



Review paper

Potential therapeutic effects and applications of *Eucommiae Folium* in secondary hypertension

Mengyuan Li ^{a,1}, Yanchao Zheng ^{a,1}, Sha Deng ^a, Tian Yu ^b, Yucong Ma ^c, Jiaming Ge ^a, Jiarong Li ^a, Xiankuan Li ^{a,*}, Lin Ma ^{a,**}

^a College of Chinese Materia Medica, Tianjin University of Traditional Chinese Medicine, Tianjin, 301617, China

^b Pharmaceutical Research Development Center, Tianjin Yibei Yuan Natural Products Technology Co., Ltd., Tianjin, 300457, China

^c College of Traditional Chinese Medicine, Changchun University of Chinese Medicine, Changchun, 130117, China

ARTICLE INFO

Article history:

Received 24 March 2021

Received in revised form

12 October 2021

Accepted 20 October 2021

Available online 22 October 2021

Keywords:

Eucommiae folium

Secondary hypertension

Ingredient

Target

Pathway

ABSTRACT

Eucommiae Folium (EF), a traditional Chinese medicine, has been used to treat secondary hypertension, including renal hypertension and salt-sensitive hypertension, as well as hypertension caused by thoracic aortic endothelial dysfunction, a high-fat diet, and oxidized low-density lipoprotein. The antihypertensive components of EF are divided into four categories: flavonoids, iridoids, lignans, and phenylpropanoids, such as chlorogenic acid, geniposide acid and pinoresinol diglucoside. EF regulates the occurrence and development of hypertension by regulating biological processes, such as inhibiting inflammation, regulating the nitric oxide synthase pathway, reducing oxidative stress levels, regulating endothelial vasoactive factors, and lowering blood pressure. However, its molecular antihypertensive mechanisms are still unclear and require further investigation. In this review, by consulting the relevant literature on the antihypertensive effects of EF and using network pharmacology, we summarized the active ingredients and pharmacological mechanisms of EF in the treatment of hypertension to clarify how EF is associated with secondary hypertension, the related components, and underlying mechanisms. The results of the network pharmacology analysis indicated that EF treats hypertension through a multi-component, multi-target and multi-pathway mechanism. In particular, we discussed the role of EF targets in the treatment of hypertension, including epithelial sodium channel, heat shock protein70, rho-associated protein kinase 1, catalase, and superoxide dismutase. The relevant signal transduction pathways, the ras homolog family member A (RhoA)/Rho-associated protein kinase (ROCK) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase/eNOS/NO/Ca²⁺ pathways, are also discussed.

© 2021 The Authors. Published by Elsevier B.V. on behalf of Xi'an Jiaotong University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Hypertension is a chronic disease that is associated with higher morbidity and mortality [1]. Hypertension is mainly divided into primary and secondary hypertension [2]. According to the World Health Organization statistics, approximately 9 million people die from hypertension every year [3], and 29.2% of adults will suffer from hypertension in 2025 [4]. Therefore, reducing the prevalence of hypertension is a global issue that needs to be addressed.

Hypertension is mainly controlled and treated with synthetic drugs [5], which have a number of side effects. *Eucommiae Folium* (EF), a natural Chinese herbal medicine that uses the dried leaves of EF [6], has pharmacological effects, including anti-oxidation, lowering blood pressure (BP), lowering blood sugar, treating osteoporosis, and affecting uterine function [7–9]. EF has antihypertensive properties, which have been examined as a potential therapeutic Chinese medicine to combat hypertension. In the 1950s, Russian scholars discovered that EF has a two-way regulation of BP, and the effect of lowering BP, which was unmatched by many chemical drugs, was obvious [10]. Since the 1970s, EF has been used as an antihypertensive drug and health food in Sichuan, China [11]. Clinical studies have been conducted to evaluate its efficacy [12]. EF is widely used in China, South Korea, and Japan to treat cardiovascular diseases [13]. In Japan, EF and its extracts are made into functional beverages approved for use by the government as

Peer review under responsibility of Xi'an Jiaotong University.

* Corresponding author.

** Corresponding author.

E-mail addresses: lixiankuan168@163.com (X. Li), malin7983@163.com (L. Ma).

¹ Both authors contributed equally to this work.

<https://doi.org/10.1016/j.jpha.2021.10.004>

2095-1779/© 2021 The Authors. Published by Elsevier B.V. on behalf of Xi'an Jiaotong University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

specific health foods [14]. Traditional Chinese medicine doctors believe that kidney deficiency, liver stasis, and blood stagnation are the causes of hypertension, which start from the kidney and change in the liver [15]. EF has a nourishing effect on the liver and kidney, lowers blood sugar and blood lipids, and reduces BP. EF has a good therapeutic effect on secondary hypertension, including renal hypertension, salt-induced hypertension, and hypertension caused by thoracic aortic endothelial dysfunction, high-fat diet, and oxidized low-density lipoprotein (ox-LDL) [14,16,17]. The phenylpropanoids, flavonoids, and lignans in EF have been confirmed to have antihypertensive activity [16,18–20]. These active ingredients exert antihypertensive effects through a series of biological processes and can improve endothelial dysfunction, reduce oxidative stress levels, regulate inflammation, and regulate the nervous system. At the same time, the mechanism of EF in the treatment of hypertension also involves the regulation of gene expression. However, no comprehensive reports on this could be found. Using network pharmacology, we found that EF could effectively treat hypertension through a multi-component, multi-target and multi-pathway molecular mechanism. With the multitude of potential antihypertensive effects of EF, this review aimed to assess the scientific evidence on the active ingredients and mechanistic investigations of EF on hypertension.

2. Antihypertensive active ingredients of EF

The antihypertensive components of EF are mainly divided into four categories: phenylpropanoids, flavonoids, lignans, and iridoids (Table S1) [17,19–27]. These active ingredients have beneficial therapeutic effects on secondary hypertension. Among these compounds, lignans have been most studied. They play a larger role in reducing BP. In total, 27 different lignans were isolated from EF. Lignans mainly reduce BP by inhibiting the activity of aldose reductase [28]; pinoresinol diglucoside (PD) and syringaresin diglucoside can treat hypertension by regulating plasma endothelin and nitric oxide levels. They have predominant therapeutic effects

on renal hypertension. Flavonoids have an important protective effect on the cardiovascular system, lower BP and blood lipids, reduce oxidation, and inhibit inflammation [29]. Quercetin (QU) and rutin in EF have antihypertensive activity. QU can lower BP by inhibiting angiotensin-converting enzymes to inhibit angiotensin II (Ang II) synthesis. QU treats salt-induced hypertension by reducing epithelial sodium channel (ENaC) expression. Most phenylpropanoid components are phenolic compounds, which not only exhibit antioxidant and anti-inflammatory properties but also can improve endothelial dysfunction activities and protect the cardiovascular system [30], such as chlorogenic acid (CHA), ferulic acid (FA), and caffeic acid (CA). CA and FA have an inhibitory effect on the increase in heat shock protein70 (HSP70) gene expression caused by salt-sensitive hypertension and reduce the expression of HSP70 to achieve a therapeutic effect. The antihypertensive activity of iridoid compounds, such as geniposide and aucubin (AU), is mainly reflected in their anti-inflammatory and antioxidant properties. Geniposidic acid (GEA) can improve endothelial vascular function and have a better therapeutic effect on hypertension caused by thoracic aortic endothelial dysfunction or high-fat diet. AU has anti-inflammatory activity, reduces the level of oxidative stress, and can be used to treat hypertension caused by ox-LDL. Studies have shown that EFE has a superior therapeutic effect on renal hypertension [7].

3. EF treatment of hypertension related to the signal transduction pathway

3.1. Ras homolog family member A (RhoA)/Rho-associated protein kinase (ROCK) signaling pathway

The therapeutic effect of the extract of EF (EFE) on hypertension is mediated by the down-regulation of transforming protein RhoA and ROCK (Fig. 1). The RhoA/ROCK pathway is involved in cell migration, cell reorganization, vascular physiological function, and BP reduction. When the RhoA/ROCK1 signaling pathway is

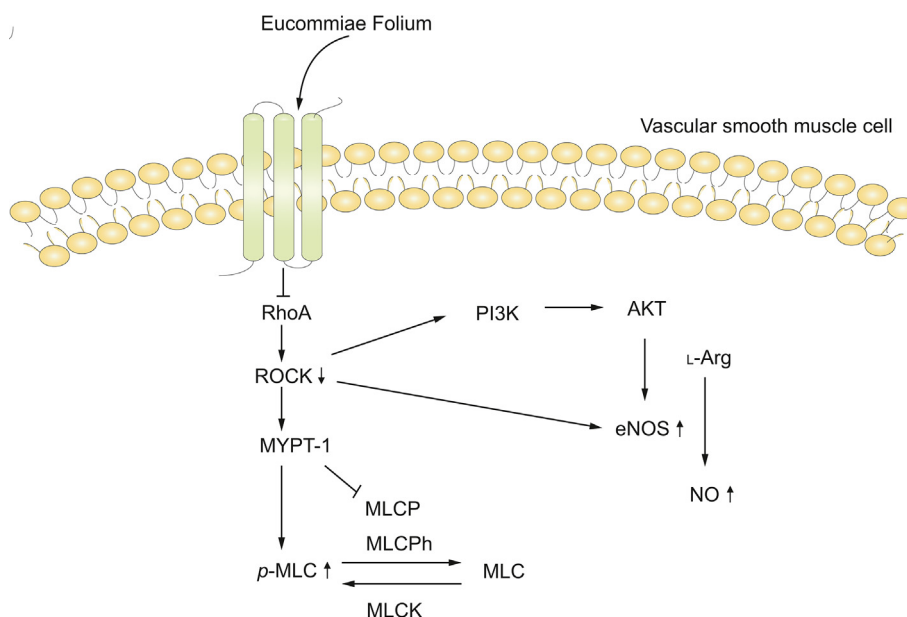


Fig. 1. Antihypertensive mechanism of Eucommiae Folium (EF) via the ras homolog family member A (RhoA)/Rho-associated protein kinase (ROCK) signaling pathway. PI3K: phosphatidylinositol 3-kinase; MYPT-1: myosin phosphatase target subunit 1; MLC: myosin light chain; eNOS: endothelial nitric oxide synthase; L-Arg: L-arginine; NO: nitric oxide; p-MLC: phospho-myosin light chain; MLCP: myosin light chain phosphatase; MLCPh: myosin light chain phosphor; MLCK: myosin light chain kinase.

abnormal, it can lead to the occurrence of hypertension and other diseases [31]. ROCK participates in the regulation of vascular tone, endothelial dysfunction, inflammation, and remodeling when activated [32]. RhoA plays an important role in the construction of cytoskeletal proteins, cell migration, cell proliferation, and transcriptional activity [33]. The balance between the RhoA/Rho kinase pathway and the nitric oxide (NO) system plays a significant role in cardiovascular and renal insufficiency [34]. EFE can significantly reduce the expression of RhoA in hypertensive rats and inhibit the expression of ROCK, which is a key downstream effector of RhoA.

EF inhibits the phosphorylation of the myosin light chain, reduces the activity of integrin-linked kinases, and activates myosin light chain phosphatase by downregulating ROCK causing smooth muscle relaxation and lowering BP [35]. EFE increases endothelial nitric oxide synthase (eNOS) activity and upregulates NO levels by downregulating ROCK expression. NO acts as a vasodilator to relax blood vessels and lower BP. The expression of ROCK decreases, which involves the activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway. The PI3K/AKT pathway can increase the expression of eNOS, promote the increase of L-arginine, enhance NO activity, and restore vascular function [32].

3.2. NO/soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate (cGMP) pathway

QU has endothelium-protecting effects against cardiovascular diseases. QU can reduce BP and has therapeutic potential as a cardiovascular agent [36]. QU also affects the function of vascular smooth muscle cells (VSMCs) in the progression of cardiovascular diseases and reduces the risk of cardiovascular diseases [37]. The vascular relaxation mechanism of QU in EF is endothelial-dependent [38,39]. EF enhances the activity of eNOS and promotes the synthesis of NO by inducing the mRNA expression of inducible NOS [40,41]. QU exerts its antihypertensive effects by regulating NO levels and increasing the intracellular calcium concentration ($[Ca^{2+}]_i$) in endothelial cells (ECs). QU can also downregulate the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, inhibit the production of reactive oxygen species (ROS), and increase the activity of NO [42,43]. NO is synthesized by L-arginine through eNOS catalysis [44] and plays a critical role in regulating BP [45]. NO diffuses from ECs to VSMCs, activates sGC in VSMCs, increases the level of cyclic guanosine monophosphate, activates the cyclic guanosine monophosphate-protein kinase G axis, stimulates the K^+ channel activated by Ca^{2+} [46], and reduces the Ca^{2+} concentration in VSMCs. This process induces membrane hyperpolarization. ECs transmit hyperpolarization to VSMCs through myoendothelial junctions, inhibiting Ca^{2+} influx and intracellular Ca^{2+} release and causing vasodilation [47,48] (Fig. 2). In addition, QU can also be used to treat salt-sensitive hypertension by reducing the expression of ENaC mRNA [49].

EF has the effect of lowering BP by regulating the RhoA/ROCK and NO/sGC/cGMP signaling pathways. Studies have shown that the NO/sGC/cGMP signaling pathway plays a key role in regulating cardiovascular diseases [50]. QU in EF can improve the level of NO and downregulate the activity of NADPH oxidase to treat hypertension. According to reports, activation of RhoA/ROCK signaling pathway is associated with pulmonary arterial hypertension (PAH) and the NO/sGC/cGMP signaling pathway is protective in PAH [51,52]. Whether EF can regulate the RhoA/ROCK and NO/sGC/cGMP signaling pathways to ameliorate PAH needs further research. It is a clinically meaningful way to conduct research on the RhoA/ROCK and NO/sGC/cGMP signaling pathways and explore the relevant biological processes involved in the treatment of secondary hypertension by EF.

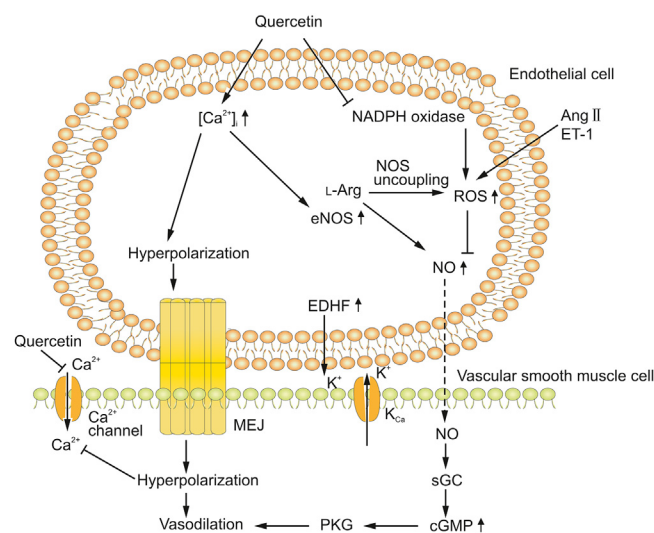


Fig. 2. Antihypertensive effect of quercetin in *Eucommiae Folium* (EF) via the NO/sGC/cGMP pathway. NADPH: nicotinamide adenine dinucleotide phosphate; EDHF: endothelium-derived hyperpolarizing factor; Ang II: angiotensin II; ET-1: endothelin-1; MEJ: myoendothelial junctions; sGC: soluble guanylate cyclase; ROS: reactive oxygen species; cGMP: cyclic guanosine monophosphate; L-Arg: L-arginine; PKG: protein kinase G; eNOS: endothelial nitric oxide synthase

4. Pharmacological mechanisms of EF in the treatment of hypertension

4.1. Suppressing oxidative stress

Oxidative stress refers to the pathological state of the imbalance between the production of free radicals and antioxidant defenses in the body. Excessive oxidative stress leads to endothelial cell dysfunction, affects the release of endothelial cell-active substances, leads to vasomotor dysfunction [10], and causes hypertension. EF contains various active antioxidant ingredients, such as CHA, coumaric acid, protocatechuic acid (PA), and other phenylpropanoids. PA is the main antioxidant in EFE [23]. Several studies have shown that the ability of CHA to scavenge free radicals in vitro is better than that of vitamin E [53]. CHA, which can protect against free radicals and scavenge free radicals by activating endogenous antioxidants, relieves oxidative stress [54]. It can also form a chelate with iron to reduce hydroxyl free radicals [55], thereby reducing the level of oxidative stress to reduce BP. PA can effectively scavenge hydroxyl free radicals, reduce the generation of hydroxyl free radicals by inhibiting the reaction of Cu^{2+} and H_2O_2 [56], and reduce the level of oxidative stress. Previous studies have shown that AU in EF can protect cell components from oxidative stress [57,58]. Some studies have shown that at the early stage of inflammation, ox-LDL damages ECs by inhibiting the production of NO [59] and accelerating endothelial cell dysfunction [60]. Dephosphorylation of eNOS-Thr495 enhances eNOS activity and promotes NO release [61,62]. AU inhibits the uncoupling of eNOS induced by ox-LDL in human umbilical vein ECs, reduces the phosphorylation level of eNOS-Thr495, increases NO activity, and reduces the level of oxidative stress, achieving an antihypertensive effect [17]. Many enzymes regulate oxidative stress, including catalase, glutathione peroxidase, myeloperoxidase, and superoxide dismutase [63]. Lignans of EF can significantly upregulate the activity of various oxidative stress enzymes in liver tissues, increase the expression levels of important proteins during oxidative stress, and reduce superoxide production [13].

4.2. Improving endothelial dysfunction

ECs regulate the release of the vasodilator NO, prostacyclin, and vasoconstrictor factors (Ang II, endothelin-1, and ROS) to maintain their balance, thus playing a key role in regulating vascular tension [35]. Endothelial dysfunction is a marker of cardiovascular diseases [64]. Hosoo et al. [14] studied the therapeutic effect of EF on spontaneously hypertensive rats and concluded that EF has a repairing effect on vascular endothelial function. They found that GEA in EF is one of the main active components with antihypertensive effect. FA and CA of EF can improve vascular endothelial dysfunction, dilate blood vessels, and lower BP. Lignans of EF can increase the activity of cyclic adenosine monophosphate (cAMP) by inhibiting cAMP phosphodiesterase, thereby promoting the release of NO, leading to vasodilation and improving endothelial function. According to previous reports, the water extract of EF can cause anti-vascular endothelial dysfunction, and its vasodilation effect is endothelial-dependent, exerting a relaxing effect on the vascular endothelium via the nitric oxide synthase pathway [65]. After seven weeks of administration to middle-aged spontaneously hypertensive rats, treatment with EFE significantly reduced endothelial dysfunction, improved the vascular function of the thoracic aorta, reduced the thickness of the thoracic aorta, and restored blood vessel function [66].

4.3. Inhibiting the renin-angiotensin-aldosterone system (RAAS)

Excessive activation of RAAS can lead to hypertension. Angiotensin converting enzyme (ACE) can further catalyze Ang I and transform it into Ang II, a cell membrane peptidase [67]. Ang II can cause vascular endothelial dysfunction [68]. QU is an ACE inhibitor that can chelate with Zn^{2+} , inhibit ACE activity, interfere with RAAS, and reduce the conversion of Ang I to Ang II [69], thereby reducing the damage of Ang II to vascular endothelial function. Renin protein is an upstream enzyme regulator of the RAAS system. EF can maintain normal BP by reducing renin level. ACE2 is the main component of RAAS. EF can inhibit the activation of the RAAS system by inhibiting the generation of ACE. The RAAS system is associated with a variety of diseases. RAAS inhibitors are generally used to treat abnormal RAAS system function, but RAAS inhibitors can cause adverse reactions, the most common of which is hyperkalemia. EF can inhibit the abnormal activation of the RAAS system; thus, the therapeutic effect of EF on hyperkalemia is worthy of investigation for potential use to ameliorate hypertension.

4.4. Activating ion channels

Changes in BP are related to the contraction of blood vessels and the ion channels in VSMCs. EFE involves the activation of K^+ channels in the process of inducing vasodilation. This response is mediated by endothelium-derived hyperpolarizing factor. It is also affected by gap junctions between ECs and smooth muscle cells [70]. QU in EF can open the K^+ channels of endothelium-derived hyperpolarizing factors to induce the hyperpolarization of vascular smooth muscle [71] and inhibit Ca^{2+} influx and intracellular Ca^{2+} release, thereby causing vasodilation and lowering BP [48,72]. The imbalance of elevated Ca^{2+} in vascular endothelial cells may lead to the loss of endothelial-dependent vasodilation and cause endothelial dysfunction. Ca^{2+} flows into vascular endothelial cells through transient receptor potential (TRP) channels. Among these TRP channels, the transient receptor potential vanilloid (TRPV4) channel is widely expressed in vascular endothelial cells and has relatively high permeability of Ca^{2+} . As for whether QU in EF inhibits Ca^{2+} influx is related to endothelial TRPV4 channels, there is no relevant report, and it is highly worth researching the correlation.

4.5. Regulating the autonomic nervous system

The imbalance and dysregulation of the autonomic nervous system can lead to the occurrence and development of hypertension and can be accompanied by the development of hypertension [73–75]. AU in EF stimulates the parasympathetic nerves [76]. Namba et al. [77] conducted a preliminary pharmacological study on a water-based EFE and pointed out that the water extract of EF could achieve a short-term antihypertensive effect by stimulating the parasympathetic nervous system. The study results showed that hyperinsulinemia in fructose-drinking rats could cause neuronal vascular control system dysfunction, leading to the development of hypertension [78,79]. Jin et al. [71] asserted that *Eucommia ulmoides* Oliv. leaves extract (ELE) could improve the abnormal vascular peripheral innervation of adrenergic and calcitonin gene-related peptide-containing nerves in fructose-drinking rats by improving insulin resistance, reducing the density of tyrosine hydroxylase-like immunoreactive nerve fibers, and increasing the density of calcitonin gene-related peptide immunoreactive nerve fibers to achieve an antihypertensive effect.

5. Screening of the targets and potential mechanism of EF in hypertension treatment based on network pharmacology

Few studies have examined the targets and pathways related to the treatment of hypertension with EF. To study the molecular mechanisms underlying the effects of EF in the treatment of hypertension and explore its targets and pathways, this review employed network pharmacology to predict the targets and protein interactions of EF in the treatment of hypertension and provide scientific predictions for the targets and pathways of EF. The results of the network pharmacology analysis showed that EF treated hypertension through multiple targets and pathways.

Through the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, <https://tcmsp.com/tcmssp.php>) as well as the UniProt database (<http://www.uniprot.org/>), the gene targets of the active components of EF were normalized and standardized. 16 active ingredients (Table S2) and 167 potential targets of EF that could relate to the treatment of hypertension were identified. The Online Mendelian Inheritance in Man (<https://omim.org/>) and GeneCards (<https://www.genecards.org/>) databases were used to search for genes that regulate hypertension. The UniProt database was used to normalize and standardize the collected disease protein targets. In total, 557 related gene targets for the regulation and treatment of hypertension were obtained. After intersecting and deleting duplicates, the targets of the active ingredients and disease targets of EF were intersected, and 66 common targets were identified (Table S3). The data, active ingredients of EF, and the co-action targets that corresponded to active ingredients and hypertension of EF were imported into Cytoscape 3.7.2 software to construct an “active ingredient-target-disease” network diagram (Fig. 3).

The targets, namely, RhoA, ROCK, superoxide dismutase 1 (SOD1), catalase (CAT), tumor necrosis factor (TNF), the Bcl-2-associated X protein (BAX), and interleukin-6 (IL-6), were verified. Among them, TNF, SOD1, CAT, cyclooxygenase-2 (COX-2), IL-6, and RAC-alpha serine/threonine-protein kinase (AKT1) have been identified to play a pivotal role in the treatment of hypertension with EF. EF can reduce BP by regulating these targets (Table 1) [80–83]. According to the network pharmacology analysis, there are 66 intersections of targets between the active components of EF and hypertension. The 66 common targets were mainly related to chemical components such as rutin, QU, and AU.

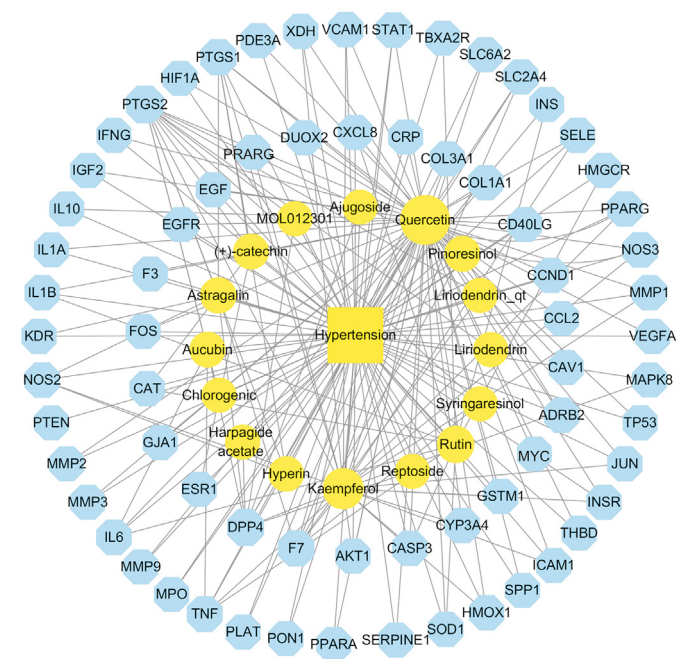


Fig. 3. Active ingredient-target-disease network diagram of Eucommiae Folium (EF) in the treatment of hypertension.

They play major roles in anti-inflammatory and anti-oxidative stress and help to improve vascular function. The main targets include insulin (INS), AKT1, IL-6, cellular tumor antigen p53, TNF, and vascular endothelial growth factor A. INS has a regulatory effect on the intrinsic apoptotic signaling pathway induced by oxidative stress [84]. AKT1 is an important mediator of transforming growth factor-beta signal transduction and is a key regulator of endothelial barrier function [85]. TNF can induce vascular ECs to produce vascular endothelial growth factor by cooperating with IL-1β and IL-6 [86]. COX-2 and prostaglandins are involved in angiogenesis [87,88], and these targets play a vital role in the treatment of hypertension with EF. We imported the relevant targets of EF in the treatment of hypertension into the Database for Annotation, Visualization, and Integrated Discovery (DAVID, <https://david.ncicrf.gov/>) and Metascape (<https://metascape.org/>) databases. Then, we performed a gene ontology analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis on the targets of EF in the treatment of hypertension (Figs. S1 and S2). The results showed that the regulation of hypertension by EF involves biological processes such as apoptosis regulation and regulation of blood vessel development, the

influence of cells on nitrogen compounds, and regulation of cell death, involves components such as plasma membrane protein complex, cytoplasmic nucleus, and vesicles, which are involved in molecular functions such as green factor binding, protein domain specific binding, and protein kinase binding (Fig. S3). Therefore, the action mechanism of EF in treating hypertension is complex. The unverified components, targets, and pathways can be used as the basis for future research on the mechanism of EF in the treatment of hypertension.

The network pharmacological analysis revealed that EF has the characteristics of multi-component, multi-target and multi-pathway in the treatment of hypertension. Kaempferol, (+)-catechin, and pinorensinol, which exert antihypertensive effects, are related components of EF. Although the antihypertensive effects of kaempferol and pinorensinol in EF have not been proven, studies have shown that they have antihypertensive activity. Kaempferol, found in the leaves of *Bauhinia forficata*, has been shown to relax blood vessels [89]. Through the regulation of the asymmetric dimethylarginine/dimethylarginine dimethylaminohydrolase II/eNOS/NO pathways, kaempferol can inhibit oxidative stress and protect vascular ECs [90]. Therefore, kaempferol in EF has the potential to lower BP, which can provide a theoretical basis for follow-up research. Pinorensinol of *Cedrela serrata Royle* has been reported to be negatively correlated with the onset of hypertension and has a good therapeutic effect on hypertension. Moreover, (+)-catechin induces vasodilation [91]. A KEGG analysis showed that the mitogen-activated protein kinase (MAPK) signaling pathway, TNF signaling pathway, pathways in cancer, and the advanced glycation end products (AGE)/receptor for advanced glycation end products (RAGE) signaling pathway participate in the treatment of hypertension with EF. Targets such as transcription factor AP-1, matrix metalloproteinase-3, TNF, matrix metalloproteinase-9 (MMP9), IL-6, and MAPK8 are involved in the TNF signaling pathway, and they have been shown to exert antihypertensive effects. Some studies have indicated that pathways in cancer associated with hypertension and chrysanthemum could reduce BP [92,93]. Zhang et al. [94] confirmed that pulmonary hypertension due to left heart disease mediates the activation of the MAPK signaling pathway. The MAPK signaling pathway could be involved in upregulating the expression of MMP9 and transforming growth factor β-1 proprotein mediated by mechanical stretching. Furthermore, mechanical stretching may be a key cause of vascular remodeling. Litchi chinensis polyphenol-rich extract from seeds can reduce BP and treat hypertensive kidney damage by regulating the TNF signaling pathway [95]. The advanced glycation end products (AGE)-receptor for advanced glycation end products (RAGE) signaling pathway is regulated in spontaneously hypertensive rats, which can suppress the accumulation of AGEs and the expression of RAGE as well as inhibit angiogenesis and thrombosis [96].

Table 1

Intersection of targets of Eucommiae Folium (EF) in the treatment of hypertension from the literature and network pharmacology analysis.

| Gene | Protein name | Change | Function | Refs. |
|-------|---|-----------------|---|-------|
| SOD1 | Superoxide dismutase 1 | Down-regulation | Destroying radicals | [80] |
| TNF | Tumor necrosis factor | Down-regulation | Cytokine that binds to TNFRSF1A/TNFR1 and TNFRSF1B/TNFR2 | [81] |
| CAT | Catalase | Up-regulation | Promoting growth of cells | [82] |
| IL-6 | Interleukin-6 | Down-regulation | Cytokine with a wide variety of biological functions | [83] |
| AKT1 | RAC-alpha serine/threonine-protein kinase | Up-regulation | Regulating many processes including metabolism, proliferation, cell survival, growth and angiogenesis | [83] |
| COX-2 | Cyclooxygenase-2 | Down-regulation | With a particular role in the inflammatory response | [80] |

TNFRSF1A: tumor necrosis factor receptor superfamily member 1A; TNFR1: tumor necrosis factor receptor 1; TNFRSF1B: tumor necrosis factor receptor superfamily member 1B; TNFR2: tumor necrosis factor beta receptor 2.

6. Conclusion and perspectives

In conclusion, this review clarified the active ingredients and mechanisms of EF in the treatment of hypertension at pharmacological and molecular levels. The active antihypertensive ingredients of EF are phenylpropanoids, flavonoids, lignans, and iridoids. The literature search and network pharmacology analysis found 29 active antihypertensive ingredients in EF, 18 of which have been confirmed to play a crucial role in the treatment of hypertension with EF. The other 11 ingredients require further research and verification. EF can reduce BP by inhibiting oxidative stress, improving endothelial dysfunction, regulating the autonomic nervous system, activating ion channels, and regulating the RAAS system. At the molecular level, EF has antihypertensive effects by regulating the RhoA/ROCK signaling and NO/sGC/cGMP pathways. Using network pharmacology, we confirmed that EF treats hypertension through a multi-component, multi-target and multi-pathway approach. The network pharmacology analysis identified 16 active compounds in EF that have antihypertensive activity, including kaempferol, (+)-catechin, and pinoreosin. EF regulates the RhoA/ROCK pathway and controls BP by inhibiting the gene expressions of RhoA and ROCK. FA and CA, which are phenylpropanoids in EF, can inhibit the expression of the HSP70 gene in deoxycorticosterone acetate-salt hypertensive rats and achieve a hypotensive effect. QU regulates hypertension via the NO/sGC/cGMP pathway. QU can reduce the increase in ENaC expression induced by a high-salt diet and reduce hypertension induced by such as diet. EF promotes the release of NO by increasing the expressions of SOD1 and CAT genes and lowering BP. The expression of BAX gene affects vascular remodeling, and EF reverses vascular remodeling and protects blood vessels by up-regulating BAX gene expression. Genipin exerts anti-inflammatory effects via the PI3K/AKT signaling pathway, increases NO activity, and regulates BP. The MAPK signaling pathway, TNF signaling pathway, pathways in cancer, and AGE-RAGE signaling pathway play crucial roles in the treatment of hypertension with EF. The efficacy of EF in the treatment of hypertension has been confirmed, but the mechanism of action requires further study. EF has a therapeutic effect on secondary hypertension, including renal hypertension and salt-sensitive hypertension, as well as hypertension caused by thoracic aortic endothelial dysfunction, high-fat diet, and oxidized low-density lipoprotein. However, the possibility of side effects of EF in the treatment of hypertension has not been verified. Efficacy of EF in the treatment of other types of secondary hypertension and related mechanisms remains to be further studied. This review provides a reference for further exploration of the molecular mechanism of EF in the treatment of hypertension, including related components, targets, and pathways.

CRedit author statement

Mengyuan Li: Conceptualization, Methodology, Writing - Original draft preparation, Software; **Yanchao Zheng:** Software, Writing - Reviewing and Editing; **Sha Deng:** Formal analysis; **Tian Yu:** Formal analysis; **Yucong Ma:** Resources; **Jiaming Ge:** Software, Visualization; **Jiarong Li:** Data curation; **Xiankuan Li:** Supervision, Project administration; **Lin Ma:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This work was supported by the Scientific Research Project of the Tianjin Educational Committee (Project No.: 2019KJ081).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpha.2021.10.004>.

References

- [1] J.-R. Zhang, H.-J. Sun, Extracellular vesicle-mediated vascular cell communications in hypertension: Mechanism insights and therapeutic potential of ncRNAs, *Cardiovasc. Drugs Ther.* 36 (2022) 157–172.
- [2] T. Verma, M. Sinha, N. Bansal, et al., Plants used as antihypertensive, *Nat. Prod. Bioprospect.* 11 (2021) 155–184.
- [3] M. Yousefi, M. Shadnough, N. Khorshidian, et al., Insights to potential antihypertensive activity of berry fruits, *Phytother Res.* 35 (2021) 846–863.
- [4] B. Li, F. Li, L. Wang, et al., Fruit and vegetables consumption and risk of hypertension: A meta-analysis, *J. Clin. Hypertens.* 18 (2016) 468–476.
- [5] H. Hu, H. Xiao, H. Bao, et al., Tissue distribution comparison of six active ingredients from an *Eucommia* cortex extract between normal and spontaneously hypertensive rats, *Evid. Based Complement. Alternat. Med.* 2020 (2020), 2049059.
- [6] National Pharmacopoeia Commission, *Pharmacopoeia of the People Republic of China*, Chemical Industry Press, Beijing, 2020, pp. 173.
- [7] T. Yuan, L. Fang, Y. Lu, et al., Advances in studies on the pharmacological effects of *Eucommia folium*, *China J. Chin. Mater. Med.* 38 (2013) 781–785.
- [8] C.-Y. Wang, L. Tang, J.-W. He, et al., Ethnobotany, phytochemistry and pharmacological properties of *Eucommia ulmoides*: A review, *Am. J. Chin. Med.* 47 (2019) 259–300.
- [9] Nanjing University of Traditional Chinese Medicine, *Dictionary of Traditional Chinese Medicine*, first ed., Shanghai Science and Technology Press, Shanghai, 2006, pp. 1518.
- [10] L. Jiang, Y. Jiang, J. Guo, et al., Research progress of *Eucommia ulmoides* Oliv. in the treatment of hypertension, *Shandong J. Tradit. Chin. Med.* 36 (2017) 249–252.
- [11] Z. Qin, Y. Wu, Z. Yu, et al., Studies on the eucommia cortex and leaves, *West-North Univ. J.* 7 (1977) 64–72.
- [12] F. Greenway, Z. Liu, Y. Yu, et al., A clinical trial testing the safety and efficacy of a standardized *Eucommia ulmoides* Oliv. bark extract to treat hypertension, *Altern. Med. Rev.* 16 (2011) 338–347.
- [13] B. Liu, C.-P. Li, W.-Q. Wang, et al., Lignans extracted from *Eucommia ulmoides* Oliv. Protects against AGEs-induced retinal endothelial cell injury, *Cell. Physiol. Biochem.* 39 (2016) 2044–2054.
- [14] S. Hosoo, M. Koyama, M. Kato, et al., The restorative effects of eucommia ulmoides oliver leaf extract on vascular function in spontaneously hypertensive rats, *Molecules* 20 (2015) 21971–21981.
- [15] L. Xiao, R. Zhou, Research progress on the antihypertensive effect of *Eucommia*, *Guid. Chin. Med.* 11 (2013) 501–502.
- [16] S. Hosoo, M. Koyama, A. Watanabe, et al., Preventive effect of *Eucommia* leaf extract on aortic media hypertrophy in Wistar-Kyoto rats fed a high-fat diet, *Hypertens. Res.* 40 (2017) 546–551.
- [17] G.-H. Lee, H.-Y. Lee, M.-K. Choi, et al., *Eucommia ulmoides* leaf (EUL) extract enhances NO production in ox-LDL-treated human endothelial cells, *Biomed. Pharma* 97 (2018) 1164–1172.
- [18] Y. Zhang, Y. Zhang, D. Guo, et al., Experimental study on hypotensive effect of compound folium *Eucommiae* mixture on body, *Chin. Tradit. Patent Med.* 23 (2001) 418–421.
- [19] X. Li, T. Liu, S. Chen, et al., Optimization of extraction process for chlorogenic acid from *Eucommia ulmoides* leaves and its hypotensive effect on spontaneously hypertensive rats, *Food Sci.* 34 (2013) 30–34.
- [20] J. Lai, L. Xu, H. Rao, et al., General situation of research on chemical constituents and pharmacological effects of *Eucommia folium*, *Practical Clin. J. Integrated Tradit. Chin. West. Med.* 4 (2004) 67–68+78.
- [21] C.-L. Hsieh, G.-C. Yen, Antioxidant actions of du-zhong (*Eucommia ulmoides* Oliv.) toward oxidative damage in biomolecules, *Life Sci.* 66 (2000) 1387–1400.
- [22] G.-C. Yen, C.-L. Hsieh, Inhibitory effect of *Eucommia ulmoides* Oliv. on oxidative DNA damage in lymphocytes induced by H₂O₂, *Teratog. Carcinog. Mutagen.* 1 (2003) 23–34.
- [23] G.-C. Yen, C.-L. Hsieh, Reactive oxygen species scavenging activity of du-zhong (*Eucommia ulmoides* Oliv.) and its active compounds, *J. Agric. Food Chem.* 48 (2000) 3431–3436.
- [24] X. Lan, X. Zhang, G. Gong, Research progress of chlorogenic acid in *Eucommia folium*, *Chin. Agricult. Sci. Bull.* 25 (2009) 86–89.
- [25] W. Mu, Q. Chen, C. Duan, et al., Research progress of active ingredients and pharmacokinetics of *Eucommia ulmoides*, *Chin. J. Mod. Appl. Pharm.* 36 (2019) 2598–2604.
- [26] Y. Deng, T. Lu, P. Yang, et al., Extraction of geniposide from leaves of *Eucommia*, *Technol. Development Chem. Indust.* 48 (2019) 6–16.
- [27] H. Shi, X. He, D. Ouyang, et al., Research progress in the pharmacodynamics of geniposide and its derivatives, *Chin. Pharm. J.* 41 (2006) 4–6.
- [28] X. Jing, W.-H. Huang, Y.-J. Tang, et al., *Eucommia ulmoides* Oliv. (Du-Zhong) lignans inhibit angiotensin II-stimulated proliferation by affecting P21, P27, and bax expression in rat mesangial cells, *Evid. Based Complement Alternat. Med.* 2015 (2015), 987973.

- [29] L. Wen, Y. Jiang, J. Yang, et al., Structure, bioactivity, and synthesis of methylated flavonoids, *Ann. N. Y. Acad. Sci.* 1398 (2017) 120–129.
- [30] J.M. Alves-Silva, M. Zuzarte, C. Marques, et al., Protective effects of phenylpropanoids and phenylpropanoid-rich essential oils on the cardiovascular system, *Mini Rev. Med. Chem.* 19 (2019) 1459–1471.
- [31] Study on antihypertensive effect and mechanism of Duzhongye granules [master's thesis], Henan University, Henan.
- [32] M. Dong, B.P. Yan, J.K. Liao, et al., Rho-kinase inhibition: A novel therapeutic target for the treatment of cardiovascular diseases, *Drug Discov. Today* 15 (2010) 622–629.
- [33] P. Vabres, A. Sorlin, S.-S. Kholmanskikh, et al., Postzygotic inactivating mutations of RHOA cause a mosaic neuroectodermal syndrome, *Nat. Genet.* 51 (2019) 1438–1441.
- [34] E. Pagnin, A. Fragasso, et al., Angiotensin II and cardiovascular-renal remodeling in hypertension: Insights from a human model opposite to hypertension, *High Blood Press Cardiovasc. Prev.* 22 (2015) 215–223.
- [35] R.A. Elrashidy, J. Zhang, G. Liu, Long-term consumption of Western diet contributes to endothelial dysfunction and aortic remodeling in rats: Implication of Rho-kinase signaling, *Clin. Exp. Hypertens.* 41 (2019) 174–180.
- [36] R.V. Patel, B.M. Mistry, S.K. Shinde, et al., Therapeutic potential of quercetin as a cardiovascular agent, *Eur. J. Med. Chem.* 155 (2018) 889–904.
- [37] M. Kondo, Y. Izawa-Ishizawa, M. Goda, et al., Preventive effects of quercetin against the onset of atherosclerosis-related acute aortic syndromes in mice, *Int. J. Mol. Sci.* 21 (2020), 7226.
- [38] Q. Deng, X.X. Li, Y. Fang, et al., Therapeutic potential of quercetin as an anti-atherosclerotic agent in atherosclerotic cardiovascular disease: A review, *Evid. Based Complement Alternat. Med.* 2020 (2020), 5926381.
- [39] K. Yamagata, Polyphenols regulate endothelial functions and reduce the risk of cardiovascular disease, *Curr. Pharm. Des.* 25 (2019) 2443–2458.
- [40] X.-M. Zhou, H. Yao, M.-L. Xia, et al., Comparison of vasodilatation effect between quercetin and rutin in the isolated rat thoracic aorta, *Zhejiang Da Xue Xue Bao Yi Xue Ban* 35 (2006) 29–33.
- [41] S. Nishida, H. Satoh, Comparative vasodilating actions among terpenoids and flavonoids contained in Ginkgo biloba extract, *Clin. Chim. Acta* 339 (2004) 129–133.
- [42] Y.-M. Zhang, Z.-Y. Zhang, R.-X. Wang, Protective mechanisms of quercetin against myocardial ischemia reperfusion injury, *Front. Physiol.* 11 (2020), 956.
- [43] M. Luo, R. Tian, N. Lu, Quercetin inhibited endothelial dysfunction and atherosclerosis in apolipoprotein E-deficient mice: Critical roles for NADPH oxidase and heme oxygenase-1, *J. Agric. Food Chem.* 68 (2020) 10875–10883.
- [44] X. Chen, H. Li, Z. Wang, et al., Quercetin protects the vascular endothelium against iron overload damages via ROS/ADMA/DDAHII/eNOS/NO pathway, *Eur. J. Pharmacol.* 868 (2020), 172885.
- [45] M. Houston, L. Hays, Acute effects of an oral nitric oxide supplement on blood pressure, endothelial function, and vascular compliance in hypertensive patients, *J. Clin. Hypertens. (Greenwich)* 16 (2014) 524–529.
- [46] D. Maaliki, A.A. Shaito, G. Pintus, et al., Flavonoids in hypertension: A brief review of the underlying mechanisms, *Curr. Opin. Pharmacol.* 45 (2019) 57–65.
- [47] Y. Gao, T. Chen, J.U. Raj, Endothelial and smooth muscle cell interactions in the pathobiology of pulmonary hypertension, *Am. J. Respir. Cell Mol. Biol.* 54 (2016) 451–460.
- [48] C.R. Kuhlmann, C.A. Schaefer, C. Kosok, et al., Quercetin-induced induction of the NO/cGMP pathway depends on Ca²⁺-activated K⁺ channel-induced hyperpolarization-mediated Ca²⁺-entry into cultured human endothelial cells, *Planta Med.* 71 (2005) 520–524.
- [49] W. Aoi, N. Niisato, H. Miyazaki, et al., Flavonoid-induced reduction of ENaC expression in the kidney of Dahl salt-sensitive hypertensive rat, *Biochem. Biophys. Res. Commun.* 315 (2004) 892–896.
- [50] P. Sandner, E.-M. Becker-Pelster, J.P. Stasch, Discovery and development of sGC stimulators for the treatment of pulmonary hypertension and rare diseases, *Nitric Oxide* 77 (2018) 88–95.
- [51] S. Lei, F. Peng, M.-L. Li, et al., LncRNA-SMILR modulates RhoA/ROCK signaling by targeting miR-141 to regulate vascular remodeling in pulmonary arterial hypertension, *Am. J. Physiol. Heart Circ. Physiol.* 319 (2020) H377–H391.
- [52] A. Rühle, C. Elgert, M.G. Hahn, et al., Tyrosine 135 of the β subunit as binding site of BAY-543: Importance of the Y-x-S-x-R motif for binding and activation by sGC activator drugs, *Eur. J. Pharmacol.* 881 (2020), 173203.
- [53] J.S. Zhao, W. Deng, H.W. Liu, Effects of chlorogenic acid-enriched extract from *Eucommia ulmoides* leaf on performance, meat quality, oxidative stability, and fatty acid profile of meat in heat-stressed broilers, *Poult. Sci.* 98 (2019) 3040–3049.
- [54] N. Liang, D.D. Kitts, Role of chlorogenic acids in controlling oxidative and inflammatory stress conditions, *Nutrients* 8 (2016), 16.
- [55] Y. Kono, S. Kashine, T. Yoneyama, et al., Iron chelation by chlorogenic acid as a natural antioxidant, *Biosci. Biotechnol. Biochem.* 62 (1998) 22–27.
- [56] S.J. Duthie, A.R. Collins, G.G. Duthie, et al., Quercetin and myricetin protect against hydrogen peroxide-induced DNA damage (strand breaks and oxidised pyrimidines) in human lymphocytes, *Mutat. Res.* 393 (1997) 223–231.
- [57] H.-Y. Xue, G.-Z. Gao, Q.-Y. Lin, et al., Protective effects of aucubin on H₂O₂-induced apoptosis in PC12 cells, *Phytother. Res.* 26 (2012) 369–374.
- [58] I.-C. Young, S.-T. Chuang, C.-H. Hsu, et al., Protective effects of aucubin on osteoarthritic chondrocyte model induced by hydrogen peroxide and mechanical stimulus, *BMC Complement Altern. Med.* 17 (2017), 91.
- [59] J. Cheng, C.-C. Wu, K.H. Gotlinger, et al., 20-Hydroxy-5,8,11,14-eicosatetraenoic acid mediates endothelial dysfunction via I κ B kinase-dependent endothelial nitric-oxide synthase uncoupling, *J. Pharmacol. Exp. Ther.* 332 (2010) 57–65.
- [60] M. Zhang, L. Jiang, Oxidized low-density lipoprotein decreases VEGFR2 expression in HUVECs and impairs angiogenesis, *Exp. Ther. Med.* 12 (2016) 3742–3748.
- [61] R. Kuroda, K. Kazumura, M. Ushikata, et al., Elucidating the improvement in vascular endothelial function from sakurajima daikon and its mechanism of action: A comparative study with raphanus sativus, *J. Agric. Food Chem.* 66 (2018) 8714–8721.
- [62] X.-P. Lin, H.-J. Cui, A.-L. Yang, et al., Astragaloside IV improves vasodilatation function by regulating the PI3K/Akt/eNOS signaling pathway in rat aorta endothelial cells, *J. Vasc. Res.* 55 (2018) 169–176.
- [63] E.-D. Harris, Regulation of antioxidant enzymes, *FASEB J.* 6 (1992) 2675–2683.
- [64] B.C. Bai, Y.Y. Yang, Q. Wang, et al., NLRP3 inflammasome in endothelial dysfunction, *Cell Death Dis.* 11 (2020), 776.
- [65] C.-Y. Kwan, C.-X. Chen, T. Deyama, et al., Endothelium dependent vaso-relaxant effects of the aqueous extracts of the *Eucommia ulmoides* Oliv. leaf and bark: Implications on their antihypertensive action, *Vasc. Pharmacol.* 40 (2003) 229–235.
- [66] S. Tsukamoto, Y. Yamaguchi, T. Ueda, et al., Hypotensive effects of beverage containing 'Eucommia leaf glycoside' on high normal blood pressure and mild hypertensive subjects, *Int. Symp. Eucommia Ulmoides.* 1 (2007) 47–54.
- [67] J. Mei, F. Yang, Progress of *Eucommia ulmoides* in treatment of hypertension, *World Latest Med. Inform (Electr. Vers.)* 18 (2018) 35–36.
- [68] E. Józefczuk, R. Nosalski, B. Saju, et al., Cardiovascular effects of pharmacological targeting of sphingosine kinase 1, *Hypertension* 75 (2020) 383–392.
- [69] J.-Y. Moon, Recent Update of Renin-Angiotensin-Aldosterone System in the Pathogenesis of Hypertension, *Electrolyte Blood Press.* 11 (2013) 41–45.
- [70] G. Edwards, K.A. Dora, M.J. Gardener, et al., K⁺ is an endothelium-derived hyperpolarizing factor in rat arteries, *Nature* 396 (1998) 269–272.
- [71] X. Jin, K. Amitani, Y. Zamami, et al., Ameliorative effect of *Eucommia ulmoides* Oliv. leaves extract (ELE) on insulin resistance and abnormal perivascular innervation in fructose-drinking rats, *J. Ethnopharmacol.* 128 (2010) 672–678.
- [72] H. Chen, W. Zhao, Y. Liu, et al., Effect of quercetin on calcium-activated potassium channels in mesenteric artery smooth muscle cells in essential hypertension patients, *Chin. J. Hypertens.* 16 (2008) 707–711.
- [73] G. Mancia, G. Grassi, The autonomic nervous system and hypertension, *Circ. Res.* 114 (2014) 1804–1814.
- [74] G. Seravalle, L. Lonati, S. Buzzi, et al., Sympathetic nerve traffic and baroreflex function in optimal, normal, and high-normal blood pressure states, *J. Hypertens.* 33 (2015) 1411–1417.
- [75] D. Hering, T. Kara, W. Kucharska, et al., Longitudinal tracking of muscle sympathetic nerve activity and its relationship with blood pressure in subjects with prehypertension, *Blood Press.* 25 (2016) 184–192.
- [76] T. Deyama, S. Nishibe, Y. Nakazawa, Constituents and pharmacological effects of *Eucommia* and *Siberian ginseng*, *Acta Pharmacol. Sin.* 22 (2001) 1057–1070.
- [77] T. Namba, M. Hattori, J. Yie, et al., Studies on *Tu-Chung* leaves (1): Pharmacological effects of the water extract *in vivo*, *J. Tradit. Med.* 3 (1986) 89–97.
- [78] S. Takatori, Y. Zamami, M. Mio, et al., Chronic hyperinsulinemia enhances adrenergic vasoconstriction and decreases calcitonin gene-related peptide-containing nerve-mediated vasodilation in pithed rats, *Hypertens. Res.* 29 (2006) 361–368.
- [79] Y. Zamami, S. Takatori, K. Yamawaki, et al., Acute hyperglycemia and hyperinsulinemia enhance adrenergic vasoconstriction and decrease calcitonin gene-related peptide-containing nerve-mediated vasodilation in pithed rats, *Hypertens. Res.* 31 (2008) 1033–1044.
- [80] X. Wang, X. Zeng, W. Luo, et al., Antihypertensive and target organ protection effect of *Eucommia ulmoides* and its mechanism, *Chin. J. Clin. Pharmacol. Therapeut.* 21 (2016) 1429–1433.
- [81] T. Fujikawa, T. Hirata, A. Wada, et al., Chronic administration of *Eucommia* leaf stimulates metabolic function of rats across several organs, *Br. J. Nutr.* 104 (2010) 1868–1877.
- [82] S.A. Park, M.-S. Choi, U.J. Jung, et al., *Eucommia ulmoides* Oliver leaf extract increases endogenous antioxidant activity in type 2 diabetic mice, *J. Med. Food* 9 (2006) 474–479.
- [83] D. Luo, T.C. Or, C.L. Yang, et al., Anti-inflammatory activity of iridoid and catechol derivatives from *Eucommia ulmoides* Oliver, *ACS Chem. Neurosci.* 5 (2014) 855–866.
- [84] X.-R. Yu, G.-R. Jia, G.-D. Gao, et al., Neuroprotection of insulin against oxidative stress-induced apoptosis in cultured retinal neurons: Involvement of phosphoinositide 3-kinase/Akt signal pathway, *Acta Biochim. Biophys. Sin. (Shanghai)* 38 (2006) 241–248.
- [85] H. Sabbineni, A. Verma, S. Artham, Pharmacological inhibition of β -catenin prevents EndMT *in vitro* and vascular remodeling *in vivo* resulting from endothelial Akt1 suppression, *Biochem. Pharmacol.* 164 (2019) 205–215.
- [86] H. Nakahara, J. Song, M. Sugimoto, Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis, *Arthritis Rheum.* 48 (2003) 1521–1529.
- [87] M.K. Jones, H. Wang, B.M. Peskar, et al., Inhibition of angiogenesis by non-steroidal anti-inflammatory drugs: Insight into mechanisms and implications for cancer growth and ulcer healing, *Nat. Med.* 5 (1999) 1418–1423.

- [88] C.S. Williams, M. Tsujii, J. Reese, et al., Host cyclooxygenase-2 modulates carcinoma growth, *J. Clin. Invest.* 105 (2000) 1589–1594.
- [89] C.C. Cechinel-Zanchett, R.C.M.V.A.F. da Silva, A. Tenfen, et al., *Bauhinia forficata* link, a Brazilian medicinal plant traditionally used to treat cardiovascular disorders, exerts endothelium-dependent and independent vasorelaxation in thoracic aorta of normotensive and hypertensive rats, *J. Ethnopharmacol.* 243 (2019), 112118.
- [90] W. Wu, B. Yang, Y. Qiao, et al., Kaempferol protects mitochondria and alleviates damages against endotheliotoxicity induced by doxorubicin, *Biomed. Pharmacother.* 126 (2020), 110040.
- [91] G. Vechi, P. de Souza, L.M. da Silva, et al., Mechanisms underlying *Eugenia mattosii* D. Legrand leaves extract, fractions and compounds induce relaxation of the aorta from normotensive and hypertensive rats, *3 Biotech* 9 (2019), 445.
- [92] A.T. Fabro, J. Machado-Rugolo, C.M. Baldavira, et al., Circulating plasma miRNA and clinical/hemodynamic characteristics provide additional predictive information about acute pulmonary thromboembolism, chronic thromboembolic pulmonary hypertension and idiopathic pulmonary hypertension, *Front. Pharmacol.* 12 (2021), 648769.
- [93] T.-Y. Wu, T.O. Khor, C.L. Saw, et al., Anti-inflammatory/Anti-oxidative stress activities and differential regulation of Nrf2-mediated genes by non-polar fractions of tea *Chrysanthemum zawadskii* and licorice *Glycyrrhiza uralensis*, *AAPS J.* 13 (2011) 1–13.
- [94] H. Zhang, W. Huang, H. Liu, et al., Mechanical stretching of pulmonary vein stimulates matrix metalloproteinase-9 and transforming growth factor- β 1 through stretch-activated channel/MAPK pathways in pulmonary hypertension due to left heart disease model rats, *PLoS One* 15 (2020), e0235824.
- [95] Y. Yao, T. Liu, L. Yin, et al., Polyphenol-rich extract from *Litchi chinensis* seeds alleviates hypertension-induced renal damage in rats, *J. Agric. Food Chem.* 69 (2021) 2138–2148.
- [96] L. Chen, Y. Cui, B. Li, et al., Advanced glycation end products induce immature angiogenesis in *in vivo* and *ex vivo* mouse models, *Am. J. Physiol. Heart Circ. Physiol.* 318 (2020) H519–H533.