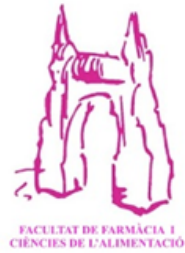




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Final degree project

Effects of bioactive compounds of *Olea europaea* L. on blood pressure

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Main field of study: Physiology and Physiopathology

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ACRONYMS

AHA: American Heart Association

ACE: Angiotensin-Converting Enzyme

ANS: Autonomic Nervous System

ANP: Atrial Natriuretic Peptide

AVP: Arginine Vasopressin

BNP: Brain Natriuretic Peptide

BP: Blood Pressure

CO: Cardiac Output

COX: Cyclooxygenase

CVC: Cardiovascular Center

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

ET1: Endothelin 1

HDL: High-density Lipoproteins

HMOD: Hypertension-Mediated Organ Damage

HR: Heart Rate

IRH: Ischemia-Reactive Hyperaemia

LDL: Low-density Lipoproteins

LV: Left Ventricle

MAP: Mean Arterial Pressure

MedDiet: Mediterranean Diet

MetS: Metabolic Syndrome

MM: Methyl Maslinate

MUFAs: Monounsaturated Fatty Acids

OA: Oleanolic Acid

PNS: Parasympathetic Nervous System

PUFAs: Polyunsaturated Fatty Acids

PVR: Peripheral Vascular Resistance

RAAS: Renin-Angiotensin-Aldosterone System

ROS: Reactive Oxygen Species

RV: Right Ventricle

SBP: Systolic Blood Pressure

SHR: Spontaneously Hypertensive Rats

SNS: Sympathetic Nervous System

SOD: Superoxide Dismutase

SV: Stroke Volume

TGs: triglycerides

UA: Ursolic Acid

UV: Uvaol

EVOO: Extra Virgin Olive Oil

FVOO: Functional Olive Oil

VOO: Virgin Olive Oil

VSMCs: Vascular Smooth Muscle Cells

WR: Wistar Rats

WKR: Wistar Kyoto Rats

ABSTRACT

Blood pressure (BP) is the hydrostatic force exerted by the blood pushing against the wall of blood vessels as it is pumped by the heart. Hypertension is a chronic progressive disorder in which BP is persistently increased above the considered normal values. This medical condition represents a major risk factor for cardiovascular disease as well as for renal events. It is estimated that hypertension affects one billion people globally, accounting for 9.4 million deaths each year. The aetiology of hypertension is the result of a complex interaction between environmental and pathological factors affecting different systems, along with genetic predisposition. Accurate blood pressure readings are essential for its proper diagnosis and treatment. Lifestyle modifications, including healthy dietary patterns and regular physical activity, play a key role in the prevention of hypertension. The Mediterranean diet has been reported to exert health benefits such as reduced chronic diseases incidence and longer life expectancy. These beneficial effects have been attributed, in part, to olive oil consumption. The olive tree (*Olea europaea* L.), a typical tree crop from the Mediterranean Basin, has been used in traditional medicine since ancient times for its biological and pharmacological properties. In this review, preclinical studies and nutritional interventions in humans assessing the effects of bioactive compounds of *Olea europaea* L. on BP with potential use in the prevention or treatment of hypertension, have been summarized.

RESUM

La pressió arterial és la força hidrostàtica exercida per la sang contra la paret dels vasos sanguinis a mesura que és bombejada pel cor. La hipertensió és una malaltia crònica i progressiva en què hi ha un augment persistent de la pressió arterial. Aquesta condició mèdica representa un factor de risc important de patir malaltia cardiovascular així com malalties renals. S'estima que la hipertensió afecta a un milió de persones a nivell mundial, sent responsable de 9,4 milions de morts cada any. L'etiologia de la hipertensió és el resultat de la complexa interacció entre factors ambientals i fisiopatològics, juntament amb la predisposició genètica de cada individu. Fer mesures precises de la pressió arterial és essencial a l'hora de diagnosticar la hipertensió i establir un tractament. Els hàbits de vida, dins dels quals s'inclouen els hàbits alimentaris, són factors modificables que poden prevenir la hipertensió. La dieta mediterrània s'ha associat a efectes beneficiosos per la salut com és la reducció de la pressió arterial i el seu conseqüent risc cardiovascular. Aquests beneficis s'atribueixen bàsicament al consum de l'oli d'oliva. L'olivera (*Olea europaea* L.), un arbre de cultiu típic de la conca mediterrània, ha estat utilitzada en la medicina tradicional des de l'antiguitat per les seves propietats biològiques i farmacològiques. En aquesta revisió, es recullen estudis preclínic i intervencions nutricionals en humans que mostren compostos bioactius d'*Olea europaea* L. amb efecte sobre la pressió arterial i amb ús potencial en la prevenció i tractament de la hipertensió.

1. INTRODUCTION

Blood pressure (BP) is regulated by different physiological systems that modify blood flow and the vascular resistance of blood vessels of organs. Therefore, any mechanism that contributes to the imbalance of BP levels, is a potential target for the development of high blood pressure (1).

Hypertension is a clinical condition characterized by a persistent rise in BP. It is one of the major risk factors for cardiovascular disease (CVD) and causes functional alterations in the wall of blood vessels and in target organs such as the brain, heart and kidneys. Hypertension is known as the “silent killer”, since it remains asymptomatic for years until it reaches advanced stages, when heart attack or stroke may occur. Stage 1 of hypertension is considered when systolic BP (SBP) and diastolic BP (DBP) are ≥ 140 mmHg and ≥ 90 mmHg, respectively. Periodic monitoring of BP is of high importance for the earliest possible diagnosis of hypertension and the prevention of its subsequent clinical complications (1–3).

The Global Burden Disease Study performed in 2015, demonstrated that hypertension kills an estimated 9.4 million people annually and is considered one of the leading preventable causes of premature mortality worldwide (1,4,5). The increasing prevalence of hypertension is not correlated with income level and becomes more common with population ageing, sedentarism and body weight gain. Most patients suffer from essential hypertension, in which the cause cannot be determined, leading to non-specific treatments (1,2).

However, hypertension can be prevented with lifestyle modifications, beginning with changes in dietary patterns. Epidemiological studies as well as nutritional interventions in humans have reported that the Mediterranean diet (MedDiet) has beneficial effects on hypertension and prevents the risk of CVD. MedDiet is based in vegetables, fresh fruit, whole grains, legumes, nuts, fish, olive oil and a moderate intake of alcohol, especially red wine. It has been observed that people adopting MedDiet have lower BP levels, improvement of lipid profile as well as better endothelial function and, in general, longer life expectancy (6).

The olive tree, *Olea europaea* L., is a widely distributed species found mainly in the Mediterranean region. It is generally used to produce olive oil, one of the most representative components in the MedDiet. Olive oil consumption has been attributed to pharmacological activities, as it is considered a source of valuable bioactive compounds. Its chemical composition is involved in the maintenance of the physiological state and in the prevention of chronic diseases associated with oxidative stress like cancer, inflammation, metabolic alterations, atherosclerosis and CVD. Although most olive fruits are intended for the production of olive oil, several of them are processed into table olives. Table olives are one of the most representative fermented foods in the MedDiet containing a non-nutritional fraction with interesting biological properties. Olive leaves have been used in Mediterranean folk medicine since ancient times, as they are rich in important bioactive compounds, chiefly polyphenols (7).

Given that medicinal plant derivatives have shown similar efficacy and tolerability to conventional drugs for the treatment of hypertension and, due to the hypotensive effect observed in the products of *Olea europaea* L. (7,8), several experimental studies have been carried out with the intention of evaluating its bioactive compounds including polyphenols, secoiridoid phenols, flavonoids, pentacyclic triterpenes, oleic acid and fatty acids with antihypertensive activity.

2. OBJECTIVES

Hypertension is among the main risk factors of CVD. Despite the availability of conventional medicines, by 2015 it was estimated that one out of four adults suffered from hypertension (1). Side effects of current antihypertensive drugs and poor accessibility to pharmacological treatment, can be some of the causes of this high mortality. However, risk of hypertension can be prevented. For these reasons, the current study aims to develop the following objectives:

- i. Define BP and its regulatory systems in the human body
- ii. Explain how BP is measured in the clinical setting and stress the importance of its regular control
- iii. Describe hypertension with its epidemiology, aetiology, clinical manifestations and complications, pathogenesis, diagnostic and treatment strategies
- iv. Analyse potential non-pharmacological therapeutic strategies to prevent and treat hypertension
- v. Assess the importance of the Mediterranean-style diet in the prevention of hypertension
- vi. Highlight the presence *Olea europaea* L. plant and its derivative products in the MedDiet
- vii. Identify the bioactive compounds of *Olea europaea* L. with BP-lowering properties
- viii. Draw conclusions from the stated objectives

3. INTEGRATION OF THE FIELDS OF STUDY

As main areas of study, this review integrates the field of physiology and physiopathology, as well as nutrition and bromatology and pharmacognosy, all of them studied in the Pharmacy degree.

The principal field of study is physiology and pathophysiology since first part covers the physiology of blood pressure in the human body, followed by the explanation of physiopathology of hypertension. Firstly, the present work defines the medical condition and how the disease develops, describing its causes, clinical manifestations and complications, pathological mechanisms, diagnostic methods and treatment options.

In the second place, the scope of nutrition and bromatology takes part, as the MedDiet is considered as one of the most potent therapeutic keys for the prevention and control of high blood pressure. In addition, the focus is directed more towards the beneficial effects of using *Olea europaea* L. and its derivative products to combat the progression of hypertension.

The integration of pharmacognosy field in this work should be also taken into account since the major purpose is to identify which natural substances from *Olea europaea* L. have therapeutic properties to prevent and treat hypertension.

4. MATERIAL AND METHODS

In order to reach the objectives of the present study, a literature review was carried out through primary and secondary bibliographical sources present in *PubMed* (<https://www.ncbi.nlm.nih.gov/pubmed/>) and *Scopus* (<https://www.scopus.com/>) electronic databases. In addition, books of human physiology and pathophysiology and international guidelines for the management of high blood pressure were consulted.

The research looked for experimental preclinical studies and clinical trials assessing the effects of *Olea europaea* L. bioactive compounds on BP. Journal articles and scientific reviews were found using keywords relating to *Olea europaea* L.: “*Olea europaea* L.” OR “olive leaves” OR “olive oil” OR “olive tables” OR “*Olea europaea* L. compounds” OR “oleic acid” OR “pentacyclic triterpenes” OR “oleanic acid” OR polyphenols OR hydroxytyrosol OR flavonoids OR oleuropein, in combination with the terms of: “blood pressure” OR hypertension OR “high blood pressure”.

When selecting articles, their quality, publication date and focus on *Olea europaea* L. and its effects on blood pressure were taken into account. Furthermore, references from extracted articles and recent reviews were examined in order to identify significant additional publications and complete data collection.

The study selection considered *in vivo*, *in vitro* and clinical trials in the English language. Research literature includes references dating from 1983 to 2019.

5. RESULTS AND DISCUSSION

5.1. BLOOD PRESSURE

BP is the hydrostatic pressure that exerts blood on the wall of the blood vessels when the heart contracts, expressed in mmHg (9). This force pushes blood through the entire vascular system, which is divided in two circuits: the systemic and pulmonary circulation (10,11).

The term systole refers to the period of contraction of the left ventricle (LV) of the heart, while the relaxed state is called diastole. The balance between systole and diastole determines an individual's BP (9).

The SBP is the maximum value of arterial pressure and the DBP corresponds to the minimum value. In optimal conditions, SBP is lower than 120 mmHg and DBP lower than 80 mmHg. The difference between SBP and DBP is known as pulse pressure (9–11).

Regarding BP, the vascular system can be divided in two parts: high-pressure part, which extends from the LV to the systemic capillaries, and the low-pressure part, which extends from the systemic capillaries to the right ventricle (RV), passes through the pulmonary circulation and reaches de LV in its relaxation phase (11).

Therefore, as blood leaves the aorta arteria and flows through the systemic circulation, BP decreases progressively. Approximately, it drops about 35 mmHg as blood moves from the systemic arteries to the systemic arterioles and capillaries. When blood flow reaches the RV, BP has dropped to 0 mmHg. This pressure gradient is what allows blood to circulate and the greater it is, the greater the blood flow (9–11).

The mean arterial pressure (MAP) is not the arithmetic mean of SBP and DBP, since SBP has longer duration than DBP. Instead, it is the area beneath the curve that determines the pressure in a cardiac cycle divided by the duration of the cycle. The value of the MAP in a large systemic artery is around 95 mmHg (11).

To understand BP, classical hemodynamic laws are applied to blood circulation. The most used is analogous to Ohm's Electricity Law: $\Delta P = F \times R$, where ΔP is the pressure difference between two points (P_1 and P_2), F is the blood flow and R is the vascular resistance between these two pressure points (3). This relation can be used for the whole circulation with the equation: $MAP = CO \times PVR$, where CO is the cardiac output and PVR the total peripheral vascular resistance (12).

The CO is the blood flow ejected by the heart. It is the product of the heart rate (HR), which is the number of heartbeats per minute, and the stroke volume (SV), which is the output of each heartbeat. The PVR is the total resistance to blood flow through peripheral vascular bed. Hence, a BP elevation may be the result of an increase in PVR , CO or a combination of both (11,12).

Vascular resistance is determined by the size of the lumen of blood vessels, the smaller the diameter is, the greater the resistance to blood flow; by blood viscosity, which occurs

when the number of red blood cells in plasma is high; and total blood vessel length, which is proportional to the resistance to blood flow (10).

The major factors that determine BP are the total blood volume, heart rate (HR), the elastic properties of blood vessels, CO and the PVR. The homeostasis of BP aims to assure constant blood flow in vital organs such as the brain, heart and kidneys (10).

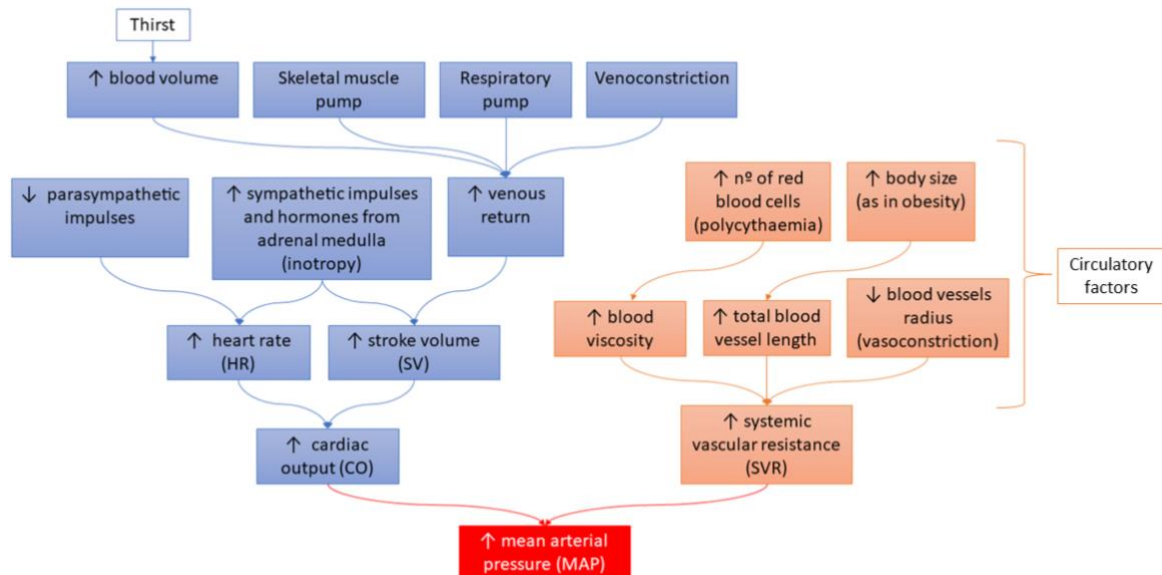


Figure 1. Major factors involved in the rise in blood pressure, adapted from (10).

5.1.1. Regulation of blood pressure

5.1.1.1. Short term regulation mechanisms

There are several systems to maintain blood pressure relatively constant in the body. The short-term regulation mechanisms allow to cope with sudden imbalances of blood pressure, such as those that occur when changing the body position, on a time scale of seconds or minutes (10).

Neural Regulation

The cardiovascular center (CVC) is a region of the human brain located in the medulla oblongata which can regulate blood pressure. It modulates the activity of the autonomic nervous system (ANS) on the heart and blood vessels diameter. The neurons scattered within CVC form the cardiostimulatory center, the cardioinhibitor center and the vasomotor center (9,10).

The cardiostimulator center stimulates the cardiac activity by transmitting sympathetic nerve impulses to the heart and to the blood vessels through the spinal cord. The cardioinhibitor center, on the contrary, slows down cardiac function via parasympathetic nerve impulses to the heart conveyed along the vagus (X) nerves. Therefore, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), influence the heart rate and the contractility of the heart in an opposite way (9,10).

The vasomotor center controls the blood vessels diameter by causing vasoconstriction or vasodilation. This region of the CVC continuously generates nerve impulses that propagate along sympathetic neurons to smooth muscle of blood vessels walls. Thus, sympathetic stimulation leads to constriction of arteries, arterioles and most veins. Consequently, the peripheral vascular resistance increases, which translates into higher blood pressure (9,10).

- a. *Baroreflex*: baroreceptors are mechanoreceptors located at strategic pressure sites as the carotid sinus, the aortic arch and the wall of the atrias. They are stimulated when there is a distention of blood vessels due to an elevation of BP. Immediately, the sensory information is sent to the CVC and as a result BP returns to normal levels. This negative feedback system is called baroreflex (11).
- b. *Chemoreflex*: chemoreceptors are specialised sensory receptor cells. The carotid bodies and the aortic bodies are peripheral chemoreceptors, whose location is close to the baroreceptors. Central chemoreceptors, on the other hand, are situated in the medulla. They sense chemical changes in the body environment such as low arterial P_{O_2} , high arterial P_{CO_2} and a decrease of blood pH, due to a BP decrease. Their activation leads to sympathetic nerves stimulation and, as a final result, to an increase of BP (11).

5.1.1.2. Long term regulation mechanisms

In addition to short-term regulation mechanisms, long-term regulatory systems act more slowly, on a time scale of hours or days. In this case, blood volume is regulated through blood vessels and kidneys, which control the volume of extracellular fluid (11).

a. *Renin-angiotensin-aldosterone system (RAAS)*

The RAAS has wide effects in the regulation of BP. This system is present in many organs, but mostly in the kidney, where it has the main part to regulate pressure-volume homeostasis (1,9).

The liver secretes angiotensinogen into the blood. When a drop in BP occurs, the kidney releases renin, which is an enzyme that converts angiotensinogen to angiotensin I (ANG I). Renin releasement is induced by various stimuli, among them, decreased renal afferent arteriolar perfusion pressure, activation of renal sympathetic nerves and several vasodilators, e.g. prostaglandin E2 (1).

Thanks to angiotensin-converting enzyme (ACE), ANG I is transformed into angiotensin II (ANG II), especially on the lung endothelial cells (1,11). ANG II is a powerful vasoconstrictor peptide and plays a key role increasing BP when significant blood loss occurs, during exercise and in other situations affecting renal blood flow. Under normal conditions, ANG II is not present in plasma in necessary concentrations to produce vasoconstriction. However, when the perfusion pressure of the kidney decreases, renin is released and, consequently, plasma levels of ANG II increase causing intense vasoconstriction in the renal circulation (11).

ANG II has other effects that rise MAP in an indirect way. When activates the angiotensin type 1 receptor (AT_1), ANG II triggers myocardial contractility, stimulates thirst sensation and reduces renal flow by enhancing sodium reabsorption and promoting the secretion of aldosterone (1,11). Aldosterone is a steroid hormone released into blood from the adrenal cortex. When aldosterone binds to its mineralocorticoid receptor, it causes sodium reabsorption and potassium excretion. Indirectly, this influences water retention, thus increasing blood volume and BP (1).

On the other hand, when ANG II stimulates the angiotensin II type receptor (AT_2), the effects are the opposite, leading to vasodilation, natriuresis and antiproliferative effects (1). In the figure below (Figure 2), RAAS mechanisms involved in BP regulation are represented.

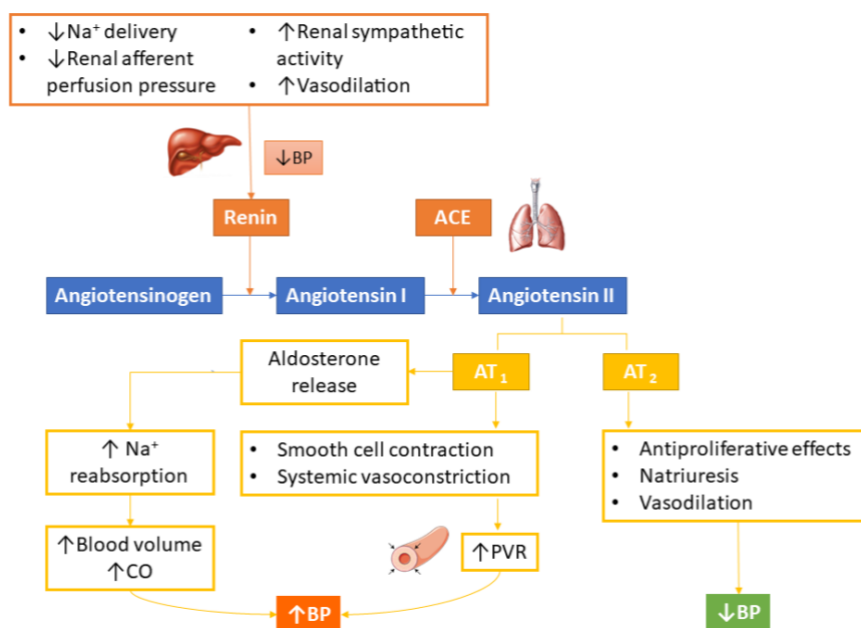


Figure 2. The role of Renin Angiotensin Aldosterone System (RAAS) in the regulation of blood pressure, adapted from (1).

ACE, Angiotensin-Converting Enzyme; PVR, Peripheral Vascular Resistance

b. Vasopressin (AVP)

When there is a reduction of blood volume, the osmotic pressure of the extracellular fluid raises. This fact activates the pituitary gland, which releases AVP. This hormone, also called antidiuretic hormone, binds to V_{1a} receptors on vascular smooth muscle cells (VSMCs). On the one hand, it increases water reabsorption in the kidney tubules of the nephron, and, on the other hand, it raises BP by increasing PVR (11).

c. Natriuretic peptides

Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) have important natriuretic and vasodilatory properties, which allow a balance between sodium and BP. They are released from atrial and ventricular cells, respectively, in response to atrial or ventricular stretch after administration of a sodium load (1).

ANP and BNP increase glomerular filtration rate and inhibit sodium reabsorption. This leads to systemic vasodilation, reduction in blood volume and, therefore, decrease in BP. Simultaneously, natriuretic peptides have indirect effects such as the inhibition of renin, aldosterone and AVP release (1,11).

d. Endothelium

The endothelium of blood vessels produces vasoactive substances, including nitric oxide (NO), which is the most important in the regulation of BP. NO is released by endothelium cells because of flow-induced shear stress and leads to vascular smooth muscle relaxation, thus resulting in vasodilation and increase of blood flow. Endothelin 1 (ET1) is another substance secreted by endothelial cells. ET1 exerts a powerful vasoconstrictive action when it binds to its receptor (ETA). The balance between NO and ET1, along with other vasoregulatory factors, determine final the endothelial tone (1).

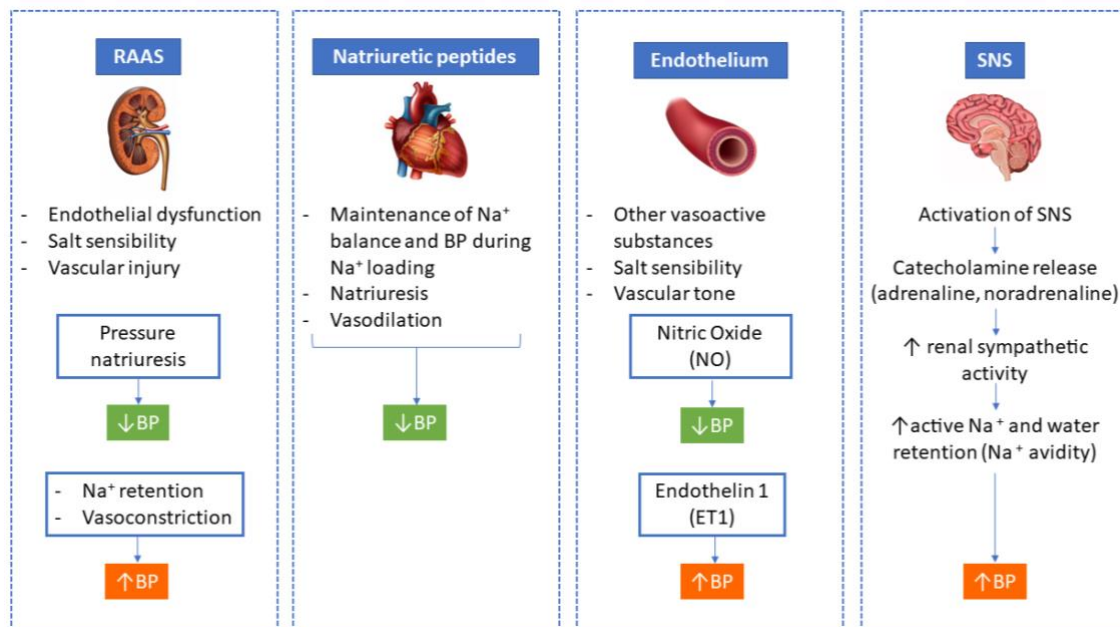


Figure 3. Main neuroendocrine systems regulating blood pressure, adapted from (1).

BP, Blood Pressure; RAAS, Renin Angiotensin Aldosterone System; SNS, Sympathetic Nervous System

5.1.2. Measurement of blood pressure

The device used in clinical measurement of BP is a sphygmomanometer. A manual sphygmomanometer consists on an inextensible cuff containing an inflatable bag which is wrapped around the arm. The clinician inflates the cuff by a rubber squeeze-bulb to a pressure higher than the expected SBP level to occlude the brachial artery and stop the blood flow. Then the pressure in the cuff, measured by means of mercury, is slowly released. In the auscultatory method, the doctor uses a stethoscope to detect the Korotkoff sounds on the brachial artery. This method allows both SBP and DBP to be determined (11).

A pressure of approximately 120 mmHg has to be applied to close blood vessels in young healthy people. When the brachial artery is closed, the physician cannot hear any sound.

The time when the SBP is reached corresponds to the first tapping sound, due to turbulent blood flow. The character of Korotkoff sounds changes as cuff pressure decreases towards DBP level, becoming cushioned and softened. Finally, the sound disappears as the artery is completely open and blood returns to a laminar flow (11).

At present, the preferred method in physician's offices to measure BP is using semiautomatic or automatic sphygmomanometers. The BP is initially measured in both upper arms using the proper cuff size according to the patient's arm circumference. The inadequate BP office measurement can lead to errors in the classification of patient's BP and, consequently, poorly indicated treatments (2).

In 2005, the American Heart Association (AHA) published guidelines for BP reading in the doctor's office. These recommendations related to the adequate position and posture of the patient, the adequate placement of the BP cuff, the rate of deflation of the sphygmomanometer mercury column as well as advice for patients to be seated in a comfortable and unstimulated way for 5 minutes before the first measurement (2,13).

For patients who monitor their BP at home, the AHA recommends resting in a chair with the cuff properly placed during 3-5 minutes before taking any readings. Three different readings have to be taken with, at least 1 minute apart. However, the European Society of Hypertension guidelines says that two readings should be taken after a 5-minute wait. For office measurement, the AHA recommends a minimum of two readings since BP has constant variations and a single measurement is less accurate rather than two or three measurements. Moreover, the third reading often results in lower BP values than the first, implying the reclassification of the patient's hypertension state (13).

Hence, to properly control hypertension, accuracy in BP readings and adherence to measurement guidelines are crucial.

5.2. HYPERTENSION

5.2.1. Definition and prevalence of hypertension

Hypertension is defined as a persistent increase in BP above normal considered values, whether in SBP, DBP or both (9). Further definition would be the level of BP in which the benefits of the treatment, either based on drugs or lifestyle modifications, outweigh its risks (14).

Hypertension is among the most common worldwide chronic diseases found in humans, especially in the Western world (14). In 2015, the global prevalence of hypertension was estimated at 1.13 billion people, with a prevalence of more than 150 million in Europe. In the adult population, the overall prevalence of hypertension was between 35-40%, with a standardized prevalence of 24% for men and 20% for women. As age increases, hypertension is more common, with a prevalence of >60% in people older than 60 years. Due to the ageing of the population, more sedentary lifestyle habits adopted and the tendency to overweight, it was estimated that hypertension prevalence between 2000 and 2025 will rise by 10% (1,15).

In long term, hypertension is a risk factor for cardiovascular disease (CVD), which includes stroke, myocardial infarction, coronary artery disease, heart failure, among others; and kidney disease (1,11,14). It is considered therefore one of the leading causes of death globally and on the European continent (2).

5.2.2. Blood pressure classification

In table 1 there is the classification of BP, used for all ages group from 16 years. Hence, hypertension is defined when SBP values are ≥ 140 mmHg and/or DBP value are ≥ 90 mmHg.

Table 1. Blood pressure values: classification and definitions of hypertension grades (2).

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	<90

On the other hand, isolated systolic hypertension occurs when only SBP rises, most commonly in the elderly. It is graded 1,2 and 3 according to SBP ranges indicated in Table 1 (2).

While SBP rises with age, DBP decline after 55 years of age. Resistant hypertension is a condition in which BP is uncontrolled despite the current use of typical treatments and therapies (14). Borderline hypertension occurs when SBP and DBP values are over 130 mmHg and 80 mmHg, respectively and it is associated with increased risk of progression to later established hypertension as well as increased risk of cardiovascular mortality (16).

5.2.3. Aetiology

Hypertension is a multifactorial disorder in which family history is an important aspect to consider. Most studies indicate that heritability ranges between from 30-35% (2).

However, there are other factors that contribute to the development of hypertension and its consequent complications. Behavioural risks factors including unhealthy diet, low physical activity, alcohol consumption, tobacco use and high mental stress are associated with hypertension. Dietary habits such as excess of sodium intake and poor intake of calcium, potassium, protein (especially those coming from vegetables), fibre and fish fats, can cause or aggravate the condition. Gut microbiota seems also to be linked to the pathogenesis of hypertension (3,17).

In addition, there are metabolic factors like overweight, obesity, diabetes or hypercholesterolemia that increase the risk of CVD. Metabolic syndrome (MetS) is a chronic disorder characterised by a clustering of pathological problems, mainly insulin resistance together with abdominal obesity, high triglycerides (TGs) and low high-density protein (HDL) cholesterol levels and hypertension. The combination of these clinical findings has an increased risk of developing type-2 diabetes and CVD. In this case,

the BP values considered to determine hypertension are ≥ 130 mmHg SBP and ≥ 85 mmHg DBP (3,18).

Socioeconomic factors, e.g. income, education and housing are determinants for the development of hypertension as they negatively influence behavioural risk factors. Living and working conditions can retard the detection of the disease and its treatment, which impedes the prevention of high blood pressure complications. Moreover, fear of unemployment often causes stress levels that have a negative effect on BP (3).

The risk of hypertension increases with ageing since blood vessels tend to stiffen over the years. This stiffening process is produced, among other factors, by vascular collagen changes and an increase in atherosclerosis. Even though, ageing of blood vessels can be delayed by healthy lifestyle habits, including healthy eating (1,3).

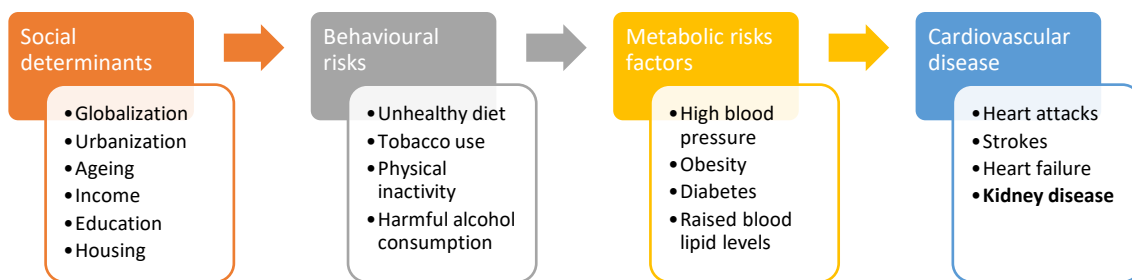


Figure 4. Main risk factors that contribute to the development of hypertension and its complications, adapted from (3).

According to its aetiology, hypertension is classified into two forms: primary or essential hypertension and secondary hypertension. In primary hypertension, the specific cause of high BP cannot be determined. By contrast, secondary hypertension is the consequence of other disease such as renal parenchymal disease, renovascular disease (including renal artery stenosis), primary aldosteronism, obstructive sleep apnoea and, less frequently, pheochromocytoma, Crushing's syndrome, hyperthyroidism, aortic coarctation (11,14,17).

Other terms used to describe high BP are malignant and transient or labile hypertension. Malignant hypertension is defined as unexpected increase in diastolic pressure above 125 mmHg which can cause damage to the brain, heart, eyes and kidney. Transient or labile hypertension is a temporarily rise in BP by the emotional reaction and stressful situations to the clinical environment (14).

5.2.4. Clinical manifestations and complications

Hypertension is a disease that develops silently while destroying the wall of blood vessels, which is why it is known as the "silent killer". In general, hypertensive patients do not experiment any symptoms, especially during the early stages of the disease. When symptoms appear, they are usually complications. However, there is an intermediate phase in which hypertension can cause clinical manifestation such as morning headache, exertional dyspnoea, feeling of dizziness when changing position, chest pain, heart palpitations and epistaxis. It is important to not ignore these symptoms but it is important to bear in that, on their own, they do not necessarily indicate hypertension (3).

5.2.4.1. Complications: target-organ damage

The higher BP levels are, the more probability to damage blood vessels in major organs such as the heart, brain, retina and kidneys. This cardiovascular risk is also dangerous in people suffering mild hypertension but with other risk factors like smoking, physical inactivity, unhealthy diet, obesity, diabetes, high lipid profile, among others (3).

In heart, clinical complications such as acute myocardial infarction, acute LV failure with pulmonary edema, unstable angina pectoris or dissecting aorta aneurism, can occur. Brain damage may result in hypertensive encephalopathy, intracerebral haemorrhage (ICH) as well as ischaemic stroke. In eyes, hypertensive retinopathy may develop which, due to an increased BP, can damage the retina causing bleeding to blindness. Persistent high BP can severely damage the kidney leading to renal failure (17).

5.2.5. Pathogenesis

The pathological mechanisms involved in hypertension are complex. In primary hypertension there is a genetic predisposition, as multiple genes are associated with higher risk of hypertension and are positively related to family history. This, together with environmental factors, contributes to suffer from hypertension (1).

a. Salt sensibility

The concentration of sodium in serum promotes fluid retention, which leads to an increase in blood volume and, consequently, an increase in BP. In normotensive individuals, when dietary sodium increases, compensatory haemodynamic changes occur to maintain BP at its physiological values. These changes consist of the reduction of vascular resistance, both renal and peripheral, as well as the increase in NO production by the endothelium. Nevertheless, endothelial dysfunction can lead to salt sensibility and, thus, hypertension. Salt-sensitive individuals, in order to cope with a high salt load, present an overproduction of the TGF β (transforming growth factor- β), responsible for increasing the risk of fibrosis, oxidative stress and low NO concentration (1,19).

Endothelial dysfunction can result from chronic high salt intake and may modify the intestinal microbiota, bringing with it changes that contribute to salt sensibility and subsequent high blood pressure. It seems that salt sensibility can induce T-helper 17 (T_H17) cells, causing autoimmunity (1,19).

b. Renin-angiotensin-aldosterone system (RAAS)

RAAS plays a crucial part in the pathogenesis of hypertension, in which ANG II is the main element of this pathogenic role. Apart from enhancing sodium reabsorption at renal level, ANG II is also related to endothelial dysfunction as well as pro-inflammatory and pro-fibrotic effects due to oxidative stress. This can lead to vascular, kidney and heart injury, which is why ANG II is strictly associated target-organ damage in hypertension. Aldosterone is a key element in the genesis of hypertension. It stimulates sodium reabsorption, but also contributes to endothelial dysfunction and vasoconstriction by inducing vascular smooth muscle cell proliferation, vascular fibrosis and oxidative stress (1).

c. Endothelium

In hypertension, circulating ET1 levels do not necessarily increase but what has been noticed is that, in hypertensive individuals, the sensitivity to the vasoconstricting effects

of ET1 is higher. In experimental models of hypertension, ETA blockers have demonstrated to be effective in attenuating or eradicating the disease and lowering BP in humans (1,20,21).

Endothelial dysfunction plays an important role in the development of hypertension. It is the result of damage induced by pressions in combination with oxidative stress. Various factors such as ANGII, vascular stretching due to cyclic changes in BP, ET1, uric acid, systemic inflammation, noradrenaline, free fatty acids and smoking habit, contribute to the generation of oxidative stress in hypertension by activating NADPH oxidase, an enzyme that generates ROS. Increased bioavailability of ROS decreases NO levels, leading to endothelial dysfunction and hypertension (1,22).

d. Sympathetic Nervous System

In general, SNS activation is higher in hypertensive individuals rather than in normotensive people. Patients with hypertension often suffer from an autonomic imbalance with increased SNS and decreased PNS activity. This SNS overactivity is responsible for both the generation of hypertension and its maintenance, since it implies increased renal sympathetic nerve activity and, consequently, increased renal reabsorption of sodium (Figure 3) (1,23,24).

Moreover, SNS hyperactivity, by activating α_1 adrenergic receptor, induces endothelial dysfunction, vasoconstriction, vascular smooth muscle proliferation arterial rigidity, also contributing to the development of hypertension (1).

e. Inflammation and the immune system

An inflammatory process increases vascular permeability and involves the release of inflammatory mediators such as cytokines, ROS and NO. Cytokines promote vascular fibrosis by increasing vascular resistance and stiffness. Furthermore, they stimulate renal synthesis of angiotensinogen and, thus, of ANG II. Still, the link between inflammation and hypertension is complex and the scientific evidence in humans is limited. It appears that C-reactive protein, TNF (tumour necrosis factor) and diverse interleukins are associated with hypertension but without a direct relationship (1).

5.2.6. Diagnosis and prevention

Primary hypertension is an asymptomatic condition that frequently, is diagnosed in lately states. It is usually detected in population screening programmes or because of opportunistic measurement of BP (2).

BP should be screened regularly in office visits, particularly in adult population. Those patients with optimal BP levels (<120/90 mmHg), should remeasure their BP every 5 years or more frequently if the opportunities arise. For patients with normal BP (120-129/80-84 mmHg), it is recommended to record their BP every 3 years. Patients with high-normal BP (130-139/85-89 mmHg), should record their BP annually due to high probabilities of progression to hypertension (2).

In almost all patients, repeated BP readings in office visits is the strategy to confirm the persistent increase of BP. The frequency and intervals between visits will vary depending on the diagnosed hypertension stage and whether there is a risk of CVD or hypertension-mediated organ damage (HMOD). Thus, BP diagnosis should also include assessment of

CVD risk, HMOD and concomitant clinical conditions that could suggest secondary hypertension (2,11).

Home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) are out-of-office BP measurement methods increasingly introduced during last decade to guide diagnosis and treatment of hypertension (Table 2). They provide estimates based on several BP readings under conditions representative of daily life. HBPM is based on BP measurements at regular intervals performed by the same patient at home or elsewhere outside the clinical setting. ABPM refers to the recording of BP at regular intervals (usually every 15 or 30 minutes) during a typical 24-hours period while individuals perform their daily activities. BP follows a circadian rhythm and dips during sleep. As ABPM provides night time readings, it is considered to have stronger prognostic evidence than office BP measurement (1,2).

Table 2. Definitions of hypertension based on 2018 ESH/ESC guidelines (2).

Category	Subtype	Systolic BP (mmHg)	Diastolic BP (mmHg)
Office BP	NA	≥140	≥90
Ambulatory BP	Daytime (awake)	≥135	≥85
	Night-time (asleep)	≥120	≥70
	24h	≥130	≥80
Home BP	NA	≥135	≥85

For the diagnosis of hypertension, Systolic BP, Diastolic BP or both have to exceed the reported values. BP, Blood Pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; NA, not applicable.

Out-of-office BP measurement methods has made it possible to detect different BP phenotypes like white-coat hypertension and masked hypertension. White-coat hypertension is characterised by high BP in the doctor's office, but normal when measured by HBPM or ABPM. On the contrary, masked hypertension refers to the untreated condition in which BP is normal for in-office readings but elevated for out-office readings (1,2).

Because of the relationship between CVD risk high BP, it is important to treat hypertension as soon as possible. It is also of high importance, to implement strategies to lower CVD risk in patients having high BP levels, but below the threshold for hypertension. In this way, it is possible to prevent CVD risk and decrease the tendency to develop hypertension with aging (11).

5.2.7. Treatment

Frequently, hypertensive patients have comorbid medical conditions, which means that multiple chronic or acute diseases are present. For this reason, these patients often require more than one medication for their proper treatment. Among the comorbid conditions diabetes mellitus is the most common (14).

Pharmacological antihypertensive therapy can be highly effective in lowering BP and its associated risks. Nevertheless, changes in lifestyle can be equally effective in reducing and preventing hypertension and CVD outcomes (1).

5.2.7.1. Non-pharmacological strategies

The most successful non-pharmacological interventions are weight-loss, dietary salt restriction, increased potassium intake, regular physical exercise, moderation of alcohol consumption, smoking cessation and diets that combine elements to prevent high BP. The most significant evidence is provided by the DASH-sodium trial in which the combination of low-sodium intake and Dietary Approaches to Stop Hypertension (DASH) diet (a diet based in fruits, vegetables and low-fat products, especially low-saturated fats and cholesterol), was associated with significant reductions in BP (1,2,17).

Some other diets, including low-calorie diets, vegetarian diets and the Mediterranean pattern, in which olive oil plays a key role as a main source of fat, have also been shown to lower BP and improve hypertension control. The DASH diet and MedDiet share similarities, but with the difference that the latter is enriched with olive oil rather than other vegetable oils and sources of fat (17,25,26). The MedDiet as a measure to combat high blood pressure, will be further developed in the point 5.3.1 below.

5.2.7.2. Pharmacological therapy

In addition of lifestyle changes, a lot of patients requires drugs to control their BP. Typically, antihypertensive therapy starts with first-line medications, either monotherapy or in combination. Combination is the therapy of choice in those patients with higher BP levels prior to treatment (1,2).

Among antihypertensive first-line medications, the most prescribed drugs are diuretics (thiazides-like), Angiotensin Converting Enzyme inhibitors (ACE inhibitors), Angiotensin II Receptor Blockers (ARBs, also called sartans), calcium antagonists (dihydropyridines, verapamil, diltiazem), β -blockers and α - β adrenergic blockers (1,2,14). Recommendations to initiate BP-lowering treatment, including lifestyle changes and drug-treatment, are shown in Figure 1 (2).

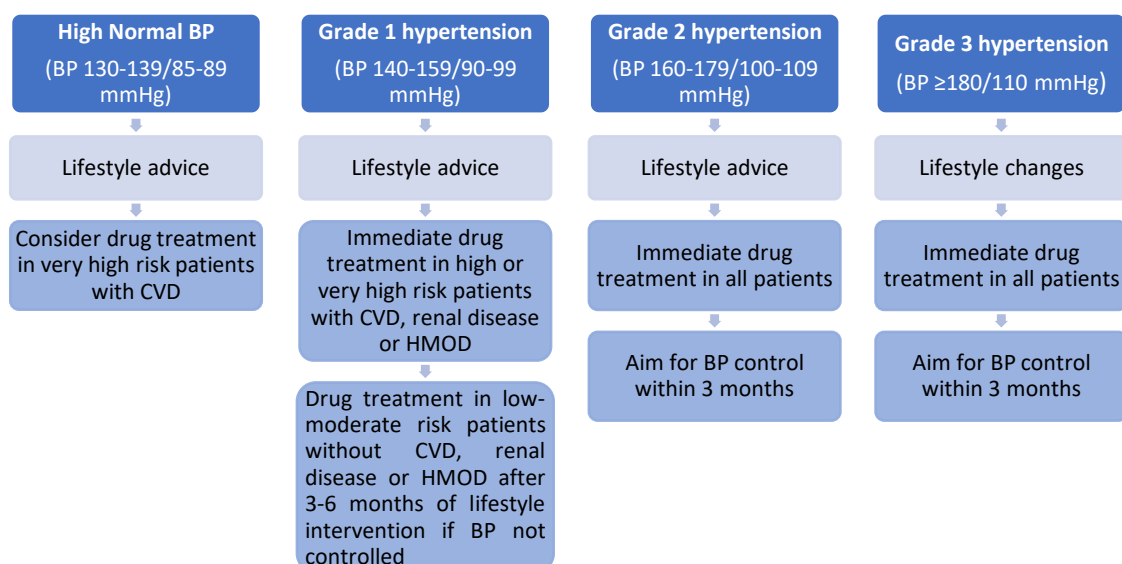


Figure 5. Initiation of bp-lowering treatment (lifestyle changes and medication) at different bp levels, adapted from (2).

BP, Blood Pressure; CVD, Cardiovascular Disease; HMOD, Hypertension-Mediated Organ Damage

5.3. FINDING POTENTIAL THERAPEUTIC TOOLS IN THE PREVENTION AND TREATMENT OF HYPERTENSION

In spite of genetic predisposition to primary hypertension, environmental factors such as poor dietary habits, high sodium intake, poor sleep quality or sleep apnoea, excessive alcohol consumption, lack of physical activity and mental stress, contribute to the development of hypertension. For this reason, a healthful lifestyle is the essential strategy for the prevention and reduction of hypertension and dietary habit is the modifiable element with the greatest effect on BP (1,6,27).

Given that most hypertensive patients need to take more than two anti-hypertensive drugs to reduce their BP to an acceptable level (<140/90 mmHg), which also implies an increased risk of adverse drug effects and medication costs, it is important to consider other therapeutic tools. The use of potential natural products such as herbal medicine and food supplementation could be a good alternative to treat hypertension (28,29).

5.3.1. The Mediterranean diet

The MedDiet is a typical diet of the Mediterranean region. Its main components are vegetables, fresh fruit, whole grains, fish and seafood, legumes, nuts, extra virgin olive oil and moderate dairy products as well as red wine consumption. In this dietary pattern, products considered to have unfavourable effect on the risk of hypertension like red meat, processed meat and poultry are limited foods (6).

Adherence to the MedDiet is widely associated with long-term benefits such as reduced total mortality, cancer, neurodegenerative diseases, hypertension and its subsequent risk of CVD. It has protective mechanisms of the cardiovascular system that include hemodynamic, metabolic and inflammatory effects (25).

Some studies have shown that people who adopt MedDiet have lower BP, oxidized low-density lipoprotein (LDL), inflammatory markers and arterial stiffness as well as better endothelial function (6,25,30).

Although the influence of the MedDiet is due to the combination of complete dietary patterns, olive oil is one of the component that has the most favourable effect on BP (6). Moreover, olive leaves have been used as a folk medicine for the treatment of hypertension (8).

5.4. *Olea europaea* L., A POTENTIAL THERAPEUTIC TOOL IN THE PREVENTION AND TREATMENT OF HYPERTENSION

5.4.1. Introduction

The olive tree (*Olea europaea* L.) is a plant widely-distributed, especially found in the Mediterranean region, used for the production of olive oil, table olives and other by-products (8). It belongs to the *Oleaceae* family, order *Lamiales*, which includes 30 genre and about 600 species of trees and shrubs. Among them, *Olea europaea* L. is the only specie producing edible fruits and is, therefore, used as food (7,31).

Olea europaea L. is originated in the coast of the eastern Mediterranean basin, but also in northern Iran, Asia Minor and northern Africa. However, nowadays, it is cultivated around the world, above all, in the Mediterranean area such as Greece, Spain, Italy, France, Turkey, Israel, Morocco and Tunisia, Asia-Pacific and South and North America (8,31,32).

Olive tree has been cultivated since ancient times as it dates back for more than 7,000 years ago. Its olives fruits, oil and leaves have been an important part of the human diet and traditional medicine, due to its nutritional and therapeutic properties (8,31). During the last decades, the demand of its products has increased because it is linked to the prevention of various pathologies associated with oxidative stress, like cancer, CVD, metabolic disorders as well as inflammation (7).

5.4.2. *Olea europaea* L. botanical description

Olive tree is a monoecious specie of evergreen. It is a short and thick tree or shrub about 10 m high. The leaves are simple, lathery, lanceolate with entire margin, dark green colour in the front and silver/whitish in the back. Their length and width are variable between 3-8 cm and 1-2 cm respectively (31).

The blooming starts at the beginning of March, but real flowers come out in April-May. The flowers are numerous, either bisexual or functionally unisexual. They are small, actinomorphic and creamy white flowers of radiated symmetry. Olives fruits are drupes of oval shape and size about 1-4 cm long and 0,6-2 cm in diameter. They are composed of three main structures: a lignified endocarp, which contains the seed; a mesocarp or pulp, which contains the oil; and an epicarp or skin (7,31).

5.4.3. Olive fruit

Olives are the fruits produced by the olive tree (*Olea europaea* L.). They cannot be eaten in their natural raw form due to their extreme bitterness and require specific processing. Despite most of the harvested crops are destined to the production of olive oil, smaller amounts are processed to be consumed as table olives (7).

In order to make them edible, table olives are fermented, pickled in brine or cured in salt. They are traditionally produced in Mediterranean countries and, unlike other fermented foods, their content is low in sugar (2-5%) and high in fat (20-35%), mostly monounsaturated fatty acids (MUFAs). Nevertheless, olives are considered a moderate source of calories since 100 g of fruits provide only 115 calories. Depending on the production method there are different types of olives with different tastes, typically bitter due to the presence of oleuropein and oleocanthal (7,8).

The composition of table olives has a high nutritional value as it includes lipids, sugars, proteins as well as water and some minerals (7). In addition, they contain non-nutritional components on which beneficial effects for human health have been described. This non-nutritional fraction represents approximately 3% of their weight and is composed mainly of phenolic compounds, the majority of which are phenolic acids and alcohols,

secoiridoids and flavonoids. Among the most important individual compounds there are hydroxytyrosol derivatives, oleuropein, verbascoside and ligstroside (7,8,31).

5.4.4. Olive oil

Olive oil is the chief product of the olive industry. According to its free acidity, the standard grades available on the market are extra virgin olive oil (EVOO), virgin olive oil (VOO), refined olive oil and pomace oil. This latter is the remaining product after the mechanical extraction of EVOO and VOO. EVOO is the purest and most expensive olive oil type, with an acidity of $\leq 0,8$ g/100g expressed as oleic acid (7,8,31,33).

Olive oil is a complex mixture of more than 230 different chemical compounds. Glycerols are the main fraction, comprising a high proportion of MUFAs and polyunsaturated fatty acids (PUFAs) as well as minor compounds such as phenolic compounds and tocopherol (vitamin E). In addition of having rich-lipid content, olives are an important source of vitamins and minerals including calcium, iron, potassium, sodium and vitamins E and K (7,8,31).

In general, olive oil has a high nutritional value. Since olive varieties, growing conditions and environmental factors can be very variable, not all olive oils have the same chemical composition (7,8,31).

EVOO and VOO consumption has been related to the reduction of BP as well as cholesterol levels and other risks factors which contribute to CVD. These biological benefits are mainly attributed to their MUFAs content but also to their minor constituents such as hydrocarbons, phytosterols, triterpenic compounds and phenolic compounds (4,33,34).

5.4.5. Olive leaves

Olive leaves are rich in bioactive compounds in which polyphenols and flavonoids have shown health benefits such as anti-carcinogenic, anti-hypertensive, anti-inflammatory and antimicrobial effects. Traditionally, infusions of olive leaves have been used as antihypertensive remedy to palliate the effects of atherosclerosis, arthritis, arthralgias, gout and diabetes (8,35).

5.4.6. Effect of bioactive compounds of *Olea europaea* L. on blood pressure

Many natural compounds from *Olea europaea* L., in particular from its leaves, have been found to have a hypotensive effect. The effects found by main bioactive compounds of *Olea europaea* L. such as oleic acid, pentacyclic triterpenes and polyphenols are explained below.

Moreover, at the end of this revision, Table 4 summarizes the effects found in preclinical studies using different experimental models and Table 5 compiles the obtained results in relevant human clinical studies.

5.4.6.1. Oleic acid and fatty acids

Distribution in Olea europaea L.

The main fatty acids isolated from the fruits of *Olea europaea* L. are oleic acid, palmitic acid, linoleic acid and stearic acid, respectively. VOO contains a large part of MUFAs, with a high proportion of oleic acid (70-80%), which is integrated into TGs (8,31,33,36).

Effects on blood pressure

Long-term consumption of VOO has been shown to decrease BP and prevent hypertension. It has been observed that oleic acid can activate α and β -adrenergic receptors and its signalling pathways. Nevertheless, some studies have claimed that olive oil cardioprotective effect is due to minority compounds such as α -tocopherol and polyphenols (36,37).

Teres *et al.* (2008) demonstrated that the increase of oleic acid in cell membranes, thanks to the intake of olive oil, regulates the structure of the lipid membrane and, in this way, G-protein associated signalling is regulated causing a hypotensive effect (Table 4). The experiment was designed in order to investigate VOO effect at the molecular level and it was found that a higher concentration of MUFAs activates the expression of adrenergic receptors signalling pathways stimulating vasodilatory pathways but restricting vasoconstrictive pathways. VOO, oleic acid and triolein, a dominant TG with three molecules of oleic acid, were administered for 14 days to rats and all showed a similar BP lowering activity. However, elaidic acid, stearic acid and soybean oil (which contains a small portion of oleic acid) had no hypotensive activity, suggesting that the molecular mechanisms associated with lipid membrane and BP regulation have high structural specificity (36).

In 2013, Miura *et al.* conducted a cross-sectional epidemiologic trial with the aim of linking MUFAs intake and BP reduction. This International Study of Macro/Micronutrients and Blood Pressure (INTERMAP) involved 4680 men and women aged 40-59 years from 17 different samples from Japan (four samples), China (three samples), UK (two samples) and USA (eight samples). Volunteers attended four visits and, in each of visit, BP was read in an average of two measurements. On the basis of the results obtained, researchers reached the conclusion that daily MUFAs intake, especially those coming from plant sources and for patients without undergoing medical or nutritional intervention, contributes to the prevention and control of high blood pressure (Table 5). For this reason, these findings support dietary recommendations based on increased consumption of vegetable MUFAs (38).

5.4.6.2. Pentacyclic triterpenes

Distribution in Olea europaea L.

Pentacyclic triterpenes are compounds widely distributed in more than 120 plant species, some of them used in the traditional medicine. In *Olea europaea* L., triterpenic compounds are present in olives, leaves and VOO. Among the minor compounds of VOO,

triterpenic compounds represent one of the chief bioactive components. However, they are found in higher concentration in olive leaves (39,40) .

Effects on blood pressure

Somova *et al.* (2003) reported the beneficial properties of four triterpenoids derivatives extracted from African and Cape cultivar *Olea europaea* L. leaves: uvaol (UV), ursolic acid (UA), oleanolic acid (OA) and methyl maslinate (MM). All of them showed a significant, dose-response, vasodepressor effect in a resistant-insulin rat model. They acted by blocking the effect of adrenaline and isoprenaline and, thus, suggesting its activity as β -adrenergic antagonists (Table 4). The strongest effect was from OA and MM (39).

Pomace oil, as a result of the refining process, has a different composition to EVOO and VOO for certain components. It lacks polyphenols but has a higher concentration of pentacyclic triterpenes. Valero-Muñoz *et al.* (2014), aimed to evaluate the protective effects of a pomace oil rich in triterpenic acids (OA and maslinic acid) on BP, cardiac haemodynamic parameters and vascular alterations caused by hypertension in SHR (spontaneously hypertensive rats), an established genetic model of hypertension. During 8 weeks, the animals received a dose of pomace oil containing 100 mg/kg/day of triterpenic compounds in which 56.8 mg/kg/day was OA and 38 mg/kg/day was maslinic acid. At the end of the experiment, SHR did not experience an increase in BP while HR was similar in both the treatment and control groups. Additionally, results showed an improved endothelial function, with an increased eNOS (endothelial Nitric Oxid Synthase) expression as well as improved cardiac haemodynamics regarding to SBP and DBP (Table 4). In conclusion, this study confirmed the potential cardiovascular benefits of an enriched triterpenoid pomace oil, a waste product of the olive oil industry, raising awareness of its biological and nutritional values (41).

Literature has described useful pharmacological properties of OA and has reported its BP lowering in normotensive animals. Thus, due to its therapeutic potential, OA has been suggested as a starting point for the synthesis of new derivatives. Madlala *et al.* (2015) made a comparison between the effects of OA administration on MAP and kidney function with those obtained with oleanane synthetic derivatives (brominated OA, Br-OA and OA-methyl ester, Me-OA) administration in normotensive animals. In terms of reducing MAP and improving renal function by increasing sodium excretion, acute infusion of OA and its oleanane derivatives had similar effects. Besides, sub-chronic oral OA treatment induced hypotensive responses in Wistar, DSS (Dahl salt-sensitive) and SHR rats. The OA lowering effect of MAP and oxidative stress was more noticeable in hypertensive animals and correlated with an increase in urinary sodium diuresis (Table 4). Thereby, this work revealed the correlation between BP and increased urinary sodium excretion by OA and a more marked hypotensive effect of OA in hypertensive animals. It was considered a study of clinical relevancy as OA was effective by oral administration (42).

5.4.6.3. Phenolic compounds

Distribution in Olea europaea L.

Olive fruits accumulate oil in the mesocarp in a percentage of 28-30%, but also contain secondary metabolites like phenolic compounds. The most abundant phenolic compounds are oleuropein, tyrosol and hydroxytyrosol. While the fruits and leaves of olives are rich in oleuropein and hydroxytyrosol, in olive oil the amounts of these compounds are lower, as they are soluble in water and end up in mills waste water of the production process (7,43).

The high level of phenolic compounds plays a key role in defence and survival of olive plant, especially in its early stages when fruits are more vulnerable to attacks by insects and pathogens. Moreover, both hydroxytyrosol and oleuropein have a high antioxidant and scavenging activity against ROS (reactive oxygen species), hence, many human health benefits have been attributed to olive oil for its phenolic content. Hydroxytyrosol contributes to the prevention of atherosclerosis and heart-coronary disease as it inhibits the expression of LDL oxidation (43).

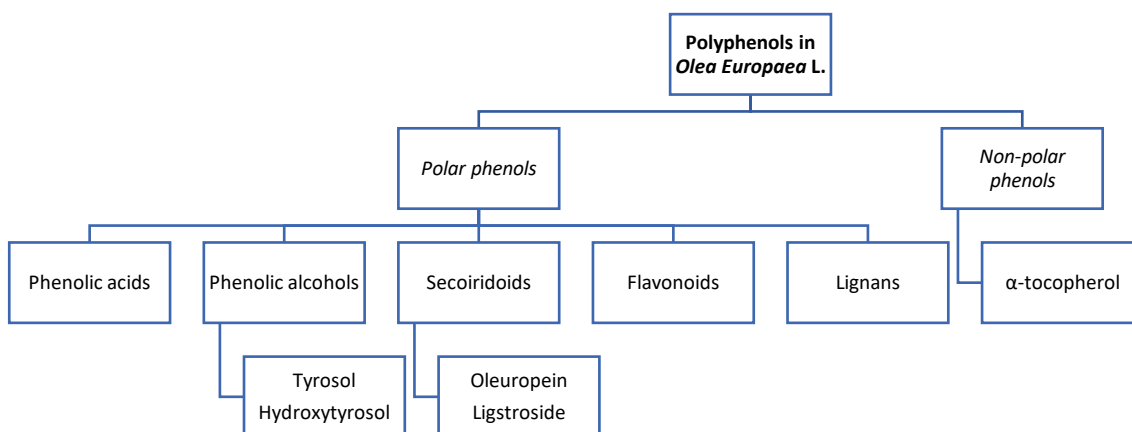


Figure 6. Classification of the main phenolic compounds of *Olea europaea* L. (7).

Contrary to olive oil, olive leaf contains the polyphenol fraction with only small quantities of oleic acid. Thereby, olive leaves represent a good opportunity to study the effect of olive oil polyphenols on the cardiovascular function, in particular on BP (44).

Effects on blood pressure

Moreno-Luna *et al.* (2012) conducted a dietary-intervention study using a polyphenol-rich olive oil in order to analyse its influence on BP and endothelial function. The study participants were 24-year-old women in high-normal BP category or in stage 1 essential hypertension. The study was double-blinded, crossover and randomized and consisted of two different diets, one with a dose of ≈ 30 mg/day of olive oil rich in polyphenols and the other with olive oil free of polyphenols. Each dietary-period had a duration of 2 months with 4 weeks of washout in between. The parameters measured during the study were: SBP, DBP, serum or plasma biomarkers of endothelial function, oxidative stress and inflammation and ischemia-reactive hyperaemia (IRH) in the forearm. The baseline values were taken during a 4-month run-in period. Compared to baseline

values, results found a significant decrease ($p<0.001$) in SBP and DBP after 2 months of daily consumption of polyphenol-rich oil. Significant decrease in asymmetric dimethylarginine, LDL-oxidation and plasma C-reactive protein was also found, as well as a significant increase in plasma nitrites/nitrates and IRH, showing an improvement in endothelial function and oxidative status (Table 5). This study, showed for the first time that, a daily intake of small amount of polyphenols contained in olive oil during the early stages of hypertension, can have similar BP-lowering effects as first-line antihypertensive drugs usually prescribed (45).

Valls *et al.* (2015) compared the effect on endothelial function of a functional virgin olive oil (FVOO) enriched with its own polyphenols with the effects of a standard VOO with polyphenol moderate content, in a randomised, double-blind and crossover trial. Thirteen volunteers with mild hypertension received a postprandial dose of 30 ml FVOO with a polyphenol content of 961 mg/kg and VOO with a polyphenol content of 289 mg/kg. Five hours after ingesting the olive oils, endothelial function was measured as ischemic reactive hyperaemia (IRH), along with associated biomarkers. Comparing both interventions, IRH values increased ($p<0.05$) after FVOO consumption while oxidised LDL was decreased ($p=0.01$). So, FVOO shown healthier effects in contrast with standard natural VOO (Table 5) (46).

a. Oleuropein

Secoiridoids represent an important part of the leaves and fruits of *Olea europaea* L. They are a phenol-conjugated compounds that may contain a glycoside part. Secoiridoids come from the opening of iridoids cyclopentane ring and, in *Oleaceae* family, the resulting carbonyl group oxidizes and conjugates with a phenolic moiety (43). The most abundant secoiridoid is oleuropein aglycon, present in large quantities in olive leaves but in lower quantities in olive oil. Nevertheless, oleuropein is one of the major phenolic compounds present in olive oil and together with hydroxytyrosol and tyrosol represent 90% of the phenolic fraction. (7,31,43).

Under *in vitro* conditions, oleuropein has demonstrated a range of beneficial properties for the cardiovascular system, among them, enhanced NO concentrations and decreased BP. This compound can be obtained from the decoction of olive leaves and in clinical trials has proved to be one of the components responsible for causing vasodilation on isolated rat aorta. In addition, it has shown an ACE inhibitory activity that may contribute to its BP-lowering effect (44,47).

b. Flavonoids

Flavonoids are polyphenolic substances which are responsible for a wide variety of food health benefits, including protection against atherosclerosis and CVD. Hypotensive properties of flavonoids from *Olea europaea* L. fruits and leaves have been found. Even though these pharmacological effects been mainly attributed to oleuropein, the presence of flavonoids derivatives is also crucial (48,49).

Loizzo *et al.* (2007) attempted to analyse ACE inhibitory activity by flavonoids. The research *Ailanthus excelsa* (Roxb) leaves plant were used for the extraction of six

flavonoids, some of which are also present in *Olea europaea* L. Then, the *in vitro* inhibitory activity toward ACE by MeOH extract and the isolated compounds was evaluated. All of them displayed ACE inhibitory activity in a dose-dependent way, showing potential antihypertensive activity (Table 4) (49).

Furthermore, flavonoids perform inhibitory activity of lipid peroxidation, platelet aggregation and enzyme systems such as cyclooxygenase (COX) and lipoxygenase, and also reduce the capillary permeability and fragility. For this reason, flavonoid preparations have been used for years in clinical practice to treat circulatory disorders. Flavonoids are also potent antioxidants, free radical scavengers and divalent cations chelators. It has been suggested that the inactivation ACE activity by flavonoids is through the generation of chelated complexes with zinc ions within the ACE active centre (48,49).

It seems that the biological mechanisms in which flavonoids modulate the vascular activity and BP are involved with NO production by the regulation of RAAS in VSMCs. However, as the actual mechanisms of ACE inhibition and the relevance of flavonoids for their supposed antihypertensive activity have not been fully established, further investigation is needed (49).

5.4.6.4. Olive Leaf Extract

Recent studies suggest the use of olive leaf extract (OLE) concentrated in phenols as a dietary supplement to reduce blood pressure, hyperglycaemia, oxidative stress, inflammation and, in turn, improve the lipid profiles and vascular function. This extract contains the same phenolic compounds as olive oil, but in higher concentrations. The predominant compound is oleuropein, but flavonoids including luteolin, apigenin and quercetin, as well as triterpenoids (oleanolic, ursolic and maslinic acid), are also important compounds in the antihypertensive activity of OLE. Olive leaves offer the possibility of providing good absorption and bioavailability of their phenolic content, which is a requirement for their bioactivity. Hence, the hypotensive effect of OLE has been studied up to now in different animal models (50,51).

In a study carried out in 2002, a prepared OLE (EFLA® 943) was tested in order to investigate its BP lowering activity. The extract was tested in hypertensive rats by daily oral doses of L-NAME (NG-nitro-L-arginine methyl ester). The extract oral administration resulted in an antihypertensive effect related to reversal of vascular changes involved in L-NAME-induced hypertension (Table 4) (52).

In 2008, the effects of commercial OLE were studied on isolated rabbit hearts. The results showed a concentration-dependent decrease of systolic left ventricular pressure and HR as well as increase in relative coronary flow, due to the direct and reversible suppression of the L-type Ca^{2+} channel by OLE (Table 4) (53).

A study conducted in 2014, aimed to investigate the immediate effects of the oral administration of a high dose of standardized OLE on blood pressure, HR and oxidative stress. *In vivo* models of SHR and normotensive Wistar rats (WR) were used. In the experiment, SBP and HR were measured before and after 60 and 120 minutes of

administration of OLE. Besides, in order to investigate the effects of OLE on the plasma lipid peroxidation and antioxidant system of erythrocytes in both rat strains, the erythrocyte activity of catalase, glutathione peroxidase, superoxide dismutase (SOD), glutathione reductase along with lipid peroxidation in plasma (pTBARS) were measured as well. The study results showed a significant difference ($p<0,001$) in the SBP and HR between WR and SHR. A high oral dose of OLE did not cause changes in BP or HR in normotensive rats. Conversely, the same dose in SHR, reduced BP by 20% and 13% after 60 and 120 minutes of OLE administration, respectively (Table 4) (50).

In hypertensive patients, it has been observed that haemodynamics alterations in carotid and renal arteries are related to the severity and extent of target organ damage. Studies have indicated that there is correlation between carotid vascular resistance and renal vascular resistance, which means that an increase of vascular resistance can develop in parallel in both vascular beds. Furthermore, oxidative stress is an important factor in the pathogenesis of CVD and, in human carotid arteries of older patients, ROS levels are higher. Some studies using models of hypertensive rats, have demonstrated that increased production of ROS in vascular tissue contributes to the development of hypertension and its maintenance (54). In 2016, Mihailovic *et al.* found that plant products rich in polyphenols lower BP and have beneficial effects on carotid artery alterations induced by hypertension (55).

An experiment undertaken in 2016 by Romero *et al.* (56) that tested the chronic antihypertensive effects of an oleuropein-enriched (15% w/w) OLE in SHR. As secondary objectives, effects based on the improvement of endothelial function and antioxidant and anti-inflammatory properties on the vascular wall were also studied. In the experiment, ten Wistar Kyoto Rats (WKR) were used as control WKR group, ten WR as control WR group and ten WR were treated with OLE at a dose of 30 mg/kg for 5 weeks. SBP, HR and cardiac hypertrophy were reduced after long-term treatment. Thanks to the reduction of pro-inflammatory and pro-oxidative status and endothelial dysfunction through various mechanisms, OLE exerted hypertensive activity in SHR (Table 4) (56).

Recently, Ivanov *et al.* (2018) examined the reducing activity, antioxidant capacity and metal ion chelating ability of a standardized oleuropein-enriched OLE (16-24% oleuropein content) in SHR. As secondary aim, the study examined the extract

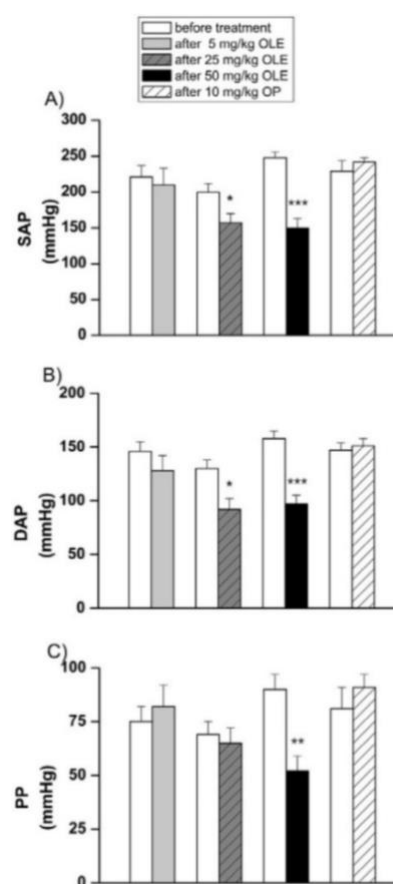


Figure 7. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and pulse pressure (PP) in SHR rats before and after treatments. Ivanov *et al.* (2018) (54).

* $p<0.005$, ** $p<0.001$, *** $p<0.0001$, significant difference between before and after treatment

influence on haemodynamics, either regional or systemic, and its antihypertensive mechanism. Additionally, lipid profile and lipid peroxidation were also investigated. The observed effects were then compared with effects obtained using oleuropein alone (OP). OLE was applied at doses of 5, 25 and 50 mg/kg whereas OP was applied at the dose of 10 mg/kg. Acute *in vivo* effects on oxidative stress and carotid, renal and systemic haemodynamic parameters of BP, HR, CO and PVR were studied. Results showed that OLE possesses higher antioxidant activity than BHT (butylated hydroxytoluene), higher reducing capacity than vitamin C, which is a strong natural antioxidant, and lower metal-ion chelating activity than EDTA (54).

Depending on the administered dose, two different antihypertensive responses were found. When SHR received the OLE dose of 25 mg/kg (OLE25), vascular resistance in systemic circulation was affected, resulting in a significant decrease in total PVR, thus also in SBP, DBP and MAP. By contrast, HR and CO parameters, which reflect cardiac mechanisms, occurred when 50 mg/kg OLE (OLE50) was applied. While in OLE25 the decreased BP was due to peripheral vasodilation, in OLE50 it was because of the reduction in HR, which leads to a decrease in CO and BP (54).

Therefore, OLE25 was the most effective reducing cardiovascular risks, improving carotid and renal haemodynamics as well as PVR. OLE50, although caused improvement of cardiac function and BP, retained high vascular resistance, which reduced blood flow to the brain and kidneys of SHR. On the other hand, OP administration did not affect systemic or regional haemodynamics, indicating that other OLE constituents may be the responsible for cardiovascular and haemodynamics changes. These results are expressed graphically in Figure 7 and summarized in Table 4 (54).

Perrinjaquet-Moccetti *et al.* (2008) tested EFLA[®]493 as a dietary supplement in 40 borderline hypertensive monozygotic twins aged between 18-60 years. The investigation consisted of an open study of twin parallel groups. Two parallel experiments were conducted (experiment I and II) and, in both of them, twin pairs were randomly assigned to different treatment groups. In experiment I, treatment group was administered daily on tablet of 500 mg of EFLA[®]493 while did not receive medication but lifestyle suggestions to combat hypertension. In experiment II, one twin from each pair received a dose

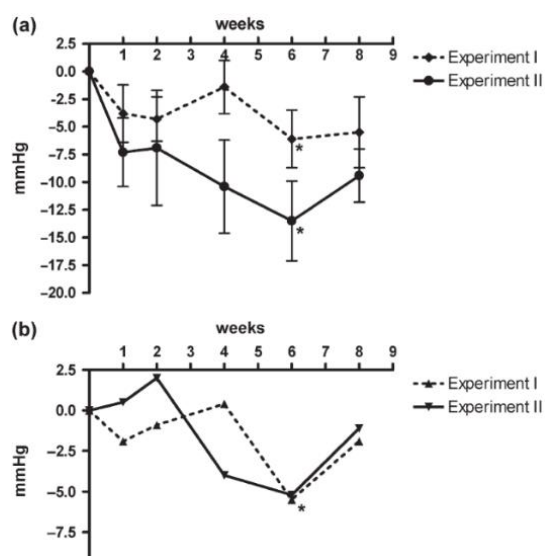


Figure 8. Mean differences of systolic blood pressure (a) and diastolic blood pressure (b) between group control and 500 mg EFLA[®]943 group (experiment I) and between 500 and 1000 mg EFLA[®]943 group (experiment II) in borderline hypertensive monozygotic twins. Perrinjaquet-Moccetti *et al.* (2008) (29) Mean values were significantly different from the initial values: * $p < 0.005$

of 500 mg/day of EFLA[®]493 and the other was administered dose of 1000 mg/day of EFLA[®]493. Both experiments lasted 8 weeks (29).

Participants BP and HR were measured in initial screening, after the first week of treatment and, from the second week, every 15 days until the end of treatment. Depending on EFLA[®]493 doses, BP values changed between the corresponding twin. In all subjects BP was reduced, but most significantly in those who received a higher dose of the extract. In addition, intake of 1000 mg/day of EFLA[®]493 clearly showed a superior effect to recommendations on lifestyle changes (Figure 8). A reduction of total cholesterol was also found in all treatment groups on a dose-dependent basis. Therefore, this clinical trial confirmed the antihypertensive and cholesterol-lowering actions of OLE in humans (29).

In 2011, a double blind, randomized clinical trial aimed to compare the tolerability and effectiveness of OLE (EFLA[®]493) with the reference drug Captopril. The volunteers were patients with stage 1 hypertension. OLE was administered orally twice a day, at a dose of 500 mg, over a period of 8 weeks. Initially, Captopril was given at a dose of 12,5 mg twice daily, but after 2 weeks, according to the patients' response to the treatment, Captopril dosage regimen would be increased to 25 mg twice daily. The results showed an important reduction in SBP as well as DBP from baseline to 8 weeks. Greater results were achieved on those subjects treated with OLE instead of Captopril. A significant reduction in the concentration of total-cholesterol and TGs was also noticed at the study dosage regimen of OLE 500 mg twice a day for 8 weeks (Table 5), showing agreement with the results of Perrinjaquet-Moccetti *et al.* (2008). This positive effect on cholesterol was not observed in Captopril treatment group (28). Table 3 provides a comparison between BP, total-cholesterol and TGs values at baseline and at the end of the study (28).

Table 3. Baseline and final study values of systolic blood pressure, diastolic blood pressure, total-cholesterol and triglycerides levels. Adapted from Susalit *et al.* (2011) (28).

Variables	BaselineMean (SD)	EndMean (SD)	p
<i>Olive group (n=72)</i>			
SBP (mm Hg)	145.0 (5.0)	133.5 (10.4)	<0.001**
DBP (mm Hg)	91.3 (5.1)	86.6 (6.9)	<0.001**
TC (mg/dl)	202.2 (34.6)	196.4 (32.0)	0.033*
TG (mg/dl)	140.3 (68.2)	128.4 (63.8)	0.032*
<i>Captopril group (n=76)</i>			
SBP (mm Hg)	144.7 (4.5)	130.9 (9.3)	<0.001**
DBP (mm Hg)	89.9 (6.6)	83.4 (7.1)	<0.001**
TC (mg/dl)	183 (27.5)	184.1 (30.2)	0.808
TG (mg/dl)	119.5 (63.0)	118.2 (67.7)	0.800

TC, total cholesterol; TG, triglycerides; V, visit; End of study, after 8-week treatment.

* $p < 0.005$ = significantly different; ** $p < 0.001$ = significantly different

Table 4. Summary of the antihypertensive effects of bioactive compounds of *Olea europaea* L. in preclinical studies.

Preclinical studies				
Compound/matrix	Model	Dose	Activity	Reference
Fatty acids				
Genetically modified animals				
VOO, oleic acid and triolein	Female Sprague-Dawley rats and SHR (n=10 in each group)	2g/kg VOO, 1g/kg triolein, 1g/kg OA	Reduction of SBP in short-term treatment by controlling G-protein through the cell lipid membrane	Teres <i>et al.</i> (2008) (36)
Pentacyclic triterpenes				
Healthy animals				
Oleanolic acid (OA), ursolic acid (UA), uvaol (UV) and methyl maslinate (MM)	Wistar Rats (n=6 in each group)	Antidysrhythmic activity at a dose of 40 mg/kg (UV, OA)	Cardiotonic and antidysrhythmic activity by β -adrenergic antagonism	Somova <i>et al.</i> (2003) (39)
Genetically modified animals				
Pomace olive oil rich in OA and maslinic acid	22-week old male SHR (n=16)	100 mg/kg/day of pomace oil from which: 56.8 mg/kg/day OA and 38 mg/kg/day maslinic acid	Attenuation of the increase in BP by improvement of endothelial function (enhanced eNOS expression) and organ target protection	Valero-Muñoz <i>et al.</i> (2014) (41)
OA and Me-OA, Br-OA	Wistar, DSS (Dahl salt-sensitive) and SHR rats (n=6 in each group)	<u>Acute (4h):</u> Infusion 90 μ g/h <u>Subchronic (9h):</u> OA doses of 30, 60 and 120 mg/kg, twice at 9h and 15h, every third day for 9 weeks	MAP-decreasing activity and increasing Na ⁺ outputs	Madlala <i>et al.</i> (2015) (42)
Phenolic compounds				
Genetically modified animals				
Flavonoids	<i>In vitro</i> assay	53.78% inhibition at the concentration of 330 μ g/ml	Hypotensive activity by ACE inhibition in a dose dependent way	Loizzo <i>et al.</i> (2007) (49)
Oleuropein enriched OLE	WKR (n=10) and SHR (n=20)	30 mg/kg OLE for 5 weeks	Reduction of BP, HR cardiac and renal hypertrophy related to the improvement of vascular function and pro-oxidative status and pro-inflammatory cytokines	Romero <i>et al.</i> (2016) (56)
OLE and oleuropein alone (OP)	24-week male SHR (n=7 in each group)	5,25, 50 mg/kg OLE 10 mg/kg OP	Improvement of oxidative stress, cardiac function and BP in SHR	Ivanov <i>et al.</i> (2018) (54)
Olive Leaf Extract (OLE)				
Genetically modified animals				
Commercial OLE	Isolated rabbit hearts n=5 samples n=4 control experiments	1, 10, 20 and 50 μ M OLE	Concentration-dependent decrease in LVP and HR by suppression of L-type Ca ²⁺ channel in a direct and reversible way	Scheffler <i>et al.</i> (2008) (53)

Table 4. Cont.

Compound/matrix	Model	Dose	Activity	Reference
<i>Olive Leaf Extract (OLE)</i>				
Genetically modified animals				
OLE	Male, adult, age matched SHR and WR (n=8 in each group)	200 mg/kg OLE	Acute hypotensive and pro-oxidative effect in SHR (increased pTBARS and SOD activity)	Dekanski <i>et al.</i> (2014) (50)
Hypertensive induced animals				
OLE	L-NAME rats	Different dose levels for 8 weeks, best effects induced by 100 mg/kg	Dose dependent prophylactic effect against BP increase in L-NAME model by reversal of vascular changes	Khayyal <i>et al.</i> (2002) (52)

ACE, Angiotensin-Converting Enzyme; BP, Blood Pressure; DBP, Diastolic BP; NO, Nitric Oxide; SBP, Systolic BP; SHR, Spontaneously Hypertensive Rats; SOD, Super Oxide Dismutase; VOO, Virgin Olive Oil; WR, Wistar Rats; WKR, Wistar Kyoto Rats

Table 5. Summary of the antihypertensive effects of bioactive compounds of *Olea europaea* L. in clinical trials

Clinical trials – Nutritional interventions				
Compound/Matrix	Study design and subjects	Dose	Activity	Reference
<i>Phenolic compounds</i>				
Polyphenol-rich olive oil	Double-blind, randomized, crossover 24 young women aged 24-27 years, with mild hypertension	30 mg/day (2 months)	Significant decrease in SBP and improvement of endothelial function by increasing NO bioavailability Antioxidant and anti-inflammatory	Moreno-Luna <i>et al.</i> (2012) (45)
FVOO polyphenol-enriched	Double-blind, randomized, crossover 13 participants aged 20-75 years with pre-hypertension or stage 1 hypertension	30 ml FVOO with 961 mg/kg of phenolic compounds	<u>Acute effects (5h):</u> Improvement of endothelial function Decrease in oxidised LDL concentrations and inflammatory biomarkers	Valls <i>et al.</i> (2015) (46)
<i>Fatty acids</i>				
MUFAs	Cross-sectional epidemiological 4680 participants aged 40-59 years	Daily MUFAs intake	Prevention of high blood pressure Better BP control in no-intervened individuals and with MUFAs from vegetable sources	Miura <i>et al.</i> (2013) (38)
<i>Olive Leaf Extract (OLE)</i>				
EFLA 943®	40 borderline hypertensive monozygotic twins	500 or 1000 mg/day for 8 weeks	Hypotensive effect with better activity in high dose treatment group	Perrinjaquet-Moccetti <i>et al.</i> (2008) (29)
EFLA 943®	Double blind, randomized, parallel 144 subjects with stage 1 hypertension aged 25-60 years	500 mg twice a day for 8 weeks	Significant decrease in SBP and DBP, efficacy similar to Captopril Improvement of lipid profile	Susalit <i>et al.</i> (2011) (28)

Blood Pressure; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure; NO, Nitric Oxide; VOO, Virgin Olive Oil

6. CONTRIBUTIONS AND CONCLUSIONS

Hypertension is a chronic disorder in which BP is elevated due to increased CO and altered PVR. The development of the disease is determined by genetic and environmental influences, being the latter modifiable risk factors. Thereby, before reaching advanced stages, hypertension can be prevented with lifestyle changes.

Following this review, it has been proven that leaves, fruits and oil of *Olea europaea* L. contain phytochemicals capable of lowering BP. It is for that reason that olive oil and table olives could be considered putative functional foods in the prevention of hypertension in the future and nutritional recommendations could be made. However, stronger evidence is needed.

Robust evidence has shown that VOO composition provides MUFAs and other minor compounds such as polyphenols, tocopherols, triterpenes, among others, which contribute to BP regulation and prevention of high BP levels. Thus, VOO intake should be recommended as the main the source of dietary fat replacing saturated fatty acids and polyunsaturated fatty acids in patients with borderline hypertension or already hypertensive. This is particularly important in individuals with MetS who, despite being at normal-high BP levels, suffer a sum of clinical alterations that greatly increase CVD risk. However, a limit consumption of VOO cannot be exceeded, as fatty acids contain 9 kcal/g and, an increase of daily calorie intake, can lead to obesity and overfeeding.

In general, table olives are restricted among hypertensive patients due to its sodium content, yet, olive fruits have high proportions of pentacyclic triterpenes and phenolic compounds of which cardioprotective activities have been described. Thus, their addition to the diet of hypertensive patients should be considered. Olive leaves contain bioactive compounds, particularly pentacyclic triterpenes and polyphenols in high concentrations. In preclinical and clinical studies, OLE has been shown to possess hypotensive activity with higher efficacy than lifestyle modifications. Therefore, olive leaves can be considered the main source for developing dietary supplements for individuals with hypertension.

Regarding the bioactive compounds studied from *Olea europaea* L., all have shown beneficial effects on BP and cardiovascular health. Oleic acid has shown to be the chief responsible for the hypotensive effect of olive oil through molecular mechanisms in the lipid membrane. These data support recommendations to increase ingestion of MUFAs from VOO to avoid unfavourable BP levels.

Among pentacyclic triterpenes evaluated, OA was the most effective in reducing BP, followed by ursolic acid and UV. OA has already been described as a potent hypotensive agent and its antihypertensive effects are correlated with natriuretic effect, reduction of aldosterone levels, vasodilation and modulation of oxidative status. Maslinic acid, despite being in smaller proportions, should be also attributed to the beneficial cardiovascular effects, according to Valero-Muñoz *et al.* (2014). Therefore, pentacyclic triterpenes clearly contribute to the overall antihypertensive effect of olive leaf extract

and may provide an inexpensive source to treat hypertension. Yet, the studies reviewed are performed pre-clinically, thus, additional studies in humans are needed.

The health benefits of *Olea europaea* L. by-products are mostly due to their high polyphenol content. Hydroxytyrosol and oleuropein are the most important phenolic compounds in olive, which have proven an indisputable antioxidant and scavenging capacity against ROS. As Table 4 and Table 5 show, polyphenolic substances exert an antihypertensive activity thanks to the improvement of the pro-oxidative and pro-inflammatory status, as well as of the endothelial function by enhancing the release of NO. These effects appear at both acute and long-term levels, and were observed in both genetically modified animal models and clinical trials in humans. In addition, polyphenols inhibit LDL oxidation, which gives them an additional cardioprotective effect in hypertensive subjects. On that account, phenolic compounds from *Olea europaea* L. as a dietary supplement to prevent hypertension deserve consideration. The ingestion of FVOO enriched with its own polyphenols should also be considered as a potential alternative to improve endothelial function in hypertensive patients.

Besides, flavonoids have shown to modulate BP by increasing the production of NO and by ACE inhibition, which is the regulatory enzyme of RAAS and represents an important pharmacological target in the fight against hypertension. Yet, further investigation is required to analyse and interpret this mechanism of ACE inhibition.

On the other hand, administration of OLE have provided a prophylactic effect against BP elevation in hypertensive animals in the reviewed investigations. In general, hypotensive effects of OLE have been greater in the high-dose treatment groups, with 1000 mg/day being the highest and showing comparable results with Captopril in its effective doses. Nevertheless, since this is a very high dose, the most effective dose to recommend for human administration is still unclear and more research is needed. Therefore, OLE has been proved to be safe and tolerable in hypertensive patients and represents a potential therapeutic tool in hypertension treatment.

In conclusion, the hypotensive activity is provided by the combination of bioactive compounds fatty acids, polyphenols and pentacyclic triterpenes, which act synergistically but also isolated, involving various mechanisms related to the pathogenesis of hypertension. The present review, supports the traditional use of *Olea europaea* L. as antihypertensive agent and provide convincing evidence for the clinical use of its bioactive phytochemicals in the medicine of the future.

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