it is essential to be determined what dosage of this extract will be safe for the body. Many studies

aimed at this indicated acute OLE toxicity (2000 mg/kg) and also 4-week OLE toxicity (100–400 mg/kg) revealed no symptoms of toxicity in subjects [47, 48]. However, another study reported the opposite result by noticing bleeding in the liver and kidneys of rats when using OLE [49].

3. Conclusions

OLE can reduce both systolic and diastolic blood pressure in human body. The effect of OLE on systolic blood pressure is more significant and mostly depends on the dose of the extract for diastolic part. The anti-hypertensive effect of OLE is mostly due to OL. The two most common methods of OL extraction are maceration and soxhlet. There are special mechanisms with which OL reduces blood pressure. For instance, inhibiting ACE, blocking L-type Ca^{2+} channels, possessing vasodilator activity by increasing NO bioavailability and having anti-oxidant properties.

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Conflict of interest

The author declares no conflict of interest.

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