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**Review Article**

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# Comparable effects of the different extracts of the same plants on blood pressure and vascular tone

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**Abstract** Many people have suffered from hypertension and comorbid diseases for long years. Before the discovery of antihypertensive drugs, plants were used in folk medicine to treat hypertension. Nowadays, sufferers still prefer medical plants versus drugs. Furthermore, researchers focus on herbal drugs. There are lots of researches about plants which are used for cardiovascular diseases both traditionally and currently. In this review, we will focus on hypotensive/vasorelaxant plant extracts which exhibit different or similar effects based on their distinct extracts prepared with several solvents. The aim of the review is that to provide researchers be taken into account this property at their studies. In this way, scientific researches about plants are conducted truly and effective therapies are ensured effortlessly.

**Keywords** plant extract, comparable effects, hypertension, blood pressure, vasorelaxation

## 1. Introduction

Hypertension is a chronic disease described as systolic blood pressure equal or higher than 140 mm Hg and/or diastolic blood pressure equal or higher than 90 mm Hg. The blood pressure values have a crucial role for the effective performances of major organs such as heart, brain and kidneys. Hypertensive patients usually have no symptoms; but sometimes symptoms may appear including headache, shortness of breath, dizziness, chest pain, palpitations of the heart and nose bleeds. Hypertension combined with other factors such as tobacco use, physical inactivity, obesity, diabetes, high cholesterol, socioeconomic conditions and family history increased the risk [1]. According to the estimation of WHO, almost 1,6 billion people will be hypertensive by 2025 [2]. All hypertensive patients do not have to use medicine [1]. Before medicine, nonpharmacological interventions should be preferred such as losing weight, decreasing salt intake [3,4]. However, some patients should use antihypertensive drugs [1]. Diuretics, Angiotensin converting enzyme (ACE) inhibitors, Beta blockers are among the commonly used antihypertensive drugs.

Nowadays, healthcare costs are increasing and for some patients antihypertensive drugs may be unaffordable because of socioeconomic status. Therefore, those people may prefer medical plants [5]. Herbs are used traditionally for treatment of any diseases from the past. According to people, plants are more reliable, have less side effects. In addition to traditional usage, many drugs were derived from plants including aspirin (from *Salix alba*), reserpine (from *Rauwolfia serpentina*) and digitoxin (from *Digitalis purpurea*) [5]. Besides, there are a lot of scientific studies about pharmacological effects of plants/active compounds of plants and plant extracts.

This review focuses on the hypotensive and vasorelaxant effects of plant extracts especially which are compared the effects of different extracts of the same plant dissolved in different solvents.

**2. Classification based on flavonoids active compound**

Flavonoids are a subclass of active compounds which are derived from plants. They have antioxidant, antiviral, antibacterial effects; protective roles against UV radiation and pigmentation in plants besides. Vegetables, fruit, seed, any cereal, wine, tea and some spices may be given example to the source of flavonoids [6]. A beneficial relationship was found between dietary flavonoids consumption and decrease of cardiovascular diseases risk [7]. It was indicated that flavonoids intake at high amounts had protective effect against hypertension [8]. Furthermore, flavonoids are antiadhesive and antiagregan. They also induce NO synthase in the layer of vascular endothelium. So, flavonoids regulate blood pressure by modulating NO which has vasodilator effect [6,9].

Many plant extracts have vasorelaxant effect associated with the active ingredients such as flavonoids. We would like to give some examples to vasorelaxant plant extracts contained flavonoids, whose effects were depended on being dissolved in different solvents.

***Ziziphora clinopodioides* Lam**. is used traditionally by Uyghur people for diseases such as hypertension, fever, edema, heart disease, neurasthenic, insomnia, tracheitis, lung abscess and hemorrhoids [10,11]. Organ bath experiments were performed to prove antihypertensive effect of *Ziziphora clinopodioides*. For this reason, vasodilator effects of hexane, dichloromethane and aqueous fractions of hydroalcoholic extract of the whole plant of *Ziziphora clinopodioides* were examined in rat thoracic aorta, precontracted with phenylephrine. The most potent was dichloromethane fractions of hydroalcoholic extract with an Emax value reaching 95.5±2.0% in aortic rings pre-contracted by phenylephrine and potassium chloride. The effect was endothelium independent; related with blockage of extracellular $Ca^{2+}$ through voltage- and receptor-operated $Ca^{2+}$ channels, intracellular stores derived $Ca^{2+}$ release, and activation of voltage-dependent $K^{+}$ channels[12]. In 2012, it was demonstrated that vasodilator effect hydroalcoholic extract of the whole plant of *Ziziphora clinopodioides* was partly via phenolic compounds. Seven compounds identified responsible from the vasorelaxant effect and these were acetovanillone, 4-hydroxyacetophenone, ethyl 4-coumarate, chrysin, acacetin, apigenin and thymonin. The last four were flavonoids [13].

***Cuphea carthagenensis*** is widely used in Brazil folk medicine [14]. As a result of studies on pharmacological effects of *Cuphea carthagenensis*, it was reported that the extract of plant inhibited angiotensin-I converting enzyme[15]. and evoked vasorelaxation on rat aorta [16]. In that study, Schuldt et al. investigated the vasodilator effects of the crude hydroalcoholic extract (CE), butanolic (BF) and ethyl acetate (EA) fractions of *Cuphea carthagenensis* in rat thoracic aorta. Although three extracts induced almost complete relaxation, butanolic fraction of hydroalcoholic extract was the most potent. The relaxation response of butanolic fraction was both endothelium dependent and independent. Endothelium related component was about NO/cGMP pathway and at least free radical-scavenging properties. Endothelium independent pathway was active at high doses and not clarified. In 2012, it was also demonstrated that *Cuphea carthagenensis* induced vasorelaxant effect in rat aortic rings related with chemical content. The percentage of relaxation varied on whether the aqueous or ethanol extracts. The relaxation evoked by aqueous extract was less than %50. On the other hand, the relaxation response of ethanol extract was above %80. Besides, it was established that *Cuphea carthagensis* induced vasodilation involve flavonoids, proanthocyanidins, tannins and these compounds act synergistically in ethanol extract [14].

***Cydonia oblonga Mill*** is used traditionally to treat hypertension and other cardiovascular diseases in Uyghur medicine [17]. In 2014 Zhou et al. investigated the possible antihypertensive effects of *Cydonia oblonga* fruit and leaf ethanol/aqueous extracts in a rat experimental model of renal hypertension. The fruit and leaf extracts of *Cydonia oblonga* Mill lowered blood pressure of hypertensive rats. But, ethanol extracts were more effective than aqueous extracts. The most effective extract was 160 mg/kg (high dose) ethanol extract of leaves which was similar to response, obtained with captopril 25 mg/kg. The antihypertensive effect of extract may be connected with flavonoid compound [18].These findings showed correlation with conventional use of plant [19].

***Euphorbia humifusa*** is a significant plant for Chinese folk medicine which is used to treat several diseases. According to previous studies, *Euphorbia humifusa* was reported to contain active compounds including flavonoids, which exhibit pharmacological effects such as hypotensive [20-22]. The effect of *Euphorbia humifusa* on vascular tone was also investigated by using methanol extract in rat aorta. Each fractions of methanol extract showed

different vasorelaxant effect. The maximum relaxation response was belonged to ethyl acetate fraction. The others were n- butanol fraction, methanol extract, water fraction; respectively. The difference between ethyl acetate fraction and water fraction was almost %15. The relaxation induced by ethyl acetate fraction was endothelium dependent. NO/cGMP, Akt-eNOS pathways and $IK_{Ca}/BK_{Ca}$ (Intermediate/Big conductance Calcium activated Potassium channels) activation played roles in vasodilator response. In addition to this; when ethyl acetate fraction of methanol extract was administered intravenously to the rats, it caused a significant reduction of both systolic blood pressure and heart rate [22].

***Jasmine (Jasminum sambac)*** is a widely used traditional medicine. The pharmacological studies on cardiovascular system were limited [23].It was found that the aqueous extract of jasmine relaxed rat thoracic aorta via the blockage of voltage-dependent $Ca^{2+}$ channel, receptor-operated $Ca^{2+}$ channel, sarcoplasmic reticulum derived $Ca^{2+}$ release and partly the activation of $K_V$ channel [24]. Furthermore, it was reported that ethanolic extract of Jasmine flower had vasodilator effect in rat aorta via stimulating nitric oxide release or affecting muscarinic receptors. The ethanolic extract of Jasminum sambac comprised antioxidants, coumarins, cardiac glycosides, essential oils, flavonoids, phenolics, saponins, and steroids according to phytochemical analysis results [25]. In another study, the vasodilator effect of Jasmine ethanol extract was proved in rat thoracic aorta. A concentration dependent relaxation response was obtained via nitric oxide, potassium channels, inhibiting extracellular calcium and inhibiting the release of calcium derived sarcoplasmic reticulum. The relaxation response may be related with containing flavonoid and iridoid glycosides [23].

***Alchemilla vulgaris***, member of the family of Rosaceaea, is used as herbal tea to treat hypertension[26,27].Liquid extracts of the plant include quercetin derivatives and gallic acid which are flavonoid glycosides [28,29].In 2014, it was determined that aqueous and methanol extracts of Alchemilla vulgaris exerted different effects. While aqueous extract induced contraction on rat aorta, methanol extract mediated vasodilation. It was thought to be related with flavonoid derivatives content. Quercetin and total flavonoid were higher in the methanol extract than aqueous extract. Conversely, gallic acid was dominant in aqueous extract. The vasorelaxant effect was endothelium dependent [30].In 2015, the effects of Alchemilla vulgaris on blood pressures of rats in vivo and mesenteric arteries of rats in vitro were investigated. Methanol extract decreased the blood pressure in L-NAME induced hypertensive rats, while aqueous extract did not make a significant change. Similar to previous study; methanol extract induced vasodilation in rat mesenteric arteries, aqueous extract induced contraction. The relaxation response was endothelium dependent, possibly related with quercetin derivatives and contraction response might depend on gallic acid [31].

## 3. Classification based on possible mechanisms of action

The endothelium is the inner layer of blood vessels which regulates vascular homeostasis. It provides homeostasis by releasing endogenous vasoactive substances that regulate vascular tone, vascular smooth muscle proliferation, thrombolytic balance, thrombosis and transendothelial leukocyte migration [32]. Several factors play key roles in regulating blood pressure and vascular tone such as Autonomic nervous system, Renin Angiotensin Aldosterone System, Autacoids. All these factors regulate vascular tone by acting on the vascular endothelium layer. They are classified as endothelium-derived relaxing factors (EDRFs) and endothelium-derived contracting factors (EDCFs). While NO (Nitric oxide), $PGI_2$ (Prostacyclin), COX (Cyclooxygenase) products, $H_2S$ (Hydrogen sulfide) are exemplified as EDRFs; ET-1 (Endothelin-1), Ang II (Angiotensin II), $TXA_2$ (Thromboxane $A_2$) are the members of EDCFs [33]. Plant extracts exert their vasodilator and hypotensive effects using these pathways. In this section we will present possible mechanisms of action of plant extracts whose effects were changing with solvent.

### 3.1. Ace Inhibition

ACE (Angiotensin converting enzyme) is a member of Renin Angiotensin Aldosterone System. It converts Angiotensin I to Angiotensin II. Angiotensin II (Ang II) mediates vasoconstriction and sodium/water reabsorption. Ang II may be existed locally in the arteries. That is why inhibiting ACE is an important target for antihypertensive treatment [34]. We will give three examples in this section, despite there are lots of examples affecting Renin

Angiotensin Aldosterone System in the literature. The reason why we tell about the first two of them were important for next sections, the last one of them provided to compare effects between different extracts.

***Cuphea carthagenensis*** is widely used in Brazil folk medicine, especially for cardiovascular diseases [14].As a result of the study on pharmacological effects of *Cuphea carthagenensis*, it was reported that the unpurified extract of the aerial parts of plant inhibited angiotensin-I converting enzyme [15].

***Schizophyllum commune*** is a common fungus which belongs to Schizophyllaceae [35].It was reported that the water extract of *Schizophyllum commune* inhibited ACE (angiotensin-converting enzyme) activities [36].

***Asystasia gangentica*** is a member of the family Acanthaceae. Itshowed antihypertensive effect via inhibition of ACE. The hypotensive effect was observed with both aqueous and methanol extracts of *Asystasia gangentica*. The ACE inhibitor effect of methanol extract was higher than aqueous extact, %51 and %20 respectively. [37].In another study, the aqueous leaf extact of *Asystasia gangentica* decreased the blood pressure and heart rate in spontaneosly hypertensive rats. The possible mechanisms were inhibition of ACE, ANG II receptors and direct inhibitor effect on the heart muscle [38].

### 3.2. Endothelium Dependent & Independent

There are three important vasorelaxant factors, derived from the endothelium layer, regulate vascular tone. These are NO (Nitric oxide), $PGI_2$ (Prostacyclin) and EDHF (Endothelium derived hyperpolarizig factor). Vasodilator substances may use these factors while exhibiting their effects. Several plants have vasorelaxant effect and mechanisms of action are usually endothelium dependent, especially via NO. In accordance with our main topic, we will classify many plants of the review based on mechanisms both endothelium dependent and independent.

***Zanthoxylum piperitum***, a member of Rutaceae, is used as a spice and in folk medicine in Asia [39-40]. The widespread usage in Korean traditional medicine is to facilitate blood circulation and control diarrhea and stomachache [41-42]. The effect of *Zanthoxylum piperitum* extracts on vascular reactivity was examined inphenylephrineprecontracted rat thoracic aortic rings. According to the investigations, it was proved that water partition of methanol extract ofleaves of *Zanthoxylum piperitum* had vasorelaxant effect in rat thoracic aortic rings. The response obtained with water partition of methanol extract was highly effective, while n-hexane and ethyl acetate partitions of the extract had lower effect. The mechanism of relaxation was endothelium dependent. It involved the activation of NO/cGMP through the Akt- and SOCE-eNOS (store operated Calcium entry – endothelial nitric oxide synthase) pathways [43].

**Osterici Radix** is the root of *Ostericum koreanum* which beleongs to Umbelliferae family [44]. The pharmacological effects of Osterici radix were reported such as antitumoral, antioxidant and antimicrobial [45-47]. The vasodilator effect of water extracts of Osterici radix was reported in rat thoracic aorta precontracted with Serotonin [48]. Otherwise, the effect of ethanol extract of Osterici radix was investigated on rat aortic rings whether was vasorelaxant. Based on these studies, the vasorelaxant effect of ethanol extract and possible mechanism were proved. The relaxation was related with NO formation from l-Arg and NO-cGMP pathways, inhibition of the extracellular $Ca^{2+}$ entry via the receptor operative $Ca^{2+}$ channel, voltage-dependent calcium channel and sarcoplasmic reticulum derived $Ca^{2+}$ release [44].

***Schizophyllum commune*** is a fungus. The active compounds of *Schizophyllum commune* had cardiovascular effects [35]. For example; cerebrosides inhibited calcium activated chloride channels in rat artery [49-50], lectins reduced mean arterial blood pressure when administered intravenously [51-52]. In 2014, a study was performed which evaluates the difference of vasorelaxant response between ethanol and aqueous extracts in rat thoracic aorta. The water extract of *Schizophyllum commune* evoked a higher relaxation (87.26 ± 4.10) than %50 and %90 ethanol extracts (62.46 ± 4.43%, 12.19 ± 8.12%). The relaxation response of aqueous extract of *Schizophyllum commune* was both endothelium dependent and independent. The endothelium related component was primary via NO-cGMP, partially $PGI_2$-cAMP pathways. The endothelium-independent part may be involved the inhibition of voltage-dependent $Ca^{2+}$ channels and intracellular $Ca^{2+}$ release [35].

***Cinnamomi ramulus*** is used in Asia and Europe to treat blood circulation and inflammation traditionally [53]. In a study, an aqueous extract of *Cinnamomi ramulus* decreased the elevation of sucrose-induced blood pressure in

spontaneously hypertensive rats [54]. In another study, the ethanol extract of *Cinnamomi ramulus* induced vasodilation via voltage dependent $Ca^{2+}$ channel blockage [55]. After that, the possible calcium related mechanisms of *Cinnamomi ramulus* ethanol extract were investigated in rat aorta. In conclusion, it was demonstrated that the vasodilator mechanism of ethanol extract is inhibition of $Ca^{2+}$ influx and release [53].

***Cinnamomum zeylanicum***, a member of Lauraceae, is used traditionally for several disorders such as rheumatism, muscular pain and hypertension [56]. The aqueous extract of *Cinnamomum zeylanicum* was shown to have acute antihypertensive and vasodilator effects in rat aorta. The vasorelaxant mechanism included partly endothelial nitric oxide increase and $K_{ATP}$ channel activation [57]. In 2013, the acute and chronic hypotensive effects of the stem bark methanol extract of *Cinnamomum zeylanicum* were demonstrated in L-NAME induced hypertensive rats [56].

## 4. Discussion

Hypertension, one of the major cardiovascular diseases, is the leading cause of death in all around the world. Before the discovery of antihypertensive drugs, plants were used to treat hypertension. In these days, people still would like to prefer medicinal plants versus drugs. For this reason, researchers are paying attention to herbal drugs; they are investigating pharmacological effects, active compounds, possible mechanisms of effects of plants. There are too many research articles and reviews about plants which are used for cardiovascular diseases, especially hypertension. Plant extracts used for hypertension are common in the literature. Researchers grouped them according to their origin, flora, traditional usage, active compounds, etc. But, there were not any reviews in the literature which grouped extracts according to different extracts of the same plant exerted different effects. So, we took Takır et al. studies which published in 2014 and 2015 as reference. We searched articles of hypotensive/vasodilator plant extracts published in last years, especially for this property and reviewed our knowledge.

In this review, we presented twelve plants; eight of them have comparable effects which are shown in Table 1. The effects on blood pressure and vascular tone of different extracts of the same plants were comparable, but not opposite; except Alchemilla vulgaris. Different extracts of the same plant such as butanolic fraction of hydroalcholic extract, ethanol extract, aqueous extract, are used in the experiment. One of them is chosen which is the most effective, to search about mechanism of action. After selection, mechanism is defined by using the most effective extract. But for Alchemilla vulgaris, the case is different. In 2014 Takır et al. determined that when aqueous and methanol extracts of Alchemilla vulgaris were used, opposite vascular effects occurred; contraction and vasodilation, respectively.

The common feature of eight plants (Table 1) is that more effective extracts were generally alcohol extracts versus aqueous extracts, except *Zanthoxylum piperitum* and *Schizophyllum commune*. This condition is about active compounds even if the active compounds of each extracts are not determined. The active ingredients responsible for vasorelaxant and hypotensive effects are phenolic compounds, flavonoids, tannins, proanthocyanidins, etc.

The effects of different extracts of remaining four plants are comparable, too. However, the results obtained from different extracts of the same plant are not in the same study. These plants are Cinnamomi ramulus, Cinnamomus zeylanicum, Osterici radix and Jasminum sambac. The pharmacological effects are similar whereas the mechanisms are not always similar.

These twelve plants do not have a lot in common, so we grouped them into two category, flavonoid active compounds and possible mechanisms of action. Whether the plant contains favonoid, it is classified according to its pharmacologic mechanism. At the classification based on possible mechanisms of action; endothelium was important. Many plants exert vasodilator effect by using NO such as *Cuphea carthagenensis* or hypotensive effect by inhibiting ACE such as *Asystasia gangentica.*

## 5. Conclusion

We indite this review to raise awareness for researchers that the distinct extracts of the same plants prepared with different solvents may exert their effects at different levels or exactly different. It is very important to know this quality for defining therapies. Thus; the most effective therapy may be applied and wasting time/money may be prevented.

**Table 1:** Comparisons of the effects of plant extracts based on solvents

| Plants | Effect | More Effective Extracts | Less Effective Extracts | Mechanism of Action | Active Compounds |
|---|---|---|---|---|---|
| ***Ziziphora clinopodioides*** | Vasodilator | Dichloromethane fractions of hydroalcoholic extract | Hexane, aqueous fractions of hydroalcoholic extract | Endothelium independent extra/intracellular $Ca^{2+}$ blockage Kv activation | Phenolic compounds Flavonoids |
| ***Cuphea carthagenensis*** | Vasodilator | Butanolic fraction of hydroalcoholic extract | Crude hydroalcoholic extract, ethyl acetate fraction | Endothelium dependent& independent NO/cGMP pathway | Flavonoids, proanthocyanidins & tannins |
| ***Cydonia oblonga*** | Vasodilator Hypotensive | Ethanol extract Ethanol extract | Aqueous extract Aqueous extract | | Flavonoids |
| ***Euphorbia humifusa*** | Vasodilator and Hypotensive | Ethyl acetate fraction | n- Butanol fraction, methanol extract, water fraction | NO/cGMP Akt-eNOS $IK_{Ca}/BK_{Ca}$ | |
| ***Alchemilla vulgaris*** | Vasodilator and Hypotensive | Methanol extract | | Endothelium independent | Flavonoids (quercetin) |
| | Vasoconstrictor | Aqueous extract | | | Flavonoids (gallic acid) |
| ***Asystasia gangentica*** | Hypotensive | Methanol extract | Aqueous extact | ACE, Ang II, heart muscle inhibition | |
| ***Zanthoxylum piperitum*** | Vasodilator | Water partition of methanol extract | n-Hexane and ethyl acetate partitions of the extract | NO/cGMP Akt- and SOCE-eNOS | |
| ***Schizophyllum commune*** | | water extract | ethanol extract | NO-cGMP $PGI_2$-cAMP inhibition of voltage-dependent $Ca^{2+}$ channels intracellular $Ca^{2+}$ release | |

**Conflict of interest**

Authors have declared that there is no conflict of interest.

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