Antihypertensive phytocomplexes of proven efficacy and well-established use: mode of action and individual characterization of the active constituents

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ABSTRACT

Hypertension has become the leading risk factor for worldwide cardiovascular diseases. Conventional pharmacological treatment, after both dietary and lifestyle changes, is generally proposed. In this review, we present the antihypertensive properties of phytocomplexes from thirteen plants, long ago widely employed in ethnomedicines and, in recent years, increasingly evaluated for their activity *in vitro* and *in vivo*, also in humans, in comparison with synthetic drugs acting on the same systems. Here, we focus on the demonstrated or proposed mechanisms of action of such phytocomplexes and of their constituents proven to exert cardiovascular effects. Almost seventy phytochemicals are described and scientifically sound pertinent literature, published up to now, is summarized. The review emphasizes the therapeutic potential of these natural substances in the treatment of the 'high normal blood pressure' or 'stage 1 hypertension', so-named according to the most recent European and U.S. guidelines, and as a supplementation in more advanced stages of hypertension, however needing further validation by clinical trial intensification.

1. INTRODUCTION

Worldwide cardiovascular diseases (CVDs) are the principal cause of death, representing around one-third of all global deaths (http://www.who.int/cardiovascular_diseases/en/). The combination of several factors, such as obesity, tobacco use, unhealthy diet, physical inactivity, and hypertension (HTN) commonly increases risk of CVDs development (Pierdomenico et al., 2009). Globally, in last decades, HTN has become the leading risk factor for CVDs, accounting for 9.4 million deaths and 7% of global disability-adjusted life years (Campbell et al., 2015). Compared with 1990, the impact of high blood pressure (BP) has increased by 2.1 million deaths. Overall, the prevalence of hypertension in adult population is 30-45%, with a proportional increase in relation to the aging (Whelton et al., 2018). Therefore, the need of innovative strategies for more effective prevention and treatment is mandatory.

Based on data related with CVD risk and on evidences from multiple RCTs of treatment with antihypertensive medication and of life-style improvement, blood pressure has been categorized into several levels and HTN is defined as office systolic BP (SBP) values ≥140 mmHg and/or diastolic BP (DBP) values ≥90 mmHg (Williams et al., 2018). HTN is etiologically classified as *primary* or *essential,* accounting about 90-95% of all cases and *secondary,* when related to other pathological conditions such as renal arteries stenosis, heart or endocrine system diseases (Beevers et al., 2001).

Although the pathogenesis of *essential* HTN is still far to be completely understood, in general population consistent data suggest that overweight and obesity are associated with increased BP (MacMahon et al., 2009). According to the most recent international guidelines (Whelton et al., 2018; Williams et al., 2018), managing of subjects with high BP should focus on overall patient health, with a particular emphasis on reducing the risk of future adverse CVD outcomes. Therefore, management of BP lower but closed to HTN threshold, in the absence of concurrent CVDs, should primarily consider nonpharmacological treatment. As patient BP and risk of future CVDs events increase, a more intense BP management with pharmacological treatment is to be considered. The most effective nonpharmacological interventions in lowering BP, which reached adequate class of recommendation and level of evidence (Whelton et al., 2018; Williams et al., 2018), include weight loss, the DASH (Dietary Approaches to Stop Hypertension) diet, sodium reduction, potassium supplementation, increased physical activity and a reduction in alcohol consumption (Whelton et al., 2018; Williams et al., 2018; Lim, 2018; He et al., 2013).

As a second line therapy, improvements of lifestyle have to be associated with pharmacological therapy. Antihypertensive agents act primarily through interaction with individual targets, but new cocktail formulations that contain more than one active component are emerging and multitarget antihypertensive drugs are considered the most innovative and effective strategy to help to counteract the pathological events that characterize this disorder (Kellici et al., 2015). Conventional pharmacological treatment for hypertension includes diuretics, renin angiotensin aldosterone system inhibitors, β-receptors blockers, calcium channel blockers, α1-receptor blockers and central α2-receptor agonists (Laurent et al., 2012; Whelton et al., 2018).

According to the most recent European guidelines (Williams et al., 2018), the defined High Normal BP (SBP 130-139 mmHg and/or DBP 85-89 mmHg) or stage 1 HTN (SBP 130–139 mmHg or DBP 80–89 mm Hg), according to the U.S. classification (Whelton et al., 2018), are recognized as risk factors in developing CVDs (Guo et al., 2013; Huang et al., 2013; Shen et al., 2013), mostly when associate with other CV risk factors (Materson et al., 2017; Berry et al., 2012). For the subjects with these BP levels, according to the above guidelines, BP-lowering drug treatment is not recommended, but it may be considered when CV risk is very high due to established CVD. Therefore, an early identification and a prompt treatment are strongly suggested. With the aim of preventing or delaying the administration of classical pharmacological therapy, with consequent related adverse events (Elliot, 2009), an improvement of lifestyle could be combined with a different approach in the early stages of HTN (Sirtori et al., 2015; Cicero and Colletti, 2017) representing the appropriate target for nutraceuticals, which are defined as foods or parts of foods providing some medical or health benefits, but even more for phytotherapeutics or herbal medicines. Phytotherapy, which is based on the combined action of a mixture of constituents, namely of one or more phytocomplexes, can be seen as a multi-target therapeutic approach *ante litteram*, which offers new treatment opportunities, in particular for diseases, such as hypertension, with a defined pre-pathological state and a multi-factorial genesis (Efferth and Koch, 2011). Conventional drugs are “magic bullets” and act on one target, while herbal drugs on many targets. Moreover, many cases exemplify synergistic and/or potentiating effects among herbal drugs constituents, whereby phytotherapeutics may exhibit greater effects than the sum of the effects of the individual components and bioactivity-guided fractionation may lead to substantial decrease or loss of activity. Indeed, dissecting the individual contribution of single phythochemicals to a synergism in bioactive phytocomplexes is a major issue and the mechanistic reasons for interactions vary and are frequently unknown. Different methods are reported to investigate combined effects of active constituents, but, in any case, individual pharmacological characterization of the phytocomplexes components is obviously essential (Efferth and Koch, 2011). The anti-hypertensive actions of phytochemicals are likely related to their anti-inflammatory, anti-oxidant, anti-angiogenic, anti-hyperlipidemic and anti-ischemic properties (Vasanthi et al., 2012). Furthermore, as here reviewed, evidences have been increasingly collected in the last decades that many of them exert their antihypertensive effects also through more specific mechanisms, such as, for instance, ACE inihibition, calcium channel blockade or diuresis. Indeed, the effects of the antihypertensive phytotherapeutics are a complex and, to some extent, unpredictable combination of more than one activity. Therefore, in the field of herbal drugs, it is necessary to define the mode of action of both individual active substances and their mixtures. This review, in the crowded landscape of reports claiming the hypotensive properties of a multitude natural products, wishes to present thirteen antihypertensive phytocomplexes, which have passed an updated literature screening based on the criterion of availability of *in vitro*, *in vivo* and clinical evidences of effectiveness, and, for each of these phytocomplexes, the constituents that have been individually characterized for antihypertensive activity and action mechanism.

The literature has been searched using Pubmed to identify published data concerning the anti-hypertensive effects of the phytocomplexes without date limitation. These were initially selected using Pubmed, Pharmacopoeias and books describing the plants used in Folk Medicine and a further selction was made based on plants allowed in food supplements according to Italian legislation and for which the claim “Regularity of arterial pressure” is authorised. Subsequently, we

searched the studies on single phytochemicals, demonstrated responsible for the antihypertensive effects of the thirteen selected plants, using Scifinder and the keywords 'hypertension' and 'antiypertensive'. While not applying date filters, almost all found references were after the year 2000.

2. PHYTOCOMPLEXES AND PHYTOCHEMICALS TARGETING HYPERTENSION

2.1. Morus alba L.

Morus alba L., commonly known as mulberry, is a plant widely used for the prevention and treatment of several cardiovascular ailments, primarily in Chinese, Japanese and Korean Traditional Medicines. Phytochemical analysis revealed the presence, in MA leaves, of flavonoids, chalcones, phenolic acids, polyphenols, and benzofurans (moracins) (Doi et al, 2001; Katsube et al., 2006; Memon et al., 2010; Yang et al., 2010).

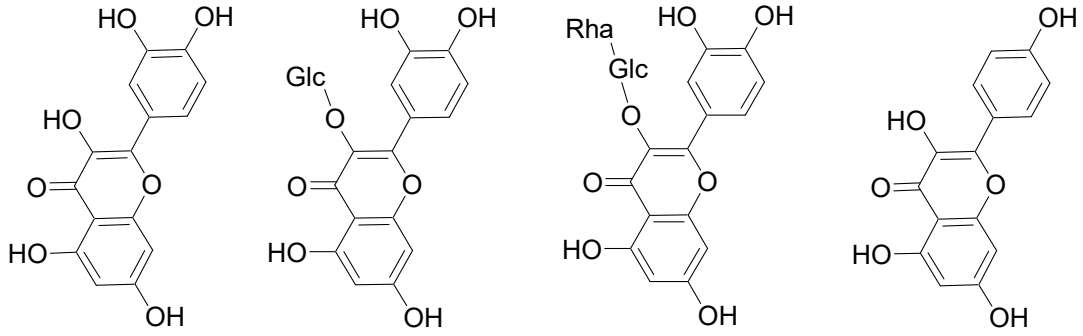
The most soundly documented modes of action of *M. alba* leaves and leaf extracts resulting in hypotensive effect are: calcium channel blockade, α1-antagonism, increased endothelium NO production. The ethyl acetate extract from *M. alba* leaves caused a concentration-dependent relaxation of the intact and endothelium-denuded aortas precontracted by KCl, suggesting a calcium antagonistic effect towards voltage operated calcium channels. In addition, this extract inhibited aorta smooth muscle contraction elicited by phenylephrine, suggesting its ability to suppress inositol trisphosphate and/or ryanodine receptor-dependent release of intracellular calcium (Xia et al., 2008). Carrizzo (Carrizzo et al., 2016) demonstrated that, in mice vessels, the extract from *M. alba* leaves evokes vasodilation, which was reverted by L-NAME, thus proposing the involvement of endothelium in its activity. Furthermore, this effect seemed to be also mediated by the activation of the stress sensors and chaperones Protein Kinase RNA-like Endoplasmic Reticulum Kinase and heat shock protein 90, which, in turn, induced the phosphorylation of endothelial isoform of NO synthase (eNOS). These data were confirmed also *in vivo*, as the oral administration of the extract was ineffective in eNOS-deficient mice, while it caused a decrease in BP in the wild type strain.

In addition, the oral administration of a *M. alba* leaf extract to diabetic rats was shown to lower the increased systolic BP, diastolic BP and mean arterial pressure and to restore the vascular responses to the vasodilators as acetylcholine and sodium nitroprusside (Naowaboot et al., 2009). These results are consistent with those obtained by Lee (Lee et al., 2011), who observed that the oral administration of a water extract from *M. alba* leaves decreases BP and partially restores the relaxation to acetylcholine of aortic rings from rats fed with an atherogenic diet.

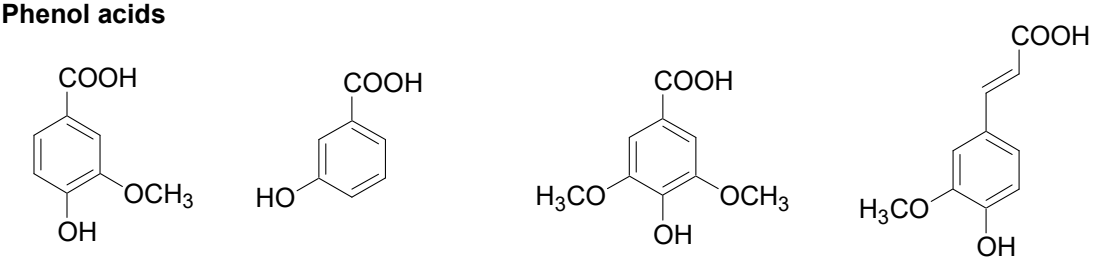
Further effects that may contribute to inhibit hypertension may be due, at least in part, to the antioxidant and antiatherosclerotic activities of *M. alba* leaf extract (Enkhmaa et al., 2005) and to mulberry leaves antidiabetic, antibacterial, anticancer, hypolipidemic, and anti-inflammatory properties, likely due to moracins (Naik et al., 2015). In particular, there are sound documented evidences for the effectiveness of *M. alba* leaf extract in control of hyperlipidemic conditions and in management of obesity (Trimarco et al., 2017; Lupo et al., 2019; Mahboubi, 2019).

Figure 1 reports the structures of the compounds that individually exert an antihypertensive effect and whose mode of action has been investigated. They can be structurally grouped into flavonoids, phenol acids and polyphenol acids. Stevioside stands alone.

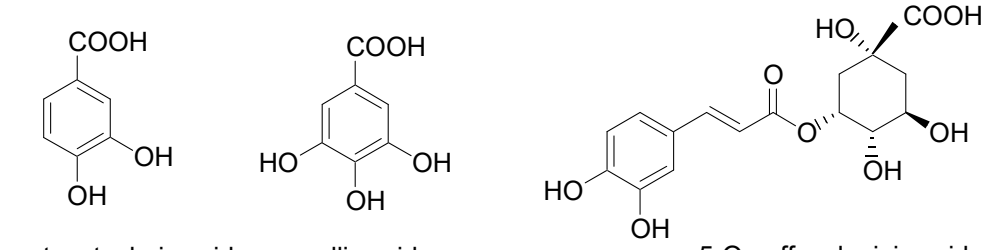
Flavonoids



Phenol acids



Polyphenol acids



Stevioside

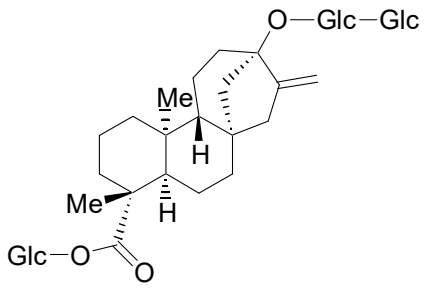


Fig. 1. Chemical structure of the compounds found in *Morus alba* L. for which the antihypertensive effect was individually demonstrated and investigated.

Enhancement of endothelial NO production is the most frequently invoked mode of action for flavonoids, namely quercetin, its more bioavailable glycosides, isquercitrin and rutin, and for kaempferol (Emura et al., 2007; Wani, 2017). In addition, for kaempferol, prevention of the angiotensin II effects has been recently documented (Chen et al., 2016), while ACE inhibition and direct and endothelium independent vascular smooth muscle relaxation through calcium channels blockade has been not excluded for quercetin (Larson et al., 2010). Reduction of oxidative stress due to antioxidant properties and consequent increased bioavailability of nitric oxide is widely documented for phenol and polyphenol acids which are present in *M. alba* leaves, namely vanillic acid (Kubar et al., 2014; Kumar et al., 2012b),

syringic acid (Kumar et al., 2012a; Kumar et al., 2012b), ferulic acid (Jain et al., 2018), protocatechuic acid (Juurlink et al., 2014; Safaeian et al., 2018), and 5-O-caffeoylquinic acid (Suzuki et al., 2006). For gallic acid, recent studies have demonstrated its antihypertensive effect via regulation of histone deacetilase 1 or 2 (Jin et al., 2017), while, among the hydroxybenzoic acid isomers exerting activity on cardiovascular system, 3-hydroxybenzoic acid has been proposed for reduction in adipocyte lipolysis by activation of the hydroxycarboxylic acid receptors with potential improvements of blood lipid profiles (Juurlink et al., 2014). Lastly, the antihypertensive effect of stevioside has been imputed to its inhibitory action on calcium influx into smooth muscle cells of blood vessels (Lee et al., 2001).

2.2. Mangifera indica Linn

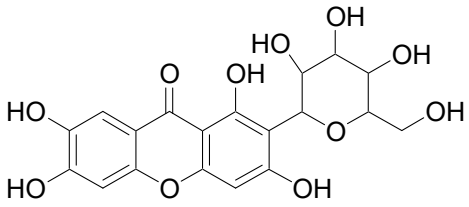
Mangifera indica Linn (Anacardiaceae) fruits, commonly known as "mango", are widely used in the tropical and subtropical regions. In folk medicine of Africa and India, stem bark- and leaves-based preparations are considered as useful tools for the treatment of several diseases, including gastrointestinal, SNC and cardiovascular pathologies, in particular hypertension (Burkill et al., 1985; Eridiweera et al., 2017; Shah et al., 2010).

Mango leaves extracts contain an essential oil, sugars, xanthones, including mangiferin, gallates, gallotannins, ellagitannins, benzophenones and flavonoids, the most important of which is quercetin-3-O-sophoroside (quercetin-3-O-α-glucopyranosyl-(1→2)-β-glucopyranoside) (Qudsia and Arshad, 2009).

A *M. indica* stem bark water extract reverted both noradrenaline- and thromboxane A2 (TP) analogue U46619-induced contraction in rat mesenteric resistance arteries, suggesting the ability of the extract to act as a non-competitive antagonist of TP receptors (Beltran et al., 2004). Further mechanisms that may contribute consist in the extract ability to inhibit the expression of different inflammatory mediators such as leukotriene B4 and prostaglandin E2 production in calcium ionophore and lipopolysaccharide-stimulated macrophages, respectively (Delgado Hernandez et al., 2001). In addition, a *M. indica* leaves dichloromethanic fraction exerts an ACE-inhibitory activity similar to captopril either *in vitro* and *in vivo*, suggesting flavonoids as main contributors to this activity (Ronchi et al., 2015).

Mangiferin is the constituent of mango individually investigated for its antihypertensive effects (Figure 2). It alleviates hypertension induced by hyperuricemia via increasing NO releases and improving endothelial function (Yang et al., 2018) and it has been found to exert anti-hepatosteatotic effects in fructose-fed spontaneously hypertensive rats (Xing et al., 2014). However, the demonstrated inhibitory effect of mango extracts on vasoconstrictor responses would be mediated by other constituents (Beltran et al., 2004), reasonably the many flavonoids and isoflavonoids because mangiferin itself has little effect on blood pressure (Yao et al., 2017).

Xanthones



mangiferin

Fig. 2. Chemical structure of mangiferin, found in *Mangifera indica* L. and investigated for its antihypertensive effects.

2.3. Hibiscus sabdariffa L.

Hibiscus sabdariffa L. (Syn: Roselle, Rozelle, Indian sorrel, Sour tea and Karkade) has been used for several purposes in folk medicine. In India, Africa and Mexico, leaves or calyces are used to prepare infusions that are believed to exert choleretic, febrifugal, diuretic, and hypotensive effects (Da-Costa-Rocha et al., 2014).

The chemical composition of *H. sabdariffa* extracts includes hibiscus acid, hibiscus acid glucosides, caffeoylquinic acids, flavonoids such as quercetin-3-rutinoside, kaempferol-3-O-rutinoside, myricetin, anthocyanins such as delphinidin-3-sambubioside and cyanidin-3-sambubioside (Fig. 3) (Da-Costa-Rocha et al., 2014; Ramirez-Rodrigues et al., 2011).
H. sabdariffa tea has been shown to be able to lower food intake, decrease lipogenesis, increase lipolysis, stimulate fatty acids β-oxidation and attenuate inflammatory responses and oxidative stress (Herranz-Lopez et al., 2017).
H. sabdariffa extracts decrease BP in normotensive and hypertensive animals by several mechanisms (Mojiminiyi et al., 2007; Onyenekwe et al., 1999). A methanolic extract from *H. sabdariffa* calyces reduces the rat aorta rings contractions induced by KCl and phenylephrine (Ajay et al., 2007), suggesting its ability to inhibit calcium influx. The relaxant effect of the hibiscus flower extract was also observed in guinea pig aorta and ileum, where it exerts a calcium antagonistic effect (Micucci et al., 2015). In addition, it was also demonstrated that the vasorelaxation was possibly mediated by the endothelium-derived nitric oxide-cGMP-relaxant pathway and by the inhibition of calcium-influx into vascular smooth muscle cells, as it was inhibited by removal of endothelium and by the presence of atropine, L-NAME or methylene blue (Ajay et al., 2007).
Another effect responsible for the hypotensive activity is ACE inhibition, which is due, at least in part, to delphinidin-3-sambubioside and cyanidin-3-O-sambubioside (Fig. 3) (Ojeda et al., 2010).
In vivo experiments demonstrated that the oral administration of the water extract from *H. sabdariffa* calyces to male albino Sprague–Dawley rats causes a diuretic effect (Alarcon-Alonso et al., 2012) probably related to quercetin. Polyphenol water extract, in fact, seems to inhibit ATPase activity (Mezesova et al., 2010) affecting the Na^+/K^+ concentration gradient in nephron tubular segment epithelial cells. In addition, the diuretic- as well as natriuretic- and potassium sparing-effects of the extract seems to be due to *H. sabdariffa* ability to downregulate aldosterone (Jimenez-Ferrer et al., 2012).
Interestingly, the hypotensive activity was observed also in humans (Nwachukwu et al., 2015). In particular, clinical studies demonstrated that the administration of *H. sabdariffa* extracts to hypertensive patients reduces BP (Nwachukwu et al., 2015; Herrera-Arellano et al., 2004; Herrera-Arellano et al., 2007; McKay et al., 2010; Nwachukwu et al., 2017). In a double-blind placebo-controlled clinical trial, daily consumption of *H. sabdariffa* L. calyx powder decreased systolic BP and serum triglycerides in metabolic syndrome patients (Asgary et al., 2016). In addition, the polyphenol content influences the course of obesity (Rodriguez-Perez et al., 2017). Moreover, *Hibiscus sabdariffa* consumption was reported to improve renal function in a population study of Nigerians with mild to moderate hypertension (Nwachukwu et al., 2017).
The compounds contained in *H. sabdariffa* extracts and individually studied for antihypertensive effects are caffeoylquinic acids, in particular the 5-caffeoyl regioisomer, and rutin previously mentioned as active constituents of *M. alba* leaves and leaf extracts. In addition, studies have been dedicated to hibiscus acid and garcinia acid, to the flavonoid myricetin and to the glucosides of the anthocyanins delphinidin and cyanidin (Fig. 3). The two acids exert vasorelaxant action likely due to the inhibition of Ca^{2+} influx via voltage-dependent Ca^{2+} channels (Zheoat et al., 2019). Myricetin has been proved to significantly inhibit atherogenesis (Sasaki et al., 2018) and it could prevent the development of high blood pressure induced by a diet rich in fructose (Godse et al., 2010). Lastly, ACE inhibition and decreasing of its mRNA production have been demonstrated for the two antocyanins and quercetin (Ojeda et al., 2010; Parichatikanond et al., 2012).

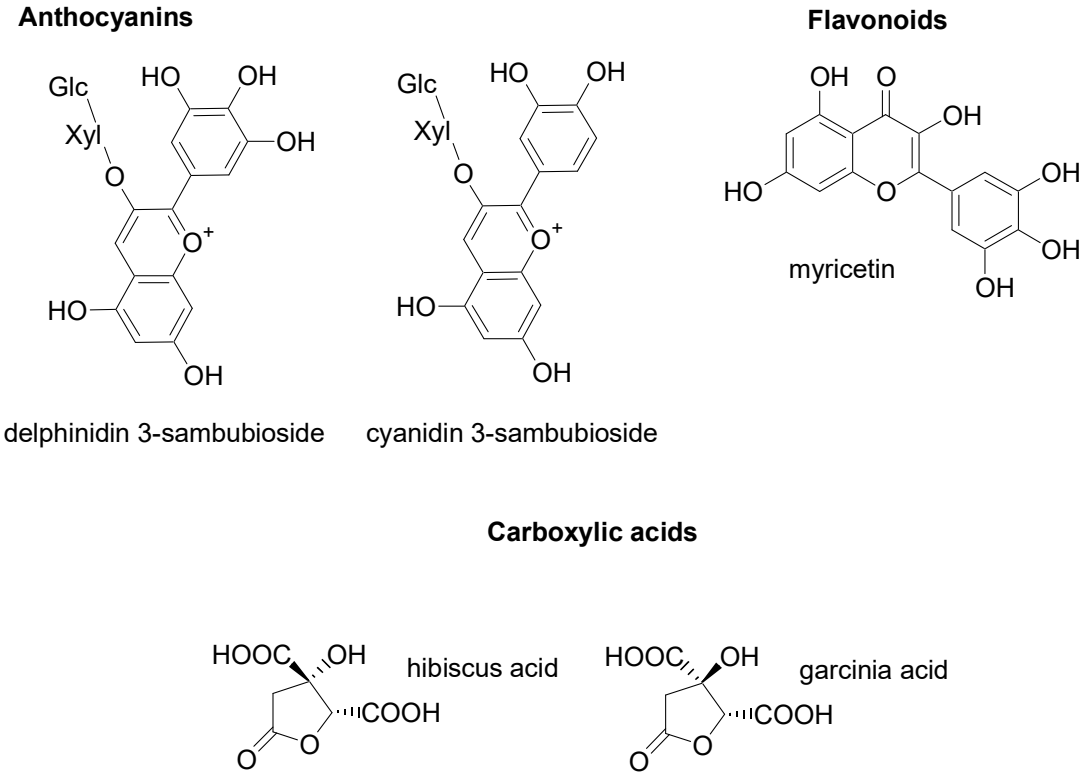


Fig. 3. Chemical structure of the compounds contained in *Hibiscus sabdariffa* extracts whose vascular and blood pressure effects were investigated.

2.4. Eucommia ulmoides Oliv.

Eucommia ulmoides Oliv. is a medicinal plant widely used for medical purposes in China. In Traditional Chinese Medicine, in fact, it is used as a treatment for hypertension, rheumatoid arthritis, kidney deficiency pain, weak bones, bone fractures and joint diseases, as well as lower back pain. (Xing et al., 2019)

The main compounds isolated from *E. ulmoides* are lignans, flavonoids, iridoids, phenolic acids, steroids and terpenoids. Fatty acids, polysaccharides, amino acids, microelements, vitamins were also detected (He et al., 2014).

The antihypertensive effect of *E. ulmoides* leaves and bark occurs by several mechanisms, including inhibition of cAMP phosphodiesterase activity, modulation of NO and renin-angiotensin system, a direct blood vessel relaxant effect and an increase in coronary flow (Kwan et al., 2004; Luo et al., 2010; Hosoo et al., 2015). In particular, the vasorelaxant effect of *E. ulmoides* bark water extracts is, at least in part, endothelium-dependent, as it was antagonized by L-NAME and blue-methilene (Kwan et al., 2004). The water extract of the leaves also possesses vasorelaxant, endothelium-dependent properties (Jin et al., 2008).

Singly studied constituents of *E. ulmoides* extracts are depicted in Figure 4. They are the iridoids (cyclopentanpyrans) geniposidic acid and asperuloside, to which increased levels of adiponectin have been imputed (Hosoo et al., 2017) and, in the case of geniposidic acid, also enhanced secretion of atrial natriuretic peptide from cardiomyocytes (Nakamura et al., 2018). The glucosides of monoepoxylignans related to olivil and of bisepoxylignans related to pinoresinol have been proposed for inhibition of hypertensive vascular remodelling (Gu et al., 2011) and for enhancing plasma level of NO and lowering levels of angiotensin II and renin activities (Luo et al., 2010). A controlled, randomized clinical trial showed that the administration of 3 grams of an *E. ulmoides* bark extract standardized to eight percent pinoresinol di-beta-D-glucoside reduces BP, has β-adrenergic blocking activity and is well tolerated (Greenway et al., 2011).

Among the flavonoids, wogonin and its iduronic acid derivative, wogonoside, may contribute to the hypotensive effect by inhibiting both Ca^{2+} influx and Ca^{2+} release in isolated rat aorta (Qu et al., 2015), while oroxylin A may be relevant to the vasorelaxant effect by acting through an endothelium-dependent mechanism which involves endothelin 1 receptors (Akinyi et al., 2014) and the quercetin 3-galattoside, hyperin, may exert ACE inhibition (Nileeka Balasuriya and Vasantha Rupasinghe, 2011).

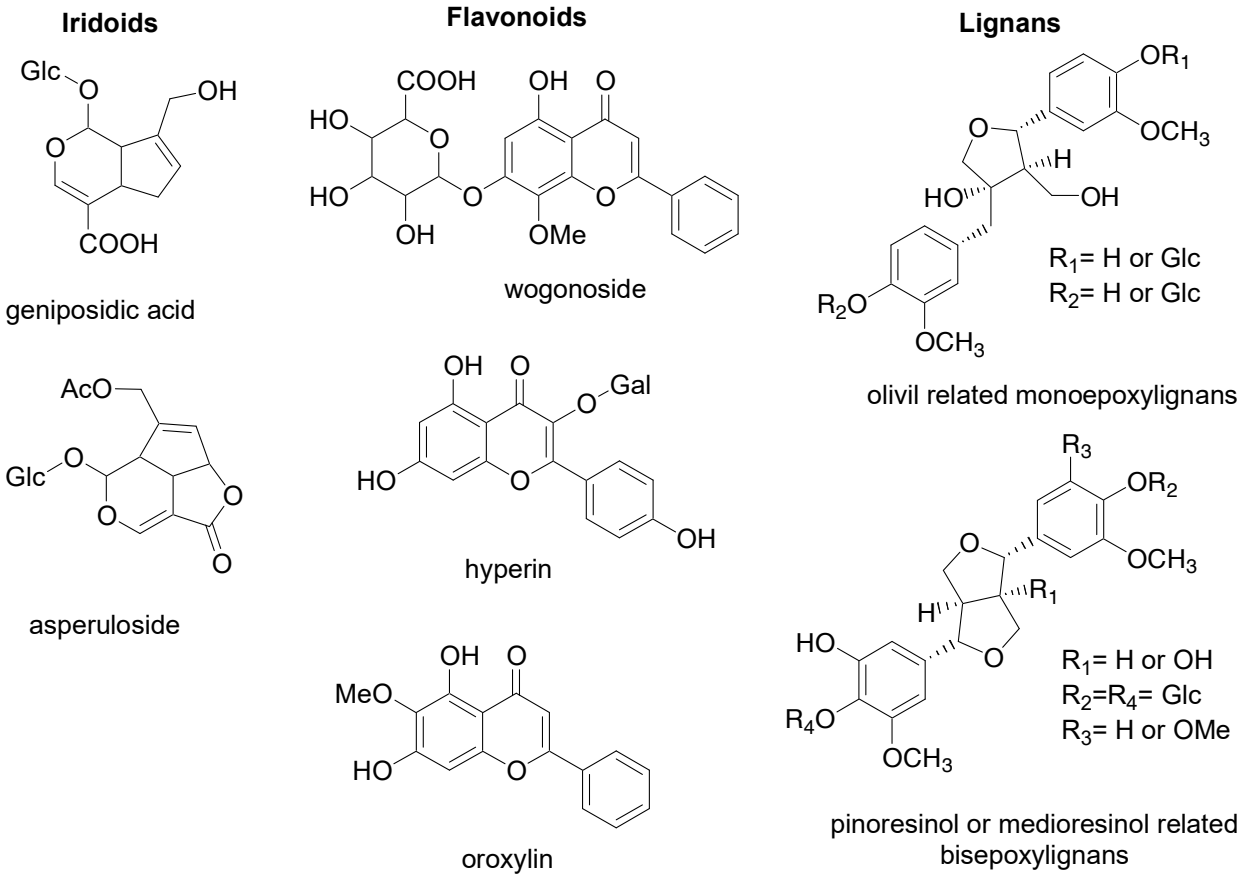


Fig. 4. Constituents of *E. ulmoides* singly studied for antihypertensive effects.

2.5. Elettaria cardamomum (L.) Maton

Elettaria cardamomum (L.) Maton, commonly known as cardamom, is widely used in India, Pakistan, Burma and Sri Lanka as a food and also as a vegetal drug for the treatment of several diseases including, among others, diarrhoea, dyspepsia, vomiting, and cardiovascular diseases (Duke, 2001). Extracts from cardamom fruits and seeds contain a wide number of cyclic and acyclic terpenes, with content prevalence of cineol and linalool, together with phytosterols (Shaban et al., 1987; Gopalakrishnan et al., 1990; Duke, 1992; Kuyumcu Savan and Kucukbay, 2013).

A crude extract from cardamom fruits was shown to relax in a concentration-dependent fashion endothelium-intact rat aorta rings pre-contracted with phenylephrine or KCl. In addition, this extract induced a concentration-dependent suppression of the atrial contractions (Gilani et al., 2008). The petroleum spirit, chloroform and the ethyl acetate fractions seem to be the most active as regards the vasorelaxant effects. These properties were confirmed *in vivo*, as the intravenous injection to anaesthetized rats resulted in a drop of arterial BP (Gilani et al., 2008). Furthermore, the administration of 3 grams of cardamom powder to patients with essential hypertension (primary hypertension) reduces systolic and diastolic BP, in addition to enhancing fibrinolysis and improving total antioxidant status (Verma et al., 2009).

Isolated components of cardamom extract characterized for antihypertensive activity are depicted in Figure 5. For cineol, the major constituent, antihypertensive effect was demonstrated in rats chronically exposed to nicotine and this effect was

associated with regulation of NO and oxidative stress (Moon et al., 2013). Another important constituent, linalool, was studied, free and β-cyclodextrin complexed, in both normotensive and hypertensive rats demonstrating antihypertensive effects associated to a direct action on the vascular smooth muscle leading to vasodilation, to increased vasodilator responsiveness and reduced sensitivity to the sympathetic agonist phenylephrine (Anjos et al., 2013; Camargo et al., 2018). For limonene, the blood pressure attenuation was imputed to antioxidant activity, lipid lowering and promotion of vascular remodelling (Santiago et al., 2010; Wang et al., 2018). Direct effect on the vascular smooth muscle leading to vasodilation was suggested for citronellol (Bastos et al., 2009; Ribeiro-Filho et al., 2016), while β-pinene was suggested to induce endothelium-independent vasorelaxation caused by the inhibition of the Ca^{2+} influx through L-type Ca^{2+} channel associated to a decrease in calcium sensitivity (Moreira et al., 2016).

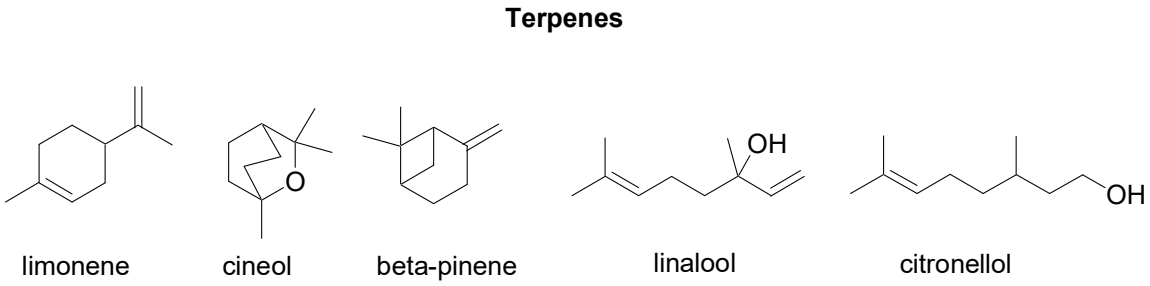


Fig. 5. Isolated components of cardamom extract characterized for antihypertensive activity.

2.6. Allium sativum L.

The use of *Allium sativum* L. (Garlic) is reported in several medical systems, including Egyptian, Greek and Indian traditions (Rivlin, 2001). Garlic-based preparations contain a large variety of phytochemicals including many organosulphides (alliin, allicin, S-allyl-cysteine, S-1-propenylcysteine, vinyldithianes and vinyldithiins, allixin, sulfides, such as diallyl-, methyl allyl-, and dipropyl mono-, di-, tri- and tetra-sulfides), flavonoids, saponins and sapogenins, phenolic compounds, amides and proteins (Kopec et al., 2013;Lanzotti et al., 2014; Rekowska and Skupien, 2009). The hypotensive activity of garlic occurs, at least in part, through an endothelium-dependent mechanism, as it inhibits the hypertensive effect of N(ω)-nitro-L-arginine methyl ester (L-NAME) in normal and two kidney-one clip (2K-1C) rats, and increases NO synthesis in *in vivo* and *in vitro* (Al-Qattan et al., 2006; Morihara et al.,2006). Fresh garlic extract exerts NO-dependent vasodilation (Ku et al., 2002) and fresh garlic homogenate inhibits angiotensin converting enzyme (ACE) and lowers BP in rats and guinea pigs (Asdaq and Inamdar, 2010). In addition, garlic and some related phytochemicals seem to modulate cellular sodium levels by inhibiting the activity of epithelial sodium channel (Krumm et al., 2012) and to augment urine sodium concentrations in urine in a kidney reperfusion injury model (Bagheri et al., 2011). It is also endowed of antihypertensive action in the 2K-1C model of hypertension, which is partly mediated by the interaction between prostanoids and the Na^+/H^+ exchanger isoforms 1 (Al-Qattan et al., 2003). Garlic extracts act also directly on vascular smooth muscle. Several garlic extracts and fractions, in fact, inhibit KCl and phenylephrine induced contractions in rats isolated aorta, suggesting calcium antagonistic and α-antagonistic properties (Ganado et al., 2004). A meta-analysis of randomized controlled trials showed that, respect to placebo, garlic is able significantly to decrease systolic and diastolic BP without any severe adverse effect (Xiong et al., 2015).

Allicin, S-allylcysteine, S-1-propenylcysteine, alliin, diallylsulfides and some dipeptides are the most studied garlic constituents (Fig. 6). Allicin exerts NO-dependent vasodilation (Ku et al., 2002), shows the ability to suppress cholesterol

biosynthesis and, by decomposition, it releases hydrogen sulphide, which lowers BP by relaxation of smooth-muscle cells (Borlinghaus et al., 2014). The above-mentioned inhibition of epithelial sodium channels by garlic has been imputed to allicin (Krumm et al., 2012). Allicin counteracts cardiovascular diseases in various ways and further efforts are necessary better to understand the molecular basis of its action. S-Allylcysteine was shown to exert angiotensin converting enzyme (ACE) inhibitory activity and to lower BP in rats and guinea pigs (Asdaq and Inamdar, 2010). Recently, S-1-propenylcysteine, but not S-allylcysteine, was shown significantly to decrease systolic BP of spontaneously hypertensive rats (Ushijima et al., 2018). Garlic ingredients, such as alliin, allyl disulphide and diallyl trisulfide result in significant increase of human endothelial cell NO production (Mousa and Mousa, 2007). Lastly, seven dipeptides with ACE inhibitory properties were isolated from garlic aqueous extracts and tested for ACE inhibition, finding that Phe-Tyr was the most potent one (Suetsuna, 1998).

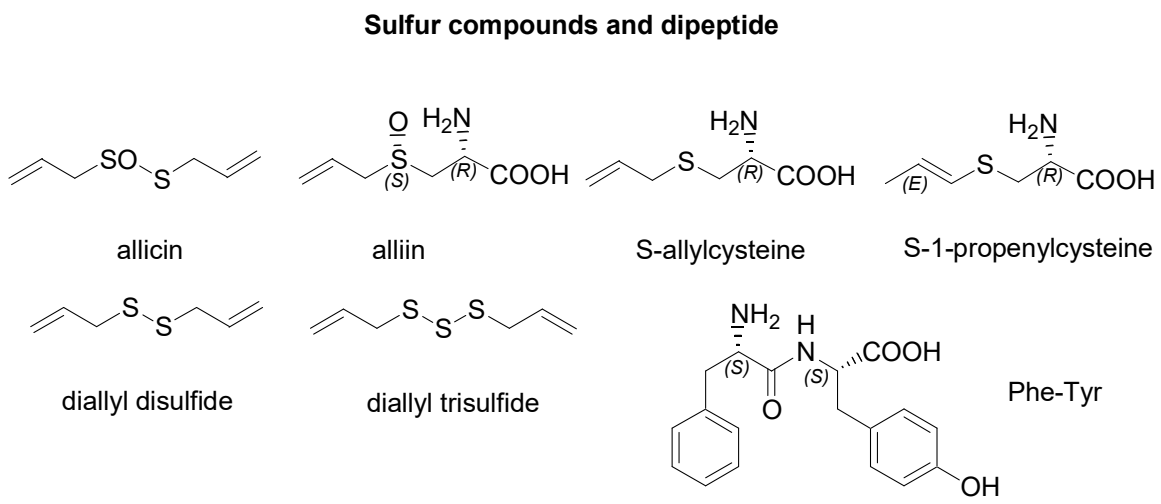


Fig. 6. The most studied garlic constituents.

2.7. Alpinia zerumbet (Pers.) B.L.Burtt & R.M.Sm.

Alpinia zerumbet (Pers.) B.L.Burtt & R.M.Sm is a tropical plant that originates in South America and Asia, whose leaves are used in folk medicine for the treatment of hypertension and gastrointestinal ailments.

Extracts from leaves mainly contain flavonoids, such as (+)-catechin, (-)-epicatechin, rutin, quercetin, kaempferol and its glucosides, and kava pyrones, including dihydro-5,6-dehydrokawain and 5,6-dehydrokawain (Mpalantinos et al., 1998). *A. zerumbet* leaves extract produces vasodilation in the mesenteric vascular bed, which was reverted by L-NAME and [1,2,3]oxadiazolo [4,4-a]quinoxalin-1-one (ODQ), suggesting the involvement of endothelium. This effect is due, at least in part, to activation of NO synthase and soluble guanylyl cyclase (GC), and to B2 bradykinin receptors antagonism (de Moura et al., 2005; Galleano et al., 2010). *In vivo* experiments showed also the involvement of endothelium-derived relaxing factors in the hypotensive action of *A. zerumbet* leaves extract (de Moura et al., 2005). Studies on the hypotensive activity of the purified flavonoids have been cited above (see *M. alba*). Here, two recent researches have to be mentioned which demonstrate the ACE inhibition activity of catechin (He, 2017) and the NO levels stimulation by epicatechin (Fig. 7) (Ramirez-Sanchez et al., 2018).

Essential oil, obtained by leaves, is also used. This contains a wide range of monoterpenes, of which terpinen-4-ol and 1,8-cineol are the main constituents (Fig. 7) (Lahlou et al., 2003; Pinto et al., 2009). The i.v. administration of the *A. zerumbet* essential oil to both Deoxycorticosterone acetate (DOCA) salt hypertensive and uninephrectomized, normotensive rats results in a decrease of BP (Lahlou et al., 2003), mainly due to terpinen-4-ol. The vasorelaxant effect

occurs also by an endothelium-independent mechanism, as *A. zerumbet* essential oil methanolic fraction, rich in terpinen-4-ol and 1,8-cineol, inhibits calcium influx, acting on receptor-operated calcium channels and voltage-operated calcium channels (VOCC) (de Cunha et al., 2013). Recently, terpinen-4-ol has been proved to change intracellular Ca^{2+} handling and to induce pacing disturbance in rat hearts (Gondim et al., 2017).

The plant has also properties of inhibiting the ox-LDL-mediated dysfunction of the vascular endothelium (Shen et al., 2012). In humans, the essential oil has effect on post-stroke muscle spasticity (Maia et al., 2016).

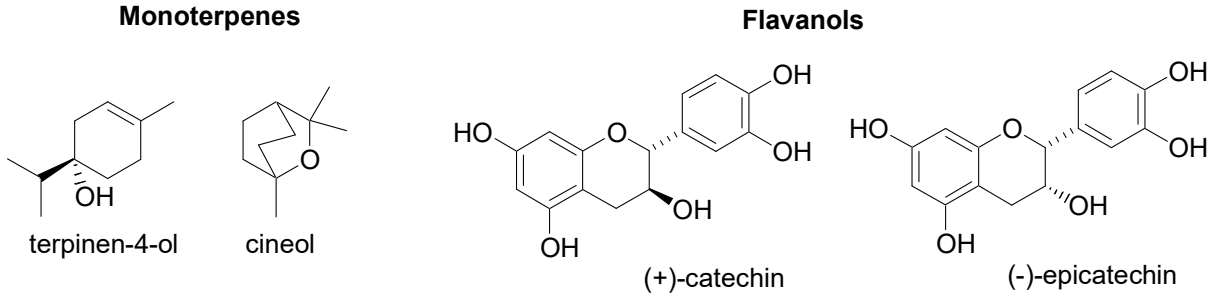


Fig. 7. Singly studied constituents of *A. zerumbet* essential oil (monoterpenes) and leaves extract (flavanols).

2.8. Aniba canelilla (Kunth) Mez

Aniba canelilla (Kunth) Mez (Lauraceae) [Syn. A. Elliptica A.C. SM., Cryptocarya canelilla Kunth], also known as ‘‘casca-preciosa’’, is a plant belonging to Lauraceae family, growing in the Amazon region. In Folk Medicine, the bark is used to prepare decoctions that are believed to exert antispasmodic, digestive stimulating, and carminative properties. Chemical composition of *A. canelilla* wood and bark oil includes benzenoids and terpenoids, 1-nitro-2-phenylethane and methyleugenol being the two major components (Fig. 8) (Giongo et al., 2017; Lahlou et al., 2005).

The essential oil causes a concentration-dependent reduction of potassium-induced contraction of rat aorta with endothelium and it counters $CaCl_2$-induced contractions, but not those induced by caffeine suggesting an inhibition of calcium inward current (Lahlou et al., 2005). In conscious rats pretreated with L-NAME, the hypotensive effect of the essential oil was partly, but significantly reduced supporting the essential oil ability to affect the endothelial L-arginine/nitric oxide pathway (Lahlou et al., 2005). These effects are mainly due to 1-nitro-2-phenylethane (Fig. 8), that was shown to induce vasorelaxant and hypotensive effects *in vit*ro and *in vivo* through a myogenic endothelium-independent mechanism (de Siqueira et al., 2010; Interaminense et al., 2011; Interaminense et al., 2013). The other main constituent, methyleugenol (Fig. 8), was also studied for its cardiovascular effects. In particular, it was found to elicit hypotension in either anesthetized or conscious rats through an active vascular relaxation, significantly reduced by pretreatment with L-NAME or mechanical endothelium removal (Lahlou et al., 2004; Magalhaes et al., 2008).

Ethanol extract of *A. canelilla* is also endowed of antioxidant properties (Martins et al., 2016).

Fig. 8. The main antihypertensive constituents of *A. canelilla* essential oil.

2.9. Arbutus unedo L.

Arbutus unedo L. belongs to Ericaceae species and, in Folk Medicine, it has been used for many diseases, including gastrointestinal and urological pathologies, hypertension and cardiac diseases. Ziyyat (Ziyyat et al., 2002) evaluated the effects of a decoction obtained from *A. unedo* roots, showing that it induced an endothelium-dependent relaxation of aorta.

In *A. unedo* roots water extracts, (+)-catechin and (−)-catechin gallate were found. Phenolic compounds, benzoic acid, caffeic acid and gallic acid were also detected (Miguel et al., 2014).

The Authors who studied the pharmacological properties of the plant focused on the investigation concerning the vasorelaxant effects of the decoction and the related mechanisms of action. The results showed that the water extract causes relaxation of rats isolated norepinephrine-precontracted aorta. This effect was endothelium-dependent and it was inhibited by L-NAME pretreatment or by ODQ. In addition, this effect was not related to endothelium muscarinic receptors activation as it was unaffected by atropine. The vasorelaxant effects may be due to the presence of polyphenolic compounds, including tannins and flavonoids, and the mechanism of action might involve the stimulation of endothelial nitric-oxide synthase (Ziyyat et al., 2002).

The antihypertensive effect of *A. unedo* roots decoction (250 mg/kg/day) and leaves infusion was assessed *in vivo*, using rats affected by hypertension induced by L-NAME (Afkir et al., 2008). The administration of the mentioned extracts and L-NAME prevented the increase in systolic BP, improved the vascular reactivity and baroreflex sensitivity, showing that chronic treatment with these extracts not only affects BP, but also exerts a protective activity towards cardiovascular and renal systems in NO-deficient hypertension. Also antiaggregant activity (El Haouari et al., 2007), as well as antidiabetic properties (Ziyyat et al., 1997), may contribute in providing cardiovascular protection.

Principal constituents of infusions and decoctions of leaves and roots examined for their antihypertensive activity are the phenolic compounds catechin, already mentioned, catechin 3-O-gallate, epicatechin 3-O-gallate, gallic acid and arbutin (Fig. 9) (Oliveira et al., 2011; Morgado et al., 2018). Catechin and epicatechin 3-O-gallates were proved to exert moderate inhibitory action on ACE (Liu et al., 2003), while gallic acid has been recently investigated for its antihypertensive activity in SHRs ascribed to its ability of attenuating oxidative stress (Jin et al., 2017). Lastly, arbutin was tested in a rat model of heart and mesenteric ischemia-reperfusion finding that it has antioxidant properties and reduces ROS production in mesenteric vessels (Broskova et al., 2013).

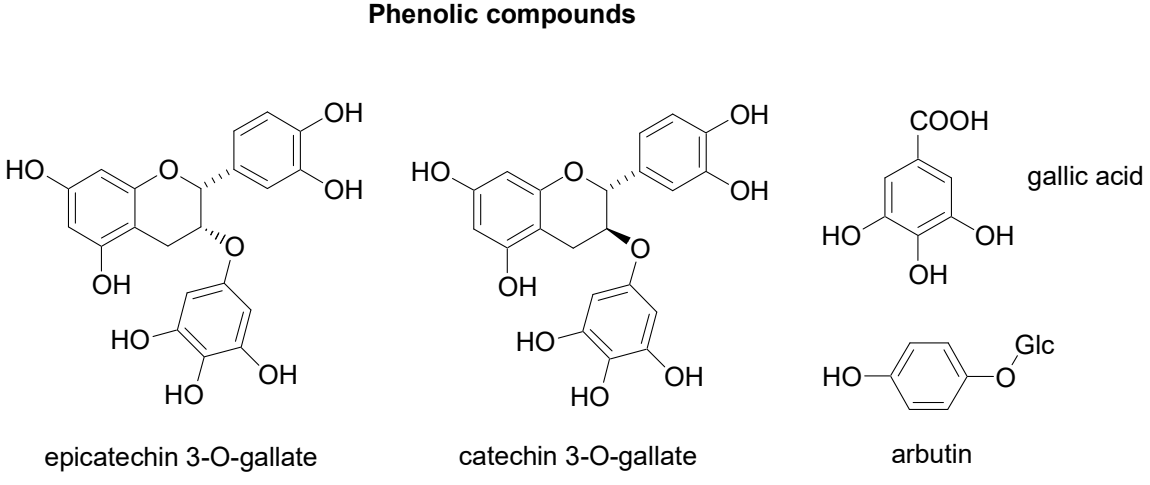


Fig. 9. Principal constituents of *A. unedo* infusions examined for antihypertensive activity.

2.10. Olea europaea L.

In folk medicine, this tree is mainly considered useful due to its diuretic, hypotensive, emollient, febrifuge and tonic actions and for urinary and bladder infections treatment.

Olea europaea L. leaves extract was shown to inhibit K^+-induced contraction in guinea pigs ileum and aorta, suggesting a calcium antagonistic effect (Scheffler et al., 2008; Micucci et al., 2015). The vasorelaxant and antihypertensive effects of *O. europaea* leaves extract were confirmed also by *in vivo* studies (Romero et al., 2016) and clinical trials (Susalit et al., 2011). The antihypertensive effect of the extract can be also related to factors involving reversal of vascular changes contributing to L-NAME-induced hypertension (Khayyal et al., 2002).

Quite recently, the combination of *O. europaea* leaves and *H. sabdariffa* flowers (13:2, respectively) has been proposed with the aim to obtain a mixture endowed with higher activity than the single components. In particular, it has been demonstrated that this mixture exerts a negative inotropic activity comparable to the singular phytocomplexes, and, at the same time, is endowed of additional properties such as vasorelaxant and a mild negative chronotropic-effect as well as higher *in vitro* cytoprotective and antioxidant activity (Micucci et al., 2015). On the basis of these results, a possible nutraceutical use of the above formulation for the management of preclinical hypertension has been suggested, especially in consideration of its antihypertensive effects along with its good toxicologic profile (Campbell et al., 2015). The combination of *H. sabdariffa* flowers and *O. europaea* leaves (2:1 respectively) is able to normalize *in vivo* BP in L-NAME-mediated hypertension. In this experimental model, the combination can also improve hepatic and renal dysfunction (Abdel-Rahman et al., 2017). Olive oil may also contribute providing cardiovascular beneficial effects, preventing LDL oxidation and maintaining normal blood HDL cholesterol concentrations as it contains oleuropein and hydroxytyrosol (Clodoveo et al., 2016; Roselli et al., 2017). According to EFSA, in fact, the daily administration of hydroxytyrosol (5mg) and its derivatives prevents LDL oxidation (Scientific opinion, EFSA Journal 2011, 9, 2033). In both leaves extract and olive oil, oleuropein and hydroxytyrosol have been demonstrated to be the main constituents responsible for the antihypertensive effects and cardiovascular benefits (Fig. 10). Hydroxytyrosol protects against the impairing effects of oxidative stress on the $NO^{\bullet}$-mediated relaxation of isolated rat aorta (Rietjens et al., 2007) and exhibits analogous antioxidant effects *in vivo* as demonstrated by studies on rats treated with cyclosporine, which causes oxidative stress, haemodynamic alterations and renal damages (Capasso et al., 2008). Recent reports have confirmed the beneficial antioxidant properties of hydroxytyrosol (Hu et al., 2014) and its ability to improve endothelial function and to lower systolic blood pressure in a diet-induced rat model of metabolic syndrome (Poudyal et al., 2017). Oleuropein attenuates, through ACE inhibition, the cardiac remodelling after infarction leading to excessive heart fibrosis (Mnafgui et al., 2015) and diminishes the increased ROS production in the hypothalamic paraventricular nucleus, associated to hypertension, by improving mitochondrial function (Sun et al., 2017).

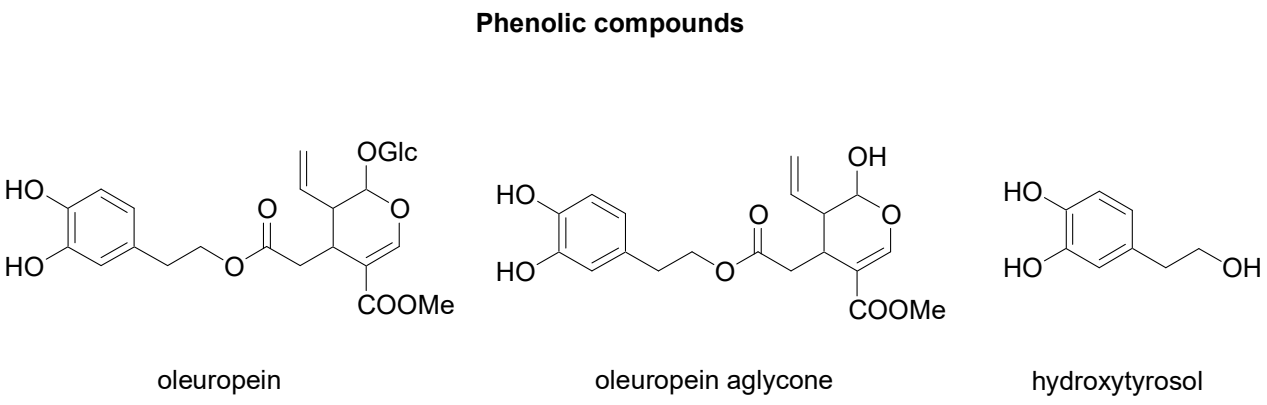


Fig. 10. The main constituents responsible for the cardiovascular benefits of *O. europaea*.

2.11. Punica granatum L.

Punica granatum L. currently known as Pomegranate, has been used in Uighur Medicine for the treatment of cardiovascular diseases. Chemical composition of pomegranate fruits extracts and juices include ellagitannins, such as punicalagin and ellagic acid, gallotannins, such as glucogallin and gallic acid, lactone derivatives, flavones such as luteolin, and anthocyans (Fig. 11) (Abdulla et al., 2017; Aguilar-Zarate et al., 2017; Brighenti et al., 2017; Garcia-Villalba et al., 2015). On the other hand, pomegranate seed oil mainly contains fatty acids like palmitic, stearic, oleic, linoleic, punicic acid, phytosterols including campesterol, stigmasterol, β-sitosterol, Δ5-avenasterol, β-amyrin, cycloartenol, citrostadienol (Caligiani et al., 2010; Siano et al., 2016).

The administration of pomegranate juice and fruit extract to rats fed with an atherogenic diet resulted in an increased acetylcholine-induced relaxation of aorta. This effect was less evident with pomegranate seed oil. In addition, pomegranate juice and fruit extract inhibited proatherogenic effects resultant from the altered shear stress. Pomegranate fruit extract administration increased vascular expression of eNOS and NOx levels, reducing Thrombospondin 1 and Transforming Growth Factor-β1 expression, augmenting the effects of NO and improving arterial functions in obese rats (De Nigris et al., 2007). The endothelium-dependent mechanisms for the antihypertensive effect of pomegranate hydroalcoholic extract was also reported by Delgado (Delgado et al., 2016), who demonstrated that it ameliorates endothelium-dependent coronary relaxation through the inhibition of eNOS phosphorylation and reduction of oxidative stress.

The modulation of renin-angiotensin system seems to be involved in the antihypertensive effect of pomegranate juice extract in diabetic rats, as its administration, by inhibiting ACE activity, prevented angiotensin II-mediated BP increase. A reduction in the diabetes-induced oxidative stress upon juice treatment was also observed (Mohan et al., 2010). Both antioxidant- and ACE-inhibitory-effects were also observed in an aging and spontaneously hypertensive rat model (Dos Santos et al., 2016).

Interestingly, ACE activity inhibition occurred also in hypertensive patients that were administered pomegranate juice (Aviram and Dornfeld, 2001) and was also sheared by other flavonoids such as luteolin (Loizzo et al., 2007), delphinidin−3-*O*-glucoside, cyanidin-3-*O*-glucoside, pelargonidin-3-*O*-glucoside (Hidalgo et al., 2012).

Finally, the *in vivo* hypotensive effect of pomegranate juice was reported to be accompanied by improved endothelial function caused by a decrease in Vascular Cell Adhesion Molecule 1 plasma concentration (Asgary et al., 2014). These properties, along with the inhibitory effect on oxidative stress and on serum ACE activity, made pomegranate juice an interesting supplement to be used against cardiovascular diseases.

The pomegranate effects towards NO are due, at least in part, to punicalagin (Chen et al., 2008; Shao et al., 2016), ellagic acid (Berkban et al., 2015; Ou et al., 2010; Olgar et al., 2014; Jordao et al., 2017), gallic acid (de Oliveira et al. 2016), flavonoids such as luteolin (Si et al., 2014), cyanidin−3-*O*-glucoside (Fratantonio et al., 2017). Furthermore, ellagic acid was found to prevent isoproterenol induced oxidative stress in myocardial infarction in rats through electrocardiological, biochemical and histological studies (Kanan and Quine, 2011). On the other hand, ACE inhibition and protection against angiotensin II activity were evidenced for luteolin (Loizzo et al., 2007; Nakayama et al., 2015).

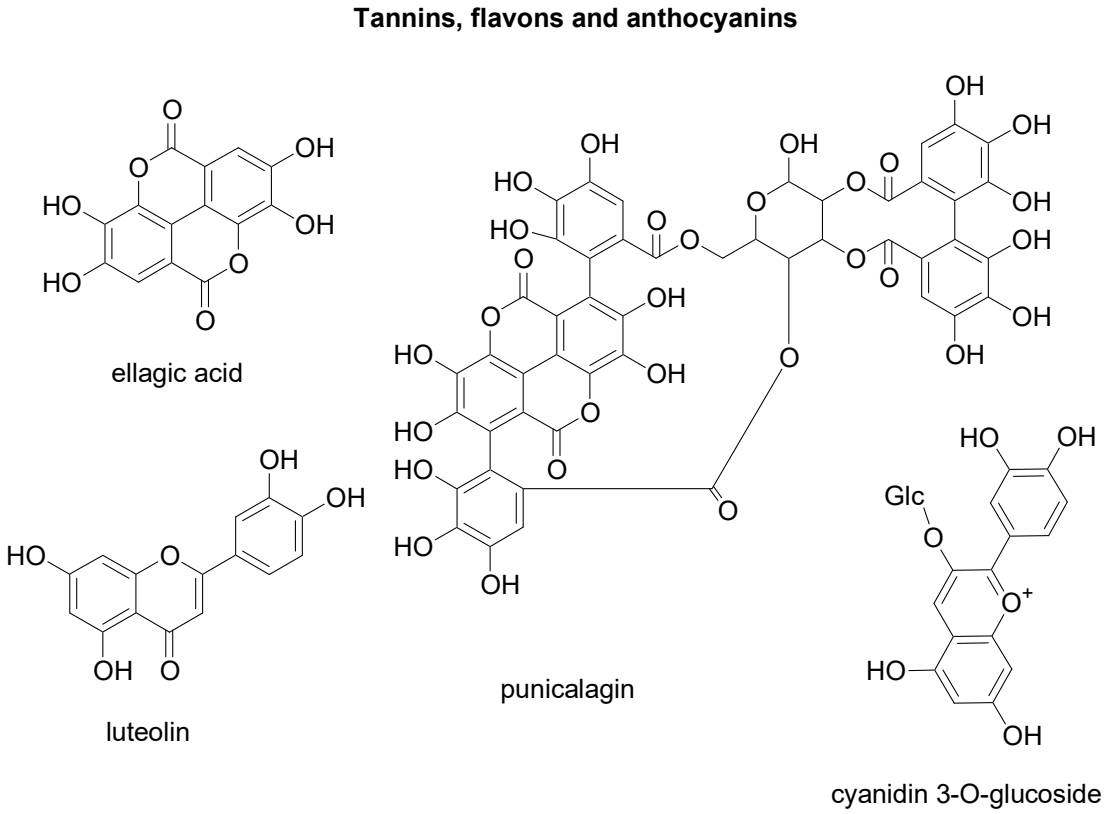


Fig. 11. Antihypertensive principles of pomegranate fruits extracts and juices.

2.12. Salvia miltiorrhiza Bunge

The dried roots from *Salvia miltiorrhiza* Bunge (Danshen in Chinese) have been used for the treatment of cardiovascular and cerebrovascular pathologies in China and Japan. The main phytochemicals isolated from *S. miltiorrhiza* roots are hydrophilic phenolic acids and lipophilic diterpene quinones (Liang et al., 2017).

The administration of a water-soluble extract of *S. miltiorrhiza* roots to rats resulted in a decrease of mean arterial BP, which was also observed in the tissues pretreated with phenylephrine (Leung et al., 2010).

These data are in agreement with those by Zhang (Zhang et al., 2016), who observed that i.p. administration of a *S. milthiorriza* water roots extract and of a mixture of four constituents of the extract caused hypotension in spontaneously hypertensive rats. This was the result of several activities such as the decrease in plasma levels of angiontensin II, endothelin-1, malondialdehyde, transforming growth factor-β1, superoxide dismutase, the mRNA expression levels of collagen type I, α-smooth muscle actin, nicotinamide adenine dinucleotide phosphate oxidases (NOX), the suppression of angiotensin II-mediated effects including ROS-generation, morphological changes in the thoracic aorta tunica media and adventitia thickness. The hypotensive effect of a water extract from *S. milthiorriza* was confirmed in 2KC-1C rats, where it mainly occurred by angiotensin converting enzyme inhibition (Kang et al., 2002).

In conclusion, the hypotensive action of *S. milthiorriza* is mainly due to ACE inhibition properties and thus to the decrease in plasma levels of angiotensin II and endothelin-1, to the suppression of ROS generation and vascular remodelling.

Figure 12 shows the main danshen constituents characterized for antihypertensive and cardiovascular effects. Salvianolic acid A is one of the above cited four components (Zhang et al., 2016) and it has been singly studied, in spontaneously hypertensive rats, for its ability to inhibit endothelial dysfunctions (Teng et al., 2016) and, in particular, to prevent cardiac remodelling through matrix metalloproteinase-9 (MMP-9) inhibition (Jiang et al., 2013; Zhang et al., 2014). For salvianolic acid B, another of the above four components (Zhang et al., 2016), ACE inhibition (Kang et al., 2003) and endothelial function restoring associated with angiotensin receptor AT_1 inhibition have been proposed (Ling et al., 2017).

Salvianolic acid A and B exert also antiatherosclerotic effects (Ba et al., 2014; Chen et al., 2011; Joe et al., 2012; Lin et al., 2007; Liu and Liu, 2002), while salvianolic acid B has been proved to inhibit platelets-mediated inflammation in vascular endothelial cells (Xu et al., 2015) and its magnesium salt, tanshinoate B, to decrease blood pressure also after treatment with phenylephrine (Leung et al., 2010) and to protect endothelium from hyperglycemia-induced dysfunction (Kim et al., 2010). Salvianic acid (danshensu), the third constituent (Zhang et al., 2016), seems to exert effects on several pharmacological targets in hypertension (Tang et al., 2011) and, in particular, it prevents pulmonary hypertension in rats inhibiting the proliferation of pulmonary artery smooth muscle (Zhang et al., 2018). For protocatechuic aldehyde, the last constituent of the four (Zhang et al., 2016), different mechanisms of action have been proposed in preventing atherosclerosis pathogenesis (Moon et al., 2012; Tong et al., 2016; Xing et al., 2012; Zhou et al., 2005).

The complex mechanisms underlying the antiatherosclerosis activity and protecting effects against cardiac hypertrophy of tanshinone IIA have been recently investigated evidencing the involvement of different signalling pathways (Wang et al., 2017; Zhao et al., 2016; Zhu et al., 2017; Pang et al., 2014; Feng et al., 2017; Wu et al. 2017). Therapeutic potential in ameliorating atherosclerosis through vasodilatatory, anti-coagulant, anti-thrombotic, anti-inflammatory, anti-oxidant, and immunomodulatory activities (Fang et al., 2018) strongly supports the option of using tanshinones from *S. milthiorriza*, in particular tanshinone IIA and cryptotanshinone, as a strategy to counteract atherosclerosis-related cardiovascular and metabolic diseases.

Interestingly, since hypertension is a common complication of type 2 diabetes mellitus, dihydrotanshinone I has been proposed as a substance with both anti-hypertensive activity, due to mineralocorticoid receptor antagonism, and antihyperglycemic effects (Liu et al., 2010). Diabetes-induced vascular dysfunction are attenuated by rosmarinic acid, which acts as a vasoactive substance and a cardioprotector through its antioxidant property (Karthik et al., 2011; Sotnikova et al., 2013; Javidanpour et al., 2017).

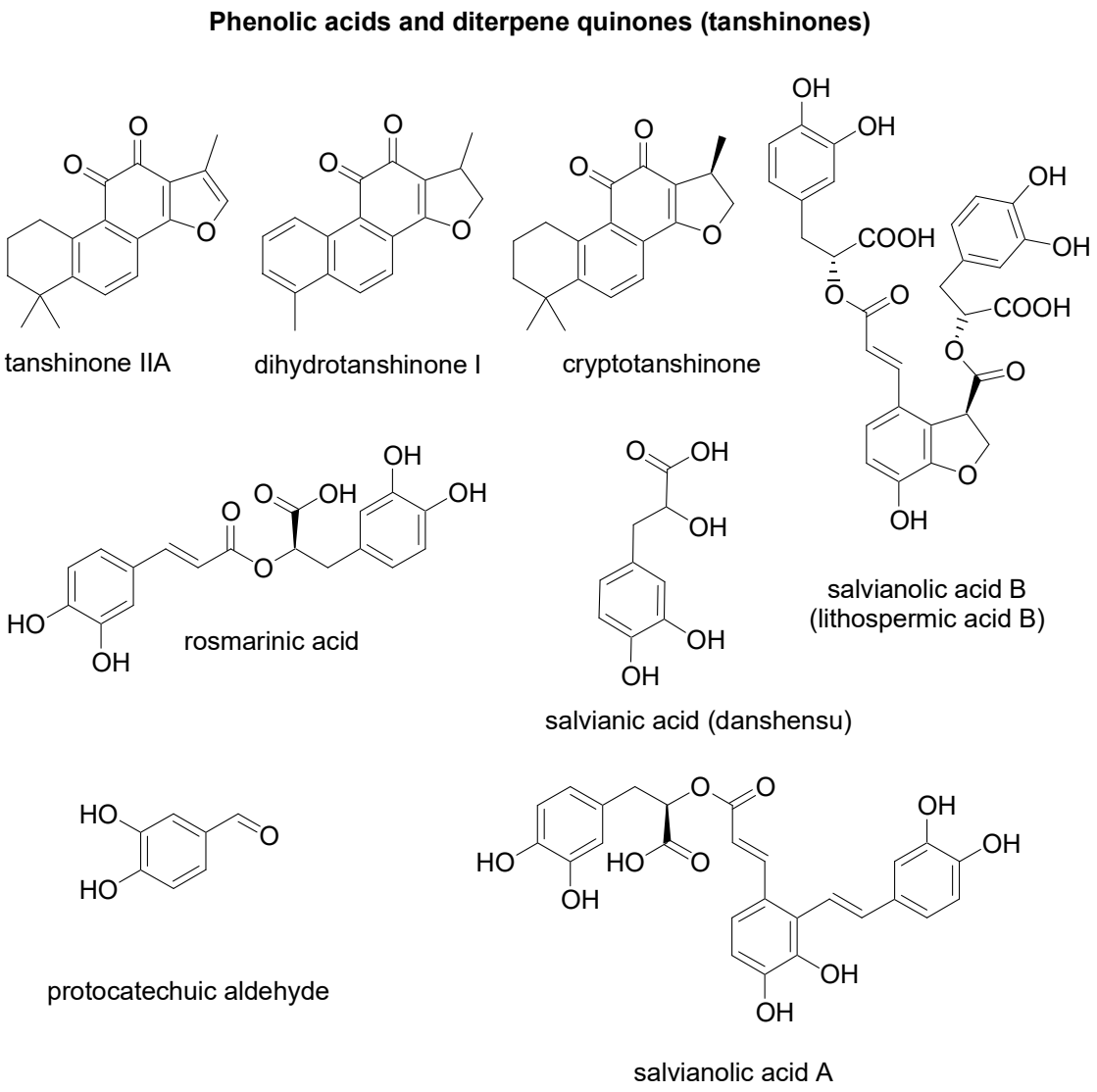


Fig. 12. The main danshen constituents characterized for antihypertensive and cardiovascular effects.

2.13. Zingiber officinale Roscoe

Zingiber officinale Roscoe rhizome is widely used in Ayurvedic medicine, as a treatment for gastrointestinal and cardiovascular ailments. The rhizome contains phenolic compounds and non-volatile pungent active principles including gingerols, paradols, shogaols and gingerones (Semwal et al., 2015).

A water extract from *Z. officinale* was shown to inhibit ACE activity in a concentration-dependent manner (Akinyemi et al., 2014). This effect occurs also *in vivo*, in rats fed with a high cholesterol diet (Akinyemi et al., 2014). The same extract reduces mean arterial BP in L-NAME induced hypertensive rats. Butanol and ethyl acetate fractions seem to be more active than the water fraction (Manosroi et al., 2013). Efficacy of ginger supplementation on BP in clinical trials has been recently reviewed (Hasani et al., 2019).

In vitro experiments on guinea pig isolated tissues showed that the decoction of ginger possesses weak negative inotropic and chronotropic intrinsic activities, along with a significant intrinsic relaxant activity on smooth muscle with a greater potency on ileum than on aorta. The study on the main pure components supports the relationship between 6- and 8-gingerol and 6-shogaol and these effects. These results are in agreement with the activity of calcium channel modulators, which influence more strongly the not vascular muscles than vascular one (Leoni et al., 2017). Previous researches had evidenced, for 6-, 8- and 10-gingerol and, to a minor extent, also for 6-shogaol (Fig. 13), a vasodilator effect through a

combination of NO releasing and calcium antagonist mechanism (Ghayur et al., 2005). More recently, 6-gingerol has been shown to attenuate the increased level of blood glucose and to improve cardiac hemodynamics in diabetic rats (El-Bassossy et al., 2016) and it has been identified as a novel angiotensin II type 1 receptor antagonist (Liu et al., 2013). Inhibition of TGF-β-stimulated biglycan synthesis by 6-gingerol suggests the potential role of ginger in the prevention of atherosclerosis (Kamato et al., 2013).

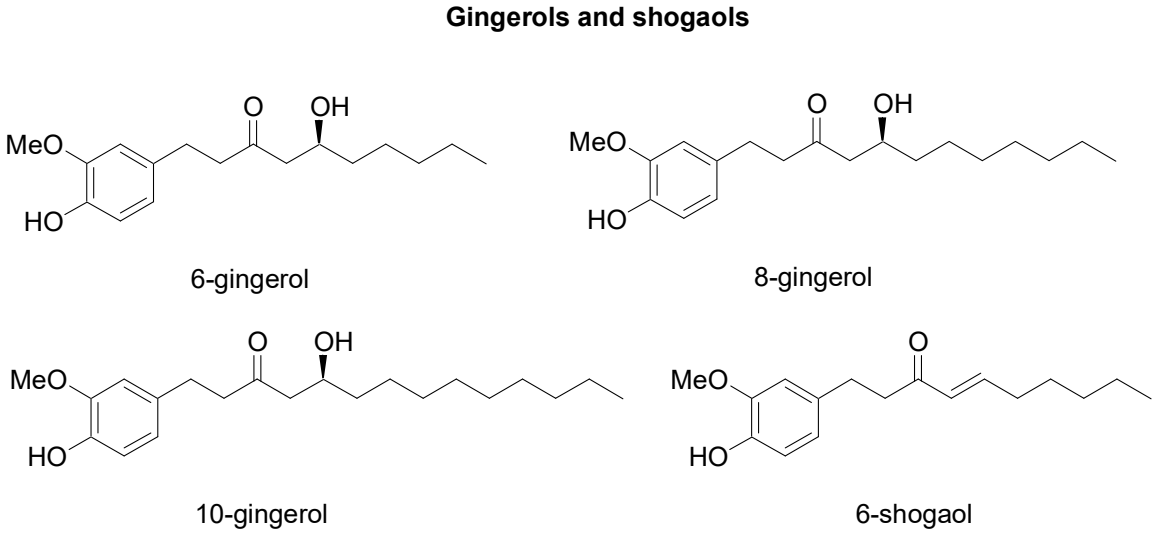


Fig. 13. Antihypertensive principles of *Z. officinale*.

3. DISCUSSION

Already in 1939, Robinson and Brucer (Robinson and Brucer, 1939) reported, in a statistical and clinical study of about 12,000 persons, that "a blood pressure history of over 120 systolic and 80 diastolic over a ten year span in a man or woman is pathologic, and is an almost infallible sign of incipient hypertension. Once a pressure is definitely established in this range it seldom if ever will become normal". Sixty years after, in 2003, the Joint National Committee on High Blood Pressure (Seventh Report -JNC 7) (Chobanian et al., 2003) used the term prehypertension (preHTN). 35% of US populations met criteria for preHTN resulting in a greater risk for developing hypertension and double risk to develop CVDs if compared to people with BP <120/80 mmHg (Egan and Julius, 2008; Kachur et al., 2018). More recently, as above out-lined, the European and U.S. guidelines for the hypertension management have categorized the BP values 5-10 mmHg lower than 140 mmHg SBP and 90 mmHg DBP as 'high normal' BP or 'stage 1' HTN, dismissing the term 'preHTN'. For these BP ranges, drug treatment is not strictly recommended: it is considered or recommended under established CVD risks, and, according to both the above guidelines, nonpharmacological lifestyle interventions can be resorted, even alone. If these interventions prove adequate to BP management, drug treatment can be avoided. In this context, introducing phytocomplexes and/or some classes of natural compounds, whose activity has been proven to lower BP, may represent, in our opinion, a real additional opportunity, very promising especially when considering that, in comparison to conventional drugs, phytocomplexes may affect multiple targets at the same time with reduced side effects and that the effectiveness of lifestyle interventions is, however, limited. To treat high normal BP, JNC 7 mostly recommended major lifestyle interventions, consisting in dietary approaches and regular physical activity. Anyway, in 2006, the TROPHY trial (Julius et al., 2006), at 4 years of follow-up, reported limited effectiveness of lifestyle approaches to reduce incident HTN among people with high normal BP. In the same study, 772 participants were assigned to receive 2 years of candesartan, an angiotensin receptor blocker *vs* placebo, and 2 more years of placebo for all participants. In the

first phase (follow-up of 2 years) HTN developed in 40.4 % of participants on placebo compared to 13.6 % of those on candesartan (16mg/daily), while, in the second phase (2 years after stopping candesartan), HTN developed in 63 % of the placebo and 53 % in the candesartan group ($p < 0.007$). The TROPHY study demonstrated the feasibility of drug treatment of high normal BP over lifestyle approaches. Drug therapy was well tolerated. Two years later, Stephan Lüders (Luders et al., 2008), in a prospective randomized controlled trial (PHARAO study), proposed to test the effect of the ACE inhibitor Ramipril (5 mg/day) in reducing the incident HTN and CVDs in 1,008 participants with high-normal BP. At 3 years of follow-up: HTN developed in 27.1 % subjects in the Ramipril group compared to 45.2 % in controls ($p = 0.0004$). Anyway, the incidence of CVDs was not different between the two groups. In PHARAO, serious adverse events occurred in 12.5 % of the Ramipril and 13.5 % of the control group, while difference in adverse events was largely represented by a 4.8 % incidence of cough in the Ramipril compared with 0.4 % in control group. At last, several meta-analyses taking in consideration more than 134,000 non-HTN participants show how these patients had reduced risks to develop CVDs when drugs are administrated (Sipahi et al., 2012; Thompson et al., 2011).

These evidences, together, support the consideration of a treatment for the population in high normal BP status, in order to prevent HTN and CVDs. However, the lack of large clinical trials represents a big challenge in order to propose these phytocomplexes for conventional treatments in clinical practice. In our opinion, an integrative approach with previously described phytocomplexes and/or phytochemicals represents a valid opportunity. The potential beneficial effects of phytocomplexes in chronic diseases such as hypertension is the result of their ability to affect several molecular networks influencing each others with the final effect to restore cellular homeostasis (Table **1**). Furthermore, important epidemiological observations raise the possibility that the transition to HTN from high normal BP is faster in African Americans than Caucasians (Egan and Laken, 2013). Therefore, we can envisage a different approach in function of basal population's features: more aggressive (drug administration) in case of higher risk and more conservative (phytocomplexes and/or other molecules) when the risk of HTN progression is relatively minor. Considering the current evidences, additional rigorous pharmacological studies and clinical trials involving both single pure natural compounds and phytocomplexes of ascertained composition, as those here described, are needed. The results of these trials could also provide the foundation for clinical guidelines, addressed also to reduce racial disparities in prevalent hypertension.

4. CONCLUSIONS

Overall, availability of new herbal drugs specifically targeting cell components involved in regulation of blood pressure mechanisms may open a new era of hypothesis-driven therapies that are improving outcomes of people with HTN and high normal BP. The increased popularity of treating patients with various illnesses using complementary and alternative medicine is evident throughout the past decades, but, despite the exponential increase in the interest and use of herbal medicine, there is not always an adequate scientific documentation. In this review, we have reported only phytocomplexes and respective constituents that have a documented *in vitro* and/or *in vivo* therapeutic effect and a clinical confirmation and, possibly, a proved mechanism of action. Further studies are needed for confirming the overall effectiveness of herbal medicine and their properties, such as improving health, alleviating symptoms of chronic diseases and lowering side effects in comparison with conventional treatments. Nevertheless, we feel to state that, among the thirteen plants reported in this review, at least six phytocomplexes can be rightly considered, on the basis of now sufficiently sound clinical evidences, for a nutraceutical intervention in a space of application beyond the diet and before the drugs, but also with an adjuvant role in antihypertensive therapies. They are *Allium sativum* L. (Sobenin et al., 2009; Ried et al., 2010), *Olea europaea* L. (Susalit et al, 2011; Perrinjaquet-Moccetti et al., 2008), *Hibiscus sabdariffa* L. (McKay et al., 2010; Herrera-Arellano et al., 2004), *Eucommia ulmoides* Oliv.(Greenway et al., 2011), *Elettaria cardamomum* (L.) Maton (Verma et

al., 2009) and *Salvia miltiorrhiza* Bunge (Yang et al., 2012). Significantly, several food supplements, containing one or more of these phytocomplexes, are proposed as coadjuvant in the treatment of hypertension and are stably employed in several countries.

Table 1. Different targets affected by natural plant extracts and their main constituents for lowering blood pressure and their additional effects

	Ca^{2+} channel block	**RAAS**	**NO**	**AR-block**	**Diuretic**	**Others**	**Additional effects**
M. alba leaves	✓		✓	α		↓ IP3 and/or RYR-dependent Ca^{2+}release	Anti-oxidant, -atherosclerotic, -diabetic, -bacterial, -cancer, -inflammation properties; cardiovascular, hypolipidemic properties
M. indica stem bark, leaves		✓	✓			TX antagonism	↓ Expression of leukotriene B4 and PGE_2
H. sabdariffa leaves or calyces	✓	✓	✓		✓	Aldosterone Modulation	↓ Food intake, ↓ lipogenesis, ↑ lipolysis, ↑ fatty acids β-oxidation, ↓inflammatory responses and oxidative stress, ↓ triglycerides
E. ulmoides leaves, bark	✓	✓	✓	β			
E. cardamomum leaves or calyces	✓		✓	α		Cholinergic antagonism	↑ Fibrinolysis, ↑ total anti-oxidant *status*
A. sativum bulbs	✓	✓	✓	α	✓		
A. zerumbet leaves	✓	✓	✓			B_2 BKR antagonism	↓ Ox-LDL-mediated endothelium dysfunction
A. canelilla wood, bark	✓		✓				Anti-oxidant properties
A. unedo roots		✓	✓				Platelet anti-aggregation, anti-oxidant, -diabetic properties
O. europaea leaves	✓	✓	✓				↓ LDL oxidation, antioxidant, ↓ MCP-1, ↓ VCAM-1, ↓ NF-kB, TNF-α
P. granatum juice and fruit extract		✓	✓				Anti-oxidant, ↓ VCAM-1, ↑ paraoxonase, ↓ NF-kB
S. mitlhiorriza roots		✓		α			Anti-atherosclerotic, -coagulant, -thrombotic, -inflammatory, -oxidant and immunomodulatory activities
Z. officinale rhizome	✓	✓	✓				↓ TX synthetase, anti-oxidant, ↑ fibrinolysis, ↓ LDL oxidation

Abbreviations: AR, adreno-receptors; BKR, bradikinin receptors; IP3, inositole triphosphate; MCP, monocyte chemoattractant protein; NF, nuclear factor; RAAS, renin–angiotensin–aldosterone system; RYR, ryanodine; TNF, tumor necrosis factor; TX, tromboxane; VCAM, vascular cell adhesion molecule; ↓, decrease, inhibition; ↑, increase, activation.

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