Current natural products with antihypertensive activity

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[ABSTRACT] Natural products have been an important source of new drugs, which also played a dominant role in the discovery and research of new drugs for the treatment of hypertension. This review article reviews the recent progress in the research and development of natural lead compounds with antihypertensive activity, including alkaloids, diterpenes, coumarins, flavonoids, and peptides. We summarized their structures, sources, as well as the antihypertensive mechanisms. These information provides instructive reference for the following structural modifications and optimization.

[KEY WORDS] Natural products; Antihypertensive activity; Lead compounds; Action mechanism

Introduction

Natural products have been an exemplary source of new drugs, and many of the currently available medicines have been directly or indirectly derived from them, which is particularly evident in the areas of cancer and infectious diseases. Meanwhile, the influence of natural product is also quite evident in other areas. The research, development, and use of natural products as therapeutic agents, especially those derived from plants, have been increasing in recent years.

Hypertension has become one of the most important preventable causes for premature morbidity and mortality worldwide. It is estimated to cause 7.5 million deaths, about 12.8% of all annual deaths. Most of the currently used antihypertensive agents cannot be used as a single drug therapy because of their limited efficacy and side effects. Therefore, the research and development of new drugs with multiple therapeutic effects is most desirable.

The treatment of hypertension with plant extracts or plant-derived products is well documented. Some plant sources of antihypertensive natural products were listed in Fig. 1. However, references about isolation, identification and mechanism research of the lead compounds really contributive to antihypertensive activity are still limited. In this review article, we discuss the recent progress in the research of natural lead compounds with antihypertensive activity, emphasizing the mechanisms underlying their antihypertensive action.

Alkaloids

(+)–Dicentrine

(+)–Dicentrine (Compound 1, Fig. 2) is an alkaloid aporphine derivative isolated from the plant Lindera megaphylla and Actinodaphne sesquipedalis. Several in vitro and in vivo evaluations have proven that this alkaloid is a good candidate for treatment of hypertension and other cardiovascular diseases. After oral administration of (+)-dicentrine (5 and 10 mg kg⁻¹, twice a day) for 4 weeks, the mean arterial pressure (MAP) in spontaneously hypertensive rats (SHRs) decreased from 160 mmHg to 102 mmHg, and the declining rates was 36.3% [7]. However, a higher dose of (+)-dicentrine (10 mg kg⁻¹, i.v.) did not cause any significant changes in heart rate (HR), cardiac output (CO), or stroke volume (SV) [8]. Mechanistic research has shown that (+)-dicentrine is an α₁-adrenoceptor antagonist which is more selective towards the putative α₁D-adrenoceptor subtype of the rat aorta than the α₁B-adrenoceptor subtype of the spleen [9].
Laurotetanine

The leaves of Laureliu sempervirens (Monimiaceae), an endemic Chilean tree known as “Laurel”, are used by the Mapuche Amerindians for treating headache and as a diuretic. Intravenous administration of a hydroalcoholic L. sempervirens extract to rats, elicited a hypotensive response of (−27.0 ± 2.0)% in the MAP of normotensive animals at a dose of 5 mg kg⁻¹. In an acute oral toxicity study, “Laurel” was proven to be a very low toxicity crude drug at doses up to 3 g crude extract. Bioassay-guided isolation led to the alkaloid laurotetanine (Compound 2, Fig. 2) as the main hypotensive principle of L. sempervirens leaves. Laurotetanine (1 mg kg⁻¹) produced a hypotensive response of (−29.0 ± 2.1)% in the MAP of normotensive rats, with a duration of 2 min, which was comparable to that of the crude extract at 5 mg kg⁻¹.[10]

Dehydroevodiamine

Dehydroevodiamine (DeHE) (Compound 3, Fig. 2) is an isoquinazolinocarboline alkaloid isolated from the Chinese herbal drug Wu Chu Yu, the dried unripe fruit of Evodia rutaecarpa, which has been shown to produce vasorelaxant and hypotensive effects. Biological tests have demonstrated that DeHE induces relaxation in precontracted rat isolated mesenteric arteries in a concentration-dependent manner. The underlying mechanisms may be complex, involving interaction with the endothelium through the NO-guanylyl cyclase pathway, α-adrenoceptor blockade, K⁺ channel activation, and Ca²⁺ channel blockade.[11]

Rhynchophylline and isorhynchophylline

Uncaria rhynchophylla is one of the original plants of the important Chinese crude drug, “Gouteng”, which is mainly used for the treatment of hypertension. Rhynchophylline (Compound 4, Fig. 2) and isorhynchophylline (Compound 5, Fig. 2) are the main hypotensive constituents in Uncaria rhynchophylla. Studies have shown that the properties of rhynchophylline and isorhynchophylline are very similar and that the latter undergoes rapid transformation into the former in acidic medium. The hypotensive potency of Compound 5 (lowering of MAP by 42.0%) is much stronger than that of Compound 4 (lowering of MAP by 32.1%) in anesthetized rats. In anesthetized thoracotomized dogs, Compound 5 (1 mg kg⁻¹, i.v.) reduced the mean arterial pressure, heart rate, and coronary blood flow by (3.58 ± 0.19) kPa, (26 ± 18) beats/min, and (0.10 ± 0.04) mL min⁻¹ g⁻¹, respectively.
active mechanisms are related to the modulation of calcium ion channel, protection of neural and neuroglial cells against β-amyloid (25–35)-induced neurotoxicity and via inducing autophagy.\textsuperscript{12-14}.

\textbf{Dihydrocorynantheine}

Dihydrocorynantheine (Compound 6, Fig. 2) is an alkaloid present in \textit{Uncaria macrophylla}, a \textit{Uncaria} genus plant. It exhibits significant vasodilating activity against phenylephrine-induced contraction in rat thoracic aorta rings (IC\textsubscript{50} 6.73 μg·mL\textsuperscript{-1}), which has potential effect for the treatment of hypertension.\textsuperscript{15}

\textbf{Isoliensinine}

Isoliensinine (Compound 7, Fig. 2) is the main alkaloid in \textit{Nelumbo nucifera} \textit{Gaertn}, which exhibits certain antihypertensive activity. In pithed rats (pretreated with phenylephrine), the systolic arterial pressure (SAP) and pressor activity. In pithed rats (pretreated with \textit{Nelumbonucifera Gaertn}), isoliensinine (Compound 7, Fig. 2) totally relaxed the contractions induced by NA (IC\textsubscript{50} 6.24 ± 0.55 μmol·L\textsuperscript{-1}) or by a high extracellular KCl concentration (IC\textsubscript{50} 5.23 ± 0.48 μmol·L\textsuperscript{-1}) in intact rat aortic rings in a concentration-dependent fashion and with almost equal effectiveness under both assay conditions. These findings indicate a therapeutic potential as an original chemical basis for the design and subsequent development of new antihypertensive drugs.\textsuperscript{20}

\textbf{Puqienine A, puqienine B and puqienine E}

It has been reported that the steroidal alkaloids in many plants have antihypertensive effects in humans. Puqienine A (Compound 10, Fig. 3), puqienine B (Compound 11, Fig. 3) and puqienine E (Compound 12, Fig. 3) are steroidal alkaloids isolated from \textit{Fritillaria puqiensis}, and their antihypertensive effects have been assessed in vitro, based on the inhibition of the purified angiotensin converting enzyme (ACE) using a high-performance liquid chromatography assay. The reported results have shown that puqienine A, puqienine B and puqienine E exhibit better inhibitory activity than ACE, with inhibition ratios of (20.4 ± 2.8)%, (24.7 ± 0.5)% and (70.2 ± 0.5)%, respectively at the concentration of 200 μmol·L\textsuperscript{-1}. The IC\textsubscript{50} of puqienine E is 68 μmol·L\textsuperscript{-1}. The screening and identification of these ACE inhibitory alkaloids could, to some extent, provide evidence for the application of \textit{F. puqiensis} or other species of \textit{Fritillaria} genus in hypertensive therapy.\textsuperscript{21}

\textbf{Reserpine and deserpidine}

Reserpine (Compound 13, Fig. 4) and deserpidine (Compound 14, Fig. 4) were first isolated in 1952 from Indian snake root, \textit{Rauwolfia serpentine}. Reserpine was introduced for the treatment of hypertension in late 1950s, but deserpidine has not been widely employed in medicine due to its poor availability from natural extracts. The antihypertensive actions of reserpine are a result of its ability to deplete catecholamines from peripheral sympathetic nerve endings. Reserpine irreversibly blocks the vesicular monoamine transporter (VMAT), which normally transports free norepinephrine, serotonin, and inhibition the increase of [Ca\textsuperscript{2+}], in a concentration-dependent manner. These results suggest that lobeline can be used for the treatment of atherosclerosis and hypertension.\textsuperscript{18-19}

\textbf{(+)-Nantenine}

(+)-Nantenine (Compound 9, Fig. 2) is an aporphine alkaloid isolated from \textit{Nandina domestica}, extracts of which have been widely used in Japan for the treatment of asthma, uterine bleeding and diabetes. In a recent research, (+)-nantenine (3–30 μmol·L\textsuperscript{-1}) totally relaxed the contractions induced by NA (IC\textsubscript{50} 6.24 ± 0.55 μmol·L\textsuperscript{-1}) or by a high extracellular KCl concentration (IC\textsubscript{50} 5.23 ± 0.48 μmol·L\textsuperscript{-1}) in intact rat aortic rings in a concentration-dependent fashion and with almost equal effectiveness under both assay conditions. These findings indicate a therapeutic potential as an original chemical basis for the design and subsequent development of new antihypertensive drugs.\textsuperscript{20}

\textbf{Tetrandrine}

Tetrandrine (Compound 15, Fig. 4) is the major bisbenzyl
isoquinoline of Han Fang Ji (*Stephania tetrandra*, Menispermaceae) and the most characteristic active constituent of this Chinese herbal remedy, which has been used for centuries in the treatment of hypertension. The smooth muscle relaxant and hypotensive action of tetrandrine is attributed to its selective blockade of calcium channels and its interaction with $\alpha_1$-adrenergic receptors [23].

**Diterpenes**

*Forskolin*

Forskolin (Compound 16, Fig. 4) is the main active compound in the Indian plant *Coleus forskohlii*. Several studies demonstrated that forskolin lowers blood pressure via relaxation of vascular smooth muscle. On the one hand, forskolin activates adenylate cyclase, producing an increase in cAMP, which in turn will activate cAMP-dependent protein kinase (PKA) and produce relaxation. On the other hand, the relaxation induced by forskolin also involves hyperpolarization of smooth muscle and Ca$^{2+}$ extrusion across the plasma membrane. In humans, forskolin (4 μg·kg$^{-1}$·min$^{-1}$, i.v.) decreases vascular resistance, improves left ventricular contractility and decreases the arterial pressure [1, 24-26].

*Stevioside*

Stevioside (Compound 17, Fig. 4), a diterpenoid glycoside comprising of an aglycone (steviol) and three molecules of glucose, is extracted from *Stevia rebaudiana* Bertoni, which is a small shrub originally grown in South America. It has previously been shown to reduce blood pressure in studies in animals and humans. The hypotensive effects on both SAP and DAP were dose-dependent for intravenous doses of 50, 100 and 200 mg·kg$^{-1}$ in conscious SHRs. The maximum reductions in SAP and DAP were (31.4 ± 4.2) % and (40.8 ± 5.6)%, respectively [27]. However, crude stevioside at doses up to 15.0 mg·kg$^{-1}$·d$^{-1}$ did not show an antihypertensive effect on previously untreated mild hypertensive patients [28]. The possible antihypertensive mechanism of stevioside is to affect vascular resistance via inhibition of extracellular Ca$^{2+}$ influx and the release of a vasodilator prostaglandin. Stevioside also produces diuresis and natriuresis resulting in reduction of extracellular fluid volume [29].

*14-Deoxy-11, 12-didehydroandrographolide*

*Andrographis paniculata* (Burm. f.) Nees (Acanthaceae) has a considerable medicinal reputation in Malaysia as a potent medicine in the treatment of diabetes and hypertension. 14-Deoxy-11, 12-didehydroandrographolide (DDA) (Compound 18, Fig. 4) is a diterpenoid isolated from *A. paniculata*. In an aesthetised rats, DDA produced significant falls in MAP and heart rate in a dose-dependent manner with the maximum decrease of (37.6 ± 2.6)% and (18.1 ± 4.8)%, respectively. It seems to work via adrenoceptors, autonomic ganglia receptor or angiotensin- converting enzyme, since the hypotensive effect of DDA is negated or attenuated in the presence of propranolol, hexamethonium and captopril. In the isolated right atria, DDA caused negative chronotropic action and antagonised isoproterenol-induced positive chronotropic actions in a non-competitive and dose-dependent manner. These results further support the bradycardia-inducing and $\beta$-adrenoceptor antagonist properties of DDA *in vivo* [30].

ent-Kaur-16-en-19-oic acid (Compound 19, Fig. 4) and ent-kaur-16-en-15-one-19-oic acid (Compound 20, Fig. 4) are two kaurane-type diterpenes isolated from *Xylopia aethiopica*, which is an evergreen and aromatic tree in Africa. Intravenous administration of these two compounds at 10 mg·kg−1 in normotensive rats produced an immediate decrease of SAP by 17% and 18%, respectively, no change of DAP, and a significant decrease of heart rate by 20% and 55%, respectively. Other similar results also show that ent-kaur-16-en-19-oic acid (15 mg·kg−1, i.v.) decreases MAP of conscious normotensive rats [31-32]. Further study on the vascular relaxation effects has proven that ent-kaur-16-en-19-oic acid blocks extracellular Ca2+ influx stimulated neuronal NO synthase and NO-cGMP pathway [33].

**Labd-8(17)-en-15-oic acid**

The diterpene 8(17), 12E, 14-labdatrien-18-oic acid (Compound 21, Fig. 4) is isolated from *Xylopia langsdorffiana* stem ethanolic extracts. In normotensive, conscious animals, this diterpene produces dose-dependent hypotension and tachycardia. In isolated mesenteric artery rings, the diterpene (10−10−1 mol·L−1) elicits concentration-dependent relaxation of phenylephrine-induced contractions (IC50 = 5.4 ± 1.4 µmol·L−1). It also causes concentration-dependent relaxation in arterial rings pre-contracted with high extracellular KCl (80 mmol·L−1). In Ca2+-free depolarized preparations, it inhibits contractions produced by cumulative increases in extracellular Ca2+ concentration. These results demonstrate that Compound 21 causes hypotension through peripheral vasodilation, which is mediated in part by NO and PGII as well as by blockade of Ca2+ entry through L-type Ca2+ channels [34].

**Labd-8(17)-en-15-oic acid**

Labd-8(17)-en-15-oic acid (Labd-8, Compound 22, Fig. 4) is a labdenediterpene isolated from methanolic extract of *Moldenhawera nutans*. Biological evaluation has shown that i.v. treatment with Compound 22 induces dose-dependent hypotensive and tachycardiac effects in both conscious and anesthetized rats. Compound 22 (1–1 000 µg·mL−1) induces a concentration-dependent reduction of potassium (60 mmol·L−1)-induced contraction (IC50 = 313.6 µmol·L−1), an effect that remains unaffected (IC50 = 440.8 µg·mL−1) by removal of vascular endothelium. The hypotension is mainly due to withdrawal of sympathetic tone to the vasculature and also partly to an active vascularrelaxation [35].

**Triptolide**

*Tripterygium wilfordii* Hook F. (TWHF) is an herb used in traditional Chinese medicine. Triptolide (Compound 23, Fig. 4) is a highly oxygenated diterpene lactone epoxide compound extracted from TWHF. In pneumonectomized rats that receive monocrotaline, triptolide attenuates the development of pulmonary hypertension and right ventricular hypertrophy, and promotes regression of pulmonary arterial neointimal formation [36].

**Coumarins**

**(+) Praeruptorin A**

**(+) Praeruptorin A** (Compound 24, Fig. 4) is a coumarin isolated from *Peucedanumpra eruptorum* Dunn, which is a well-known traditional Chinese medicine used for the treatment of respiratory diseases and pulmonary hypertension. **(+) Praeruptorin A** produces significant relaxant effects in rabbit tracheal preparations constricted with KCl or acetycholine, and completely relaxes tracheas constricted with 40 mmol·L−1 KCl at a concentration of 30 µmol·L−1. The relaxant activity is due to its calcium antagonistic action [37].

**Imperatorin**

Imperatorin (Imp, Compound 25, Fig. 5), a dietary furanocoumarin, is wide spread and found not only in the medicinal plant such as *Cnidium monnier cissus* and *Angelica dahurica*, but also in popular culinary herbs such as parsnip, parsley, and fennel. After 13 weeks of treatment with Compound 25 (25 mg·kg−1·d−1, i.g.), the SAP DAP in SHRs were reduced significantly. A series of experiments have demonstrated that Compound 25 targets the L-type calcium channel. The aortic ring is relaxed with Compound 25, and L-type calcium channel currents and intracellular calcium free ion rise are nearly disappeared when adding Compound 25. Imperatorin is a novel structure of furanocoumarins calcium antagonist, which has a potential application for the hypertension treatment in clinic [38].

**Ostruthol**

Ostruthol (Compound 26, Fig. 5) is a furanocoumarin isolated from *Peucedanum ostruthium*, which is used in traditional medicine in the treatment of cardiovascular diseases. It exhibits a much higher activity against K+-spasms than against norepinephrine-contractions; the inhibition ratio is about 35% at the concentrations of 0.01 g·mL−1, suggesting a blockade of voltage-operated calcium channel [39].

**Flavonoids**

**Quercetin and isorhamnetin**

Total flavones of *Hippophae Rhamnoides* (TFH) are extracts of *Hippophae Rhamnoides*, mainly composed of quercetin (Compound 27, Fig. 5) and isorhamnetin (Compound 28, Fig. 5), which display antihypertensive and target organ protecting activity. After 12 weeks of treatment with TFH (30 mg·kg−1·d−1), the SAP of SHRs was decreased by 14%, comparable with enalapril group (30 mg·kg−1·d−1, decreased by 16%) and hydrochlorothiazide group (25 mg·kg−1·d−1, decreased by 14%). Moreover, TFH may inhibit the expression of MCP-1 in aorta and intimal medial thickness of aorta [40].

**Astragalin**

The leaves of the persimmon *Diospyros kaki* have been traditionally used for treatment of hypertensive diseases in Japan. Several flavonoids isolated from the leaves showed...
moderate angiotensin-converting enzyme inhibitory activity. Among them, astragalin (Compound 29, Fig. 5) produces inhibition by 67% at a concentration of 300 μg·mL⁻¹. The IC₅₀ of astragalin is 180 μg·mL⁻¹ [41].

**Orientin**

Orientin (Compound 30, Fig. 5) is an active compound isolated from Bamboo leaves, *Phyllostachys nigra*, which have been used as a Chinese medicament for thousands of years. Orientin relaxes phenylephrine-induced contractions with an IC₅₀ value being 2.28 μmol·L⁻¹ in the endothelium-intact and with an IC₅₀ value being around 7.27 μmol·L⁻¹ in the endothelium removed aortic rings. The vasorelaxant effect of Orientin on endothelium-intact thoracic aortic rings is attenuated by the nitric oxide (NO) synthase inhibitor N⁵-nitro-L-arginine methyl ester, but not by indomethacin (a cyclooxygenase inhibitor), tetroxylanimonium, chloride (K⁺channels inhibitor) or propranolol (β-receptor inhibitor). Furthermore, Orientin inhibits norepinephrine (NE), CaCl₂ and KCl-induced vasoconstriction concentration-dependently in a non-competitive manner, and also reduces both the initial fast release and the sustained phases of phenylephrine-induced contractions. Orientin can stimulate NO production from endothelial cells. These results indicate that Orientin relaxes thoracic aortic rings by the nitric oxide-cGMP pathway, and inhibits the contraction induced by the activation of receptor-operating and voltage-dependent Ca²⁺ channels in the vascular smooth muscle. The inhibition of both intracellular Ca²⁺ release and extracellular Ca²⁺ influx may be one of the main vasorelaxant mechanisms of Orientin [42].

**Cardamonin and Alpinetin**

The natural vascular products cardamonin (Compound 31, Fig. 5) and alpinetin (Compound 32, Fig. 5) are isolated from *Alpinia henryi* K. Schum. Both cardamonin and alpinetin induce relaxation of phenylephrine-precontracted arteries with respective IC₅₀ of (9.3 ± 0.6) and (27.5 ± 2.8) μmol·L⁻¹. They inhibit 60 mmol·L⁻¹ K⁺-induced contraction with respective IC₅₀ of (11.5 ± 0.3) and (37.9 ± 3.6) μmol·L⁻¹. In addition, both agents inhibit the transient contraction induced by 3 μmol·L⁻¹ of phenylephrine or by 10 mmol·L⁻¹ of caffeine in Ca²⁺-free Krebs solution. These results indicate that purified cardamonin and alpinetin relax mesenteric arteries of rats through multiple mechanisms. They induce both endothelium-dependent and -independent relaxation; the former is likely mediated by nitric oxide, whereas the latter is probably mediated through non-selective inhibition of Ca²⁺ influx and intracellular Ca²⁺ release and inhibition of the protein kinase C-dependent contractile mechanism [43].

**ACE inhibitory Peptides**

ACE inhibitors have been prescribed for hypertensive patients throughout the world. Synthesized chemical drugs such as Captopril, Enalapril, Alacepriland Lisinopril are extensively used medications in treatment and prevention of hypertension. However, these drugs often cause side-effects in the patients, such as a persistent dry cough, taste disturbance, increased potassium levels, reduced renal function, and skin rashes [44].

In recent years, peptides from partial enzymatic hydrolysates of food proteins have received a greater attention than before. Many biological peptides promoting health benefits have been classified and identified from food protein hydrolysates. These peptides are inactive within the sequence of the parent protein, but can be released during enzymatic digestion or food processing [45]. Naturally sourced angiotensin converting enzyme (ACE) inhibitors raise the possibility that hypertension could be modulated through dietary intake. ACE-inhibitory peptides have been isolated from various marine proteins such as Heshiko, a fermented mackerel product, skipjack tuna muscle, sardine muscle, shark meat, Alaskan Pollack skin, marine shrimps, pacific hake, and salmon chum (Table 1) [46].

**Other natural products with antihypertensive activity**

**Daleformis**

Daleformis (Compound 33, Fig. 5) is a novel pterocarpinoid extracted from the roots of *Dalea filiciformis* Snader (Fabaceae). Biological assays have shown that daleformis is a novel inhibitor of endothelin converting enzyme inhibitory activity.
Table 1  Examples of ACE inhibitory peptides derived from marine sources

<table>
<thead>
<tr>
<th>Origin</th>
<th>Hydrolysis</th>
<th>Peptide sequence</th>
<th>IC50/μmol·L⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardine muscle</td>
<td>Alkaline protease</td>
<td>Lys-Trp</td>
<td>1.63</td>
</tr>
<tr>
<td>Dried skipjack tuna muscle</td>
<td>Thermolysin</td>
<td>Leu-Lys-Pro-Met-Asn,</td>
<td>2.4</td>
</tr>
<tr>
<td>Skipjack tuna muscle</td>
<td>Acid extract</td>
<td>Pro-Thr-His-Ile-Lys-Trp-Gly-Asp</td>
<td>2.0</td>
</tr>
<tr>
<td>Salmon chum muscle</td>
<td>Thermolysin</td>
<td>Phe-Leu, Leu-Phe, Cys-Phe, Glu-Try, Phe-Glu</td>
<td>13.6, 383.2, 1.96, 2.68, 1.45</td>
</tr>
<tr>
<td>Shark meat</td>
<td>Protease SM98011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shrimp Aceteschinensis</td>
<td>L. fermentum SM 605</td>
<td>Asp-Pro, Gly-Thr-Gly, Ser-Thr</td>
<td>2.15, 5.54, 4.03</td>
</tr>
<tr>
<td>Oyster protein</td>
<td>Pepsin</td>
<td>Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe</td>
<td>66.00</td>
</tr>
<tr>
<td>Alaska Pollack skin</td>
<td>Alcalase, PronaseE &amp; collagenase</td>
<td>Gly-Pro-Met, Gly-Pro-Leu</td>
<td>17.13, 2.60</td>
</tr>
<tr>
<td>Anchovy fermented fish sauce</td>
<td>Unknown</td>
<td>Lys-Pro</td>
<td></td>
</tr>
<tr>
<td>Algae protein waste</td>
<td>Pepsin</td>
<td>Val-Glu-Cys-Tyr-Gly-Pro-Asn-Arg-Pro-Gln-Phe</td>
<td>29.60</td>
</tr>
<tr>
<td>Wakame (Undariapinnatifida)</td>
<td>Protease S &quot;Amano&quot;</td>
<td>Ile-Tyr, Val-Trp, Ile-Trp</td>
<td>6.10, 3.30, 1.50</td>
</tr>
</tbody>
</table>

enzyme (ECE), with an IC₅₀ being 9 μmol·L⁻¹ ECE is a membrane bound neutral metalloprotease that catalyzes the conversion of a 38-residue inactive intermediate big endothelin to a 21-residue potent vasoconstrictive peptide, endothelin-1 (ET-1), which is a strong promoter for vascular contraction. As an ECE inhibitor, daleformis could reduce production of endothelin by interfering with the ET-1 biosynthesis pathway, which may have therapeutic utility for hypertension or renal failure [47].

**Magnesium lithospermate B**

Magnesium lithospermate B (Compound 34, Fig. 6) is an active component of *Salviae Miltiorrhizae* Radix, which is widely employed in China to improve blood flow and dilate blood vessels. SAP is significantly descended in SHRs given magnesium lithospermate B at 10 mg·kg⁻¹ for both 12 and 24 days. Administration of magnesium lithospermate B caused an 8% reduction in SAP from 223.7 to 206.7 mmHg on Day 12 and a 10% reduction from 230.1 to 206.3 mmHg on Day 24. Oral administration of magnesium lithospermate B also decreased the MAP of rats with renal failure. On Day 12, MAP was significantly lowered from 173.0 to 158.6 mmHg for a 10 mg dose of the compound. It also significantly increased the low urinary kallikrein level in SHRs, with a parallel increase in excretion of prostaglandin E, sodium and potassium ions. These data suggest that magnesium lithospermate B may ameliorate the development of hypertension by improving the renal circulatory state. Additionally, a study on the acute toxicity of oral magnesium lithospermate B in terms of LD₅₀ determined by the up and down method has shown a high safety of this substance (> 3 000 mg·kg⁻¹ in 6-week-old male ddY mice weighing 31–35 g) [48].

**Halistanoldisulfate B**

Sulfated sterols have been described from a wide variety of marine organisms, particularly sponges and echinoderms, and several of these steroidal sulfates have exhibited a broad range of activities. One of the sponge extracts isolated from sponge *Pachastrella* sp, collected in South Africa, has been found to be active in the ECE inhibition screen. Halistanoldisulfate B (Compound 35, Fig. 6) is the main active constituent, which is a novel inhibitor of ECE, with an IC₅₀ being 2.1 μmol·L⁻¹ [49].

**Ursolic and moronic acids**

*Phoradendron reichenbachianum* is a medicinal plant which is used in Mexican traditional medicine for the treatment of renal diseases, as well as antidiabetic and antihypertensive agent. Ursolic (Compound 36, Fig. 6) and moronic acids (Compound 37, Fig. 6) are triterpenic acids extracted from *Phoradendron reichenbachianum* and show a significant relaxant effect in a concentration and endothelium-dependent manners on rat aorta rings after contraction with NA (ursolic acid EC₅₀ 11.7 μmol·L⁻¹; moronic acid EC₅₀ 16.1 μmol·L⁻¹). Moreover, the relaxant effects induced by these two triterpenic acids seem to be involved NO release in functional experiments.
Also, the docking results indicate that they could interact with the binding pockets C1 and C2 that access the catalytic site and this interaction may activate eNOS. The results could make pentacyclic triterpenic acids as leads for the design and development of new antihypertensive drugs [50].

Isochroman-4-one XJP

The banana peel is a great resource in China, which has been widely used as a folk medicine for antihypertension, antiulceration and antibacterial treatments. A novel and structurally unique isochroman-4-one (±)-XJP (Compound 38, Fig. 7), a natural polyphenolic compound, has been isolated from banana (Musa sapientum L.) peel extract. (±)-XJP displays potent antihypertensive activity in both acute and therapeutic antihypertensive tests in renal hypertensive rats (RHRs); the maximum antihypertensive effect of (±)-XJP at the dose of 100 mg·kg\(^{-1}\) is comparable to that of captopril at the dose of 25 mg·kg\(^{-1}\). The mechanistic studies have revealed that (±)-XJP has moderate ACE inhibitory activity, suggesting that ACE may be one of its possible targets [51]. Antihypertensive evaluation has proven that (±)-XJP isomers possess similar pharmacodynamic effects, but with different potency, and that the R-(−)-XJP (Compound 39, Fig. 7) is more potent than S-(+)XJP (Compound 40, Fig. 7) [52-53].

![Fig. 7 Chemical structures of Compounds 38–40](image)

**Conclusion**

In summary, the prevalence of hypertension has been increasing dramatically in the world during the past decades. Although many antihypertensive drugs with various mechanisms of action are used, they still cannot meet the needs in the clinic. In recent years, the potential value of herbal medicines for hypertension treatment has been rediscovered [54]. Natural products as sources of new drugs have played and will continue to play a dominant role in the discovery of lead compounds for the treatment of hypertension. Plenty of herbal medicines and plants extracts with antihypertensive activity remain to be explored and identified as potential leads for further structural modifications and optimization, in hopes that they would be developed as more potent and safer antihypertensive drugs in the future.

**References**


