

Review

Natural Antihypertensive Drug Leads from Northeast India's Biodiversity Hotspots: Molecular Targets, Signaling Pathways, and Safety Profiles: A Review

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Abstract

Hypertension is a major global health concern affecting over one billion people worldwide and is a leading risk factor for cardiovascular diseases, stroke, and kidney failure. Plant-derived bioactive compounds provide promising natural strategies for hypertension management by improving endothelial function, promoting vasorelaxation and diuresis, reducing oxidative stress, and modulating key molecular pathways. This review focuses on some important traditional medicinal plants from Northeast India with potential antihypertensive activity, summarizing their phytochemical constituents, pharmacological evidence, and proposed mechanisms of action. Northeast India lies within the Eastern Himalayas and Indo-Burma biodiversity hotspots and is recognized for its rich plant diversity. We conducted a systematic literature search using PubMed, Google Scholar, ScienceDirect, and Scopus following PRISMA guidelines. We further evaluated identified compounds for ADMET using open-source computational tools. Ten medicinal plants: *Clerodendrum colebrookeanum*, *Moringa oleifera*, *Garcinia dulcis*, *Centella asiatica*, *Terminalia bellirica*, *Hibiscus sabdariffa*, *Citrus limon*, *Passiflora edulis*, *Garcinia cowa*, and *Solanum torvum* yielded 22 bioactive compounds with notable antihypertensive activity. These compounds exhibited antioxidant, anti-inflammatory, and vasorelaxant effects via nitric oxide synthase activation, MAPK/NF- κ B inhibition, ACE inhibition, calcium channel modulation, and reactive oxygen species scavenging. ADMET profiling indicated favorable pharmacokinetics, with vitexin, isovitexin, isoquercetin, and nobiletin showing low predicted toxicity and high stability.

Keywords: anti-inflammatory; antioxidant; medicinal plants; phytochemicals; vasorelaxant



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1. Introduction

Hypertension, commonly known as high blood pressure, refers to abnormally elevated arterial pressure. A normal blood pressure reading is defined as a systolic blood pressure less than 120 mmHg and a diastolic blood pressure less than 80 mmHg. Hypertension is

typically diagnosed when systolic pressure is 140 mmHg or higher and/or the diastolic pressure is 90 mmHg or higher. According to a 2010 study, the global prevalence of hypertension is increasing, primarily due to the aging population, with an estimated 31.1% of the global adult population (1.39 billion people) affected by hypertension [1,2]. According to the American Heart Association (AHA) hypertension guidelines, systolic and diastolic blood pressure levels are classified into four categories: (1) normal blood pressure: systolic BP less than 120 mmHg and diastolic BP less than 80 mmHg; (2) elevated blood pressure: systolic BP between 120 and 129 mmHg and diastolic BP below 80 mmHg; (3) stage 1 hypertension: systolic BP between 130 and 139 mmHg or diastolic BP between 80 and 89 mmHg; (4) stage 2 hypertension: systolic BP of 140 mmHg or higher or diastolic BP of 90 mmHg or higher [3]. Several factors play key roles in the development of hypertension, including obesity, insulin resistance, high alcohol intake, high salt intake, aging, a sedentary lifestyle, stress, low potassium intake, and low calcium intake [4,5]. Hypertension is strongly associated with the development of major cardiovascular and renal conditions, including peripheral artery disease, chronic kidney disease, myocardial infarction, atrial fibrillation, heart failure, stroke, coronary artery disease, and cognitive impairment (Figure 1). It is one of the leading contributors to global mortality and disability [1,6].

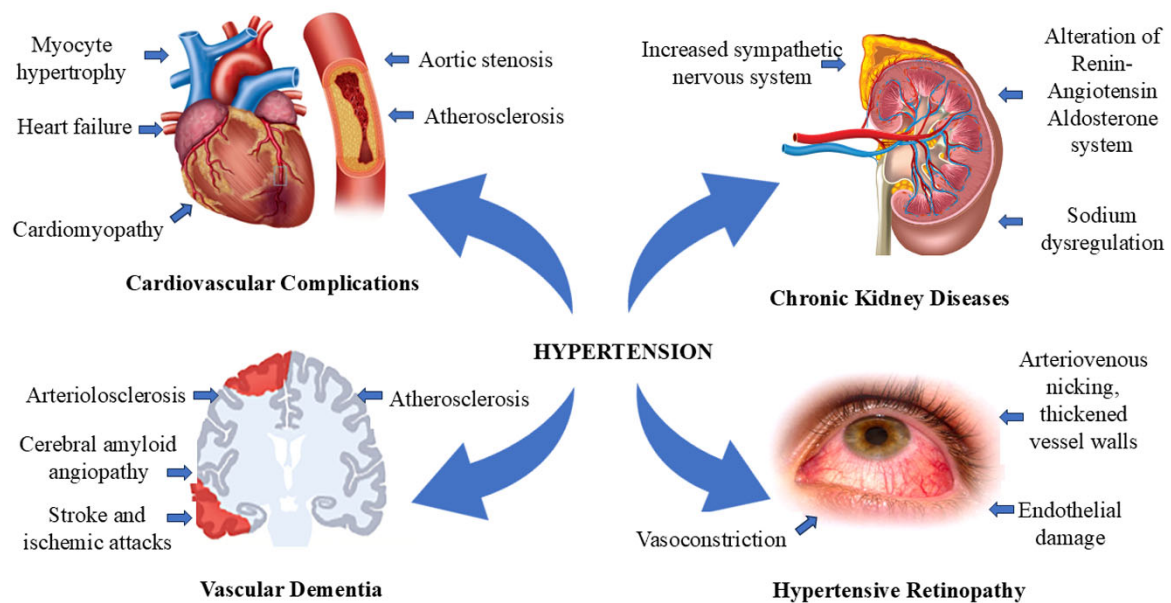


Figure 1. Pathophysiological and health-related consequences associated with hypertension.

The global prevalence of hypertension among adults remained relatively stable between 1990 and 2019. During this period, the prevalence declined in high-income countries, from 38% in 1990 to 32% in 2019, and in the WHO European Region, from 45% to 37%. However, these reductions were offset by slight to moderate increases in other regions, including the WHO Western Pacific Region (including countries such as Australia, New Zealand, China, South Korea, the Philippines, Malaysia, and Japan), where prevalence increased from 24% to 28%, and the WHO South-East Asia Region (including India, Nepal, Indonesia, and Thailand), where it rose from 29% to 32%. During this period, the number of hypertensive adults in the Western Pacific more than doubled (from 144 million to 346 million), while Europe and the Americas experienced a 41% increase, and Southeast Asia and the Western Pacific combined saw a dramatic 144% increase in the number of hypertensive individuals [4,7].

The data indicated that men had a slightly greater age-standardized incidence of hypertension (31.9%) than women did (30.1%). The prevalence was lower in high-income

countries (28.5%) than in low-income countries (31.5%). Among men, South Asia reported the lowest prevalence (26.4%), whereas Eastern Europe and Central Asia had the highest (39.0%). For women, the lowest prevalence was observed in high-income countries (25.3%), whereas 36.3% was recorded in sub-Saharan Africa [1,8,9]. In a study conducted between August 2021 and August 2023 in the United States, the prevalence of adult hypertension was 47.7%. The rate of hypertension was higher in men (50.8%) than in women (44.6%) and increased with age, ranging from 23.4% for those aged 18–39 years, 52.5% for those aged 40–59 years, and 71.6% for those aged 60 and older [10].

Hypertension is a major public health concern in India, contributing to 57% of all stroke-related deaths and 24% of deaths from coronary heart disease (CHD) [11]. It significantly impacts the country's cardiovascular health and places a burden on the healthcare system. Overall, hypertension affects approximately 33% of the urban population and 25% of the rural population. According to the 2019–2020 National Family Health Survey (NFHS-5), the prevalence of hypertension has risen to 24% in men and 21% in women, whereas it has increased to 19% and 17%, respectively, in the 2015–2016 survey [12,13]. In India, the prevalence of hypertension was highest in northeastern (NE) states, namely Sikkim (20.2%), Nagaland (17.6%), Assam (17.6%), Arunachal Pradesh (16.6%), and Tripura (15.4%), compared with other states and union territories, as per the National Family Health Survey (NFHS) 2015–2016 report [14]. According to the Indian Health Survey (2019–2020), the prevalence of hypertension in northeastern India is 27.6% in men and 22.3% in women. The different socioeconomic factors, along with diverse cultures and wide differences in dietary habits, are likely to affect the prevalence of hypertension in this region [15].

Various risk factors, including socioeconomic factors (such as low levels of education and high household economic status) and lifestyle behaviors (such as smoking, alcohol consumption, low physical activity, overweight/obesity, and dietary habits), significantly influence the development of hypertension [14–20]. Patients with hypertension may experience a range of symptoms, including chest pain, shortness of breath, palpitations, claudication, peripheral edema, headaches, blurred vision, nocturia, hematuria, and dizziness. In contrast, symptoms indicative of secondary hypertension include muscle cramps, arrhythmias (associated with hypokalaemia or primary aldosteronism), excessive sweating, frequent headaches and palpitations (seen in pheochromocytoma), muscle weakness or tetany, snoring, and daytime sleepiness [20]. An effective development strategy for the primary healthcare system should focus on delivering accessible and affordable hypertension management [21]. The advancement of digital health technologies, including non-intrusive devices for ambulatory blood pressure measurement and reliable data storage systems, enables rapid analysis and enhances physician–patient interactions, leading to more accurate BP diagnosis and treatment. The use of existing antihypertensive drugs, along with both new and established free and fixed drug combinations, can be more effective in combating hypertension [22]. In developing nations, emerging risk factors for hypertension include low birth weight, air and noise pollution, and increased sugar consumption. Two major challenges in managing hypertension are accurate diagnosis and effective blood pressure control [23].

The major causes of this failure include a lack of blood pressure monitoring practices, poor patient adherence to long-term therapy, and therapeutic inertia [24]. This low adherence to antihypertensive treatment leads to resistance and increases the risk of cardiovascular morbidity and mortality [25,26]. Several side effects are associated with prolonged use of modern antihypertensive drugs, including dizziness, tiredness, headache, an upset stomach and swelling, as well as an altered risk of incident depression [27]. On the basis of clinical observations, angiotensin-converting enzyme inhibitors (ACEIs), which are first-line drugs for the long-term treatment of chronic hypertension, can cause a dry cough

and are associated with a rare but potential risk of airway obstruction or exacerbation of bronchoconstriction in susceptible individuals [28–30]. Some studies have reported that angiotensin II receptor blockers (ARBs) are considered major precipitating factors for angioedema and should be prescribed with caution, especially in patients with cardiovascular risk factors, following ACE inhibitor-induced angioedema [31,32].

Northeast India is one of the country's richest biodiversity hotspots, harboring nearly half of India's plant diversity [33]. The region, comprising the eight states of Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, and Tripura, is also culturally diverse, home to over 200 ethnic groups with distinct languages, dialects, and sociocultural identities [34,35]. Given the rich heritage of herbal remedies, rural and indigenous communities in the region rely heavily on traditional medicine systems. Therefore, the ethnomedicinal potential of Northeast India should be prioritized, as it could lead to the discovery of more potent plant-derived bioactive compounds [36]. The main aim and objectives of the present study are to provide a systematic review highlighting the importance of potent traditional medicinal plants in Northeast India as alternative solutions for the management of hypertension. The present study focuses on the available evidence regarding the potential antihypertensive activity of crude extract/bioactive compounds derived from selected medicinal plants, and their proposed molecular mechanisms of action. In addition, an *in silico* ADMET study of identified compounds was included to provide preliminary insights into their pharmacokinetic properties and predicted safety profiles, thereby supporting their prioritization for further preclinical and clinical investigation.

2. Results and Discussion

2.1. Plants with Antihypertensive Activity

Medicinal and aromatic plants, particularly those with ethnopharmacological uses, have been utilized as a natural source of remedies and healthcare for millennia, with their bioactive molecules serving as integral components of nature that have supported the health of human societies throughout history [37,38]. The use of medicinal plants, a source of various phytochemical compounds known as secondary metabolites, is valuable for assessing the quality of therapeutic ingredients. Combinations of bioactive compounds in plant-based therapies offer protection from toxicity, enhance absorption, improve bioavailability and metabolism, and consequently reduce potential adverse effects [39,40]. Plant phenolic compounds play crucial roles in several mechanisms associated with the management of hypertension, such as reducing platelet aggregation, decreasing the oxidation of low-density lipoprotein (LDL), and increasing endothelial nitric oxide production [41]. Additionally, these plants contain various bioactive compounds that function as mediators of angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium channel blockers, β -adrenergic antagonists, and vasodilators, contributing to their therapeutic potential. Consequently, they have been widely used to manage conditions such as congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, venous insufficiency, and cardiac arrhythmia [42,43].

In this study, 22 ethnomedicinal plants traditionally used by various ethnic groups in the region for managing high blood pressure and associated cardiovascular complications were considered for their potential antihypertensive properties [44–54]. However, owing to the limited availability of *in vitro* and *in vivo* studies, as well as insufficient data on the specific bioactive compounds responsible for antihypertensive effects, only 10 species were selected for detailed analysis. The selection was based on the presence of recent phytochemical and pharmacological evidence supporting their antihypertensive potential (Table 1).

2.1.1. *Clerodendrum colebrookeanum* Walp. (Family: Lamiaceae)

Clerodendrum colebrookeanum Walp., commonly known as 'Nafafu', is widely used to treat hypertension among the different communities of hills and plains in the northeastern region of India. Tender leaves of the plants were found to be of common use in the treatment of the disease in the form of boiling in water as soup or as a decoction of tender leaves or leaf twigs with a piece of garlic prepared and taken with rice [55]. The major bioactive compounds, acteoside (verbascoside) and osmanthuside, belong to a group of phenylpropanoid glycosides and exhibit antihypertensive activity.

Lokesh and Amitsankar [56] investigated in vitro Rho-kinase (ROCK-II), phosphodiesterase-5 (PDE-5), angiotensin-converting enzyme (ACE), and in vivo fructose-induced hypertension in a rat model and isolated frog hearts, as well as ex vivo muscarinic action in isolated rat ileum. The 100 µg/mL test samples demonstrated calcium antagonism in the rat ileum, whereas the 50 µg/mL and 75 µg/mL treatments inhibited ROCK-II and PDE-5, respectively, with the ethyl acetate fraction causing a maximum inhibition of 68.62% for ROCK-II and 52.28% for PDE-5. However, the ACE inhibition assay did not significantly affect the samples, except for the ethyl acetate fraction (8.28%) and n-butanol (1.70%). The test samples also produced negative inotropic and chronotropic effects on isolated frog hearts and led to a significant reduction ($p < 0.001$) in systolic blood pressure and heart rate in hypertensive rats compared with those in the control group [56].

Molecular docking and molecular dynamics simulation studies reported that the phytoconstituents of acteoside and osmanthuside of *C. colebrookeanum* interact with the active site of antihypertensive drug target proteins of Rho-associated coiled-coil protein kinase (ROCK-I and II) and phosphodiesterase 5 (PDE5) in a stable manner [57]. Acteoside is a phenylpropanoid glycoside that can abolish nitric oxide (NO) pathway inhibitors and inhibits angiotensin-converting enzyme (ACE) at a concentration of 30 µM and an IC₅₀ value of 365 µM [58,59]. In lipopolysaccharide (LPS)-induced sepsis, acteoside increases mitochondrial biogenesis, restores sepsis-induced mitochondrial changes, and inhibits apoptosis in cardiomyocytes [60,61].

In addition to its antihypertensive effect, *C. colebrookeanum* shows potential as an anticoagulant and anti-thrombotic drug. The aqueous extract was fractionated, and the active anticoagulant fraction had an in vitro anticoagulant activity similar to warfarin and nattokinase and higher than heparin and clerofibrase. It did not inhibit thrombin or factor Xa directly, but its anticoagulant effect was mainly attributed to the fibrinolytic activity and partial inhibition of platelet aggregation. The isolated fraction and clerofibrase exhibited strong thrombolytic properties in vitro and were able to inhibit platelet aggregation in the presence of collagen and ADP without causing any cytotoxicity. In vivo, the active fraction was found to produce plasma defibrinogenating and anticoagulant effects at 12.5–50 mg/kg in mice in κ-carrageenan-induced thrombus formation, which could lead to therapeutic potential in cardiovascular disease management [62].

Acteoside has been identified as having poor oral bioavailability by pharmacokinetic studies. In rats, acteoside had plasma half-lives of about 5 and 28 min after intravenous and oral administration, respectively, and a plasma protein-binding ratio of 75.5% after intravenous administration, with an oral bioavailability of $0.12 \pm 0.04\%$ at a dose of 100 mg/kg [63]. In agreement with this observation, in vitro experiments were found to have $50.1 \pm 3.04\%$ bio accessibility after simulated gastrointestinal digestion and 0.461–0.698% transport across Caco-2 cell monolayers. The low apparent permeability coefficient ($P_{app} = 4.75 \times 10^{-7}$ cm/s) indicates poor intestinal absorption, and P-glycoprotein-mediated efflux plays a role in its low oral bioavailability [64]. Toxicological evaluation also showed a maximum tolerable human dose of 0.443 mg/kg/day, and the

oral acute (LD₅₀) and chronic toxicity values for rats were 2.527 mol/kg and 3.783 mg/kg, respectively [65].

2.1.2. *Moringa oleifera* Lam. (Family: Moringaceae)

In Assamese, *Moringa oleifera* Lam., commonly known as the “drumstick tree” or “horseradish tree,” is called *Sajina*. It is originally from the sub-Himalayan region of the northwest region of India and has spread around South America, Africa, Arabia, Southeast Asia, the Pacific Islands, and the Caribbean. The leaves and seeds have several medicinal properties such as antihypertensive, antimicrobial, anti-inflammatory, antidiabetic, antioxidant, and anticarcinogenic. In the North Eastern region, especially in Assam, the leaves are consumed as a vegetable to treat hypertension. The paste prepared from leaves is also used in the center of the head to help alleviate the symptoms of high blood pressure [66,67].

The aqueous leaf extract of *M. oleifera* showed dose-dependent vasorelaxation in isolated mesenteric arterial beds of L-NAME-induced hypertensive rats, with maximum relaxation seen at 3 mg. There is reduced vasorelaxant response to KCl-induced contractions versus methoxamine-induced contractions, implying the role of the endothelium-derived hyperpolarizing factor (EDHF) pathway. Furthermore, the extract blocked the extracellular Ca²⁺ influx mediated by voltage-operated and receptor-operated Ca²⁺ channels (VOCCs and ROCCs) and reduced the intracellular Ca²⁺ release through IP₃-sensitive channels at 1 and 3 mg/mL [68]. The extract is also rich in antioxidant phytochemicals such as catechin (767.72 µg/g), isoquercetin (811.37 µg/g), quercetin (204.66 µg/g), gallic acid (212.67 µg/g) and tannic acid (632.84 µg/g). The extract was found to inhibit vascular superoxide anion production and oxidative stress in L-NAME-induced hypertensive rats at dose levels of 30 and 60 mg/kg [69].

The antihypertensive effect of *M. oleifera* can be attributed to several bioactive peptides that have been isolated from it. Leu-Gly-Phe-Phe (LGF) and Gly-Leu-Phe-Phe (GLEF) peptides from leaves were found to inhibit both angiotensin-converting enzyme (ACE) and renin. When administered to spontaneously hypertensive rats, LGF and GLEF lowered the systolic blood pressure by 19.4 and 18.2 mmHg, respectively, and the diastolic blood pressure by 12.0 and 13.8 mmHg, respectively, with ACE IC₅₀ values of 0.29 ± 0.13 and 1.88 ± 0.08 mM, respectively, and renin IC₅₀ values of 0.31 ± 0.04 and 2.80 ± 0.08 mM, respectively [70]. The results from the in silico analyses showed that other ACE inhibitory peptides, such as IPPAYSK, ILVDR, FFFPK, and LLDPR, with IC₅₀ values of 116.06, 81.25, 510.67, and 277.16 µM, respectively, were identified from the leaves. IWHHTFYNELR is a peptide derived from the seed that showed the highest ACE inhibition with an IC₅₀ value of 0.697 µM [71,72].

The ethyl acetate extract of *M. oleifera*, which is rich in quercetin-3-O-glucoside, showed higher ACE inhibitory activity than the methanolic extract. ACE inhibition was 56.37%, 59.16%, and 75.74% at concentrations of 7, 15, and 28 µg/mL, respectively, and systolic blood pressure was reduced to 87.71 ± 0.96 mmHg in L-NAME-induced hypertensive mice [73]. Other phytochemicals play a role in cardiovascular protection. Indole alkaloid N, α-L-rhamnopyranosyl vincosamide has been shown to be a cardioprotectant against isoproterenol-induced cardiac toxicity in rats. Oral administration (40 mg/kg for 7 days) improved the antioxidant capacities, decreased lipid peroxidation, and decreased the levels of serum cardiac enzymes such as troponin-T, creatine kinase-MB, lactate dehydrogenase, and glutamate pyruvate transaminase [74]. Similarly, ethanolic extract of the leaves of the plant, which contains niaziridin and niazirin, was seen to lower the pressure in the pulmonary artery of monocrotaline-treated rats. The antihypertensive effect was accompanied by increased antioxidant activity of the superoxide dismutase (SOD) enzyme, indicating that antioxidant activity plays a role in the therapeutic action of this compound [75].

In a pharmacokinetic study of quercetin-3-O-glucoside, a single oral dose of 325 μmol resulted in a mean plasma quercetin level of $5.0 \pm 1.0 \mu\text{mol/L}$ with peak levels observed $18.5 \pm 0.8 \text{ min}$ after. The elimination half-life of $18.5 \pm 0.8 \text{ h}$ and the urinary excretion of only $3.0 \pm 0.3\%$ of the administered dose as quercetin aglycone or conjugates after 24 h indicate a high systemic bioavailability of quercetin [76]. A toxicological study showed that quercetin from the onion skin has an oral LD_{50} of 3807 mg/kg in mice. A dosage of more than 1000 mg/kg, however, resulted in damage to liver and kidney tubules and elevated serum AST, ALT, and creatinine levels [77]. Niazirin also had good pharmacokinetic characteristics. Following oral administration at doses of 5, 20, and 40 mg/kg, peak plasma concentrations (C_{max}) reached 380.66 ± 51.33 , 1203.17 ± 226.15 , and $2579.63 \pm 584.81 \mu\text{g/L}$, respectively, with corresponding half-lives of 3.36 ± 1.75 , 3.15 ± 1.11 , and $2.74 \pm 0.54 \text{ h}$. Intravenous administration produced a C_{max} of $3459.20 \pm 996.55 \mu\text{g/L}$ and a shorter half-life of $0.59 \pm 0.12 \text{ h}$. Oral bioavailability ranged from 46.78% to 52.61% [78]. In addition, the in silico ADMET analyses suggested that the LD_{50} was between 500 and 5000 mg/kg, corresponding to a relatively low acute toxicity [79].

2.1.3. *Garcinia dulcis* (Roxb.) Kurz (Family: Clusiaceae)

Garcinia dulcis (Roxb.) Kurz is a tropical fruit tree indigenous to Southeast Asia, with a rich history of use in traditional medicine for various ailments. Different parts of the plant are rich in bioactive compounds, primarily xanthenes and flavonoids, which possess significant pharmacological properties, including antiatherosclerosis, antibacterial, anticancer, antihypertensive, and antimalarial effects [80]. Camboginol, an isoprenylated benzophenone extracted from the fresh, ripe fruit of *G. dulcis*, significantly reduced the heart rate (HR), mean arterial blood pressure (MABP), diastolic blood pressure (DBP), and systolic blood pressure (SBP) in both normotensive and two-kidney, one-clip (2K1C) hypertensive rats, with pD_2 values of 9.67 ± 0.19 and 8.01 ± 0.66 , respectively. A previous study suggested that camboginol exerts its antihypertensive effects by promoting the opening of ATP-sensitive potassium channels and activating endothelial nitric oxide synthase (eNOS) and the prostacyclin signaling pathway [81]. Another bioactive compound morelloflavone, which is a biflavonoid from fruits of *G. dulcis*, can have significant diuretic and hypotensive effects by the lowering mean arterial pressure, increasing the renal blood flow, restoring blunt baroreflex sensitivity and increasing the urine flow rate compared with the vehicle control (138 ± 6 vs. $152 \pm 1 \text{ mmHg}$, 3.44 ± 0.49 vs. $2.29 \pm 0.25 \text{ mL/min/g KW}$ and 42.0 ± 9.4 vs. $18.2 \pm 3.9 \mu\text{L/min/g KW}$, $p < 0.05$) by triggering the nitric oxide signaling pathway [82]. Thongsepee et al. (2020) reported that camboginol and morelloflavone-rich flower extracts had diuretic and hypotensive effects without liver toxicity in acute and sub-chronic treatment in male Wistar rats [83].

Garcinol, a bioactive benzophenone-derived compound, exhibited significant anti-inflammatory activity in LPS-activated THP-1 and RAW 264.7 macrophage cells. The IC_{50} values of garcinol were $67.86 \pm 1.25 \mu\text{M}$ for RAW 264.7 cells and $78.45 \pm 2.13 \mu\text{M}$ for THP-1 cells after 24 h of incubation at concentrations ranging from 10 to 100 μM . Coincubation with garcinol at concentrations of 20 and 30 μM significantly suppressed the elevated mRNA and protein expression levels of proinflammatory mediators, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), as well as proinflammatory cytokines such as TNF- α , IL-8, IL-6, and IL-1 β (Figure 2). In addition, coincubation with garcinol significantly modulated the nuclear factor kappa B (NF- κB) signaling pathway in both cell lines by inhibiting the LPS-induced increases in phosphorylated NF- κB (pNF- κB), I $\kappa\text{B}\alpha$ (pI $\kappa\text{B}\alpha$), and IKK α/β (pIKK α/β) in a dose-dependent manner. This inhibition reduced the production of proinflammatory molecules by decreasing the nuclear translocation of pNF- κB from the cytosol [84]. Additionally, at a dose of 100 mg/kg, garcinol significantly

decreased the maximum rate of left ventricular pressure development (LV-dp/dt_max) and increased the heart rate (HR), left ventricular systolic pressure (LVSP), systolic blood pressure, and diastolic blood pressure. In rats with isoproterenol-induced heart failure and in cardiac H9C2 cells, garcinol treatment reduced the mRNA and protein expression levels of cleaved caspase-3, total caspase-3, and Bax, while increasing Bcl-2 levels in heart tissue, indicating its antiapoptotic effect [85].

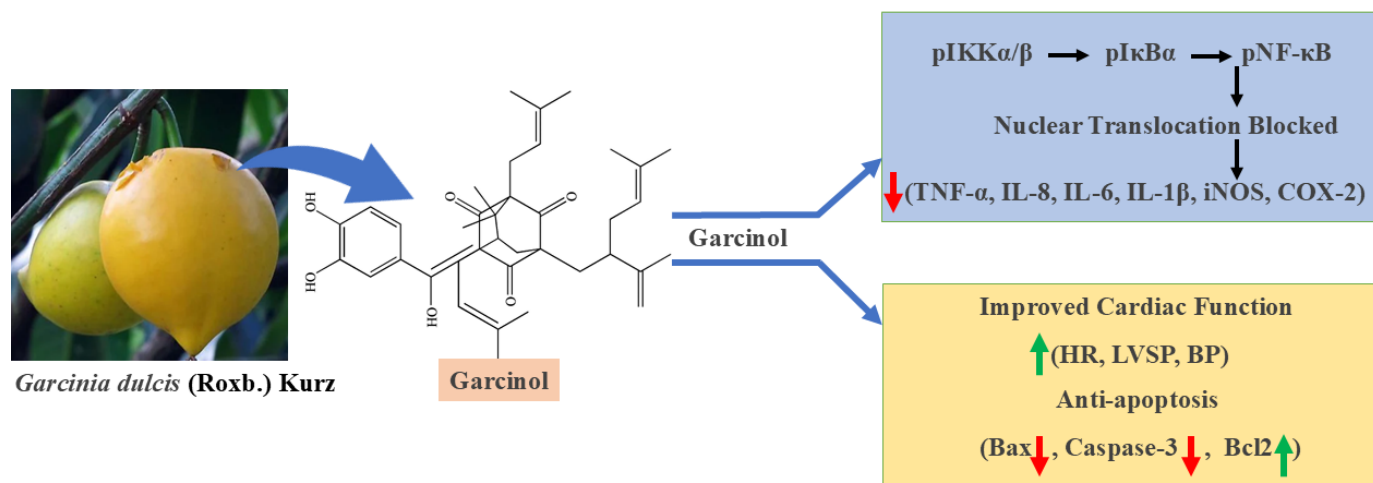


Figure 2. Garcinol, the major bioactive compound from *G. dulcis*, showed antihypertensive activities by suppressing proinflammatory mediators. (In the figure, red arrows indicate the downregulation of signaling molecules or pathways, and green arrows indicate upregulation of the respective molecules or pathways).

The pharmacokinetic analysis of garcinol in Sprague-Dawley rats revealed maximum plasma concentrations of 2317.69 ± 180.44 and 3446.14 ± 190.12 ng/mL after oral doses of 22.5 mg/kg and 45 mg/kg, respectively, and 11749.75 ± 300.00 ng/mL after intravenous administration. The half-lives of garcinol at these respective doses and administration routes were 25.43 ± 1.24 , 24.46 ± 3.52 , and 11.94 ± 5.29 h. The study also reported that bioavailability was greater in the 45 mg/kg group ($35.72 \pm 0.97\%$) than in the 22.5 mg/kg group ($26.64 \pm 0.23\%$) [86]. A study revealed that 40% garcinol had no adverse effects at a single dose of 2000 mg/kg. The study also revealed that repeated doses of 100 mg/kg/day over 28 and 90 days had no adverse effects on reproductive organs [87].

2.1.4. *Centella asiatica* (L.) Urb. (Family: Apiaceae)

Centella asiatica L., commonly known as mandukparni or Indian pennywort, is a significant medicinal herb that has traditionally been utilized in Indian Ayurvedic medicine for millennia. Despite numerous studies over the past few decades investigating its biologically active components and mechanism of action, the plant is recommended for treating various skin conditions such as eczema and psoriasis, as well as for diarrhea, fever, wound healing, epilepsy, gastric ulcers, inflammation, and venous hypertension [88]. Asiaticoside, a saponin from *C. asiatica*, attenuated pulmonary hypertension, pulmonary vascular remodeling, and right ventricular hypertrophy in hypoxia-induced pulmonary hypertension rats by restraining excessive TGF- β 1/Smad2/3 signaling and inhibiting the proliferation of pulmonary arterial smooth muscle cells [89]. In human umbilical vein endothelial cells (HUVECs) with oxidized low-density lipoprotein (oxLDL)-induced inflammation, asiaticoside at concentrations of 10–30 μ M significantly modulated endothelial hyperpermeability and the levels of key inflammatory markers. Specifically, asiaticoside altered the levels of adenosine triphosphate (ATP) to 90% ($p < 0.005$), intercellular adhesion molecule-1 (ICAM-1) to 80% ($p < 0.05$), vascular cell adhesion molecule-1 (VCAM-1) to

105% ($p < 0.01$), E-selectin to 65% ($p < 0.005$), platelet endothelial cell adhesion molecule-1 (PECAM-1) to 70% ($p < 0.05$), and endothelial hyperpermeability to 105% ($p < 0.01$) [90].

Renovascular disease results from gradual blockage of the renal arteries, leading to various symptoms, including renovascular hypertension and ischemic nephropathy. Renovascular hypertension (RVH) is a prevalent cause of secondary hypertension and has been extensively researched as the classic example of angiotensin-dependent hypertension [91]. Asiatic acid found in *C. asiatica* (30 mg/kg/day) has been shown to inhibit the renin-angiotensin-aldosterone system (RAAS), as evidenced by reduced plasma angiotensin II levels and decreased serum angiotensin-converting enzyme (ACE) activity, while also restoring the AngII-AT1R-gp91^{phox}-NF- κ B signaling pathway [92]. In L-NAME-induced hypertensive rats, asiatic acid lowered blood pressure and improved vascular function, likely by increasing nitric oxide (NO) bioavailability through the upregulation of endothelial nitric oxide synthase (eNOS) expression and by reducing inflammation and oxidative stress [93,94]. Furthermore, asiatic acid supplementation improved vascular function, suppressed RAAS activation, and alleviated metabolic and cardiovascular complications in a rat model of metabolic syndrome induced by a high-carbohydrate, high-fat (HCHF) diet [92]. Madecassoside, a triterpenoid bioactive compound derived from *Centella asiatica*, inhibited the LPS-induced production of TNF- α in neonatal rat cardiomyocytes in a concentration-dependent manner [95]. At a dose of 20 mg/kg, madecassoside significantly reduced the LPS-induced increase in plasma TNF- α levels in rats by preventing the nuclear translocation of NF- κ B and inhibiting the phosphorylation of p38 and ERK1/2 (Figure 3). Furthermore, pretreatment with madecassoside attenuated LPS-induced tachycardia and delayed the decline in mean arterial blood pressure [96].

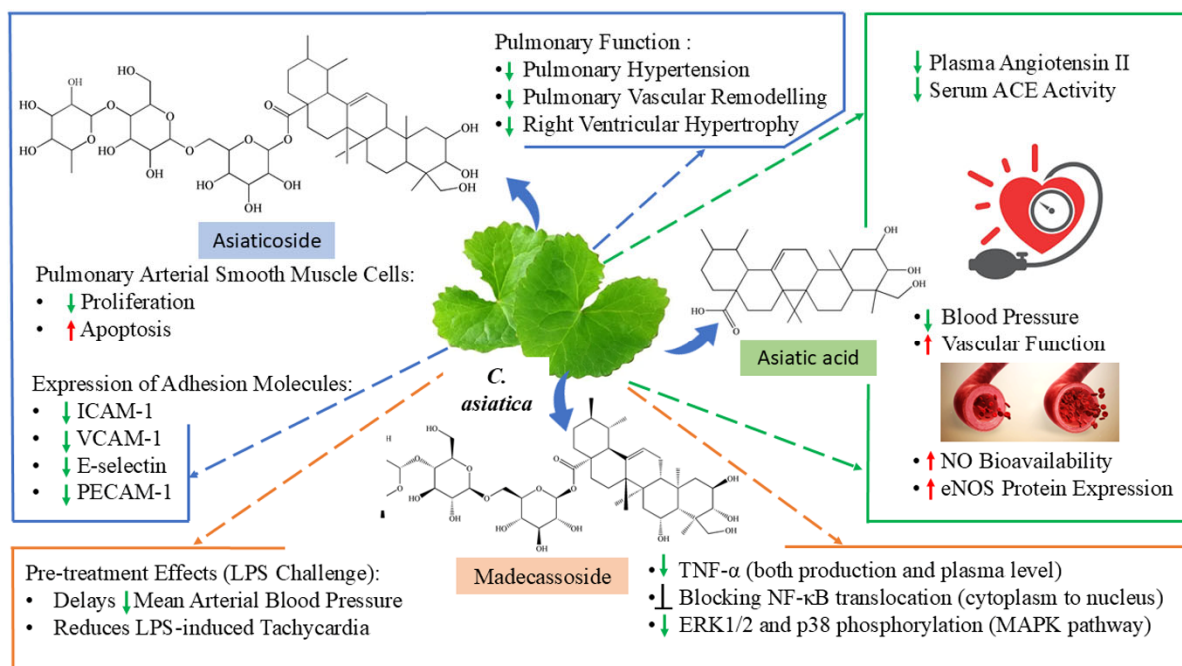


Figure 3. Three major bioactive compounds from *C. asiatica*, namely Asiaticoside. Asiatic acid and Madecassoside showed antihypertensive activity by mitigating pulmonary dysfunction, followed by enhancing nitric oxide bioavailability, eNOS expression, vascular function, and reducing and blocking TNF- α , NF- κ B, p38, and ERK1/2 pathways. (In the figure, green arrows indicate the downregulation of signaling molecules or pathways, red arrows indicate upregulation, and black inhibitory arrows indicate complete inhibition (blockade) of the respective molecules or pathways).

In a pharmacokinetic study of madecassoside, asiaticoside, and asiatic acid in humans, participants were given oral capsules (250 mg) containing these bioactive compounds.

Both madecassoside and asiaticoside reached peak plasma concentrations (9.57 ± 3.34 and 5.18 ± 3.43 , respectively) within 1 h after dosing, whereas asiatic acid reached its peak (79.76 ± 19.28) between 1 and 2 h post-treatment. During the study, the plasma concentrations increased significantly with increasing dose; however, the half-lives of asiaticoside (10.37 ± 8.84), madecassoside (8.06 ± 5.62), and asiatic acid (9.86 ± 9.77) did not significantly change. The study also revealed that madecassoside and asiaticoside exhibited bioavailabilities of $27.99 \pm 23.88\%$ and $17.09 \pm 13.52\%$, respectively, compared with $0.74 \pm 0.25\%$ for asiatic acid [97]. The LD₅₀ of *Centella asiatica* was greater than 2000 mg/kg body weight in rats. No acute (single dose of 2000 mg/kg) or sub-chronic toxicity (90-day repeated dose of 1000 mg/kg) was observed [98].

2.1.5. *Terminalia bellirica* (Gaertn.) Roxb. (Family: Combretaceae)

Terminalia bellirica (Gaertn.) Roxb, which is distributed across Southeast Asian countries, is traditionally utilized in Indian Ayurvedic medicine to treat diabetes, rheumatism, and hypertension [99]. The major polyphenolic compound gallic acid and crude extract of *T. bellirica* inhibited the inflammatory response and reactive oxygen species production by suppressing the MAPK/NF- κ B pathway and activating the Akt/AMPK/Nrf2 pathway in LPS-stimulated RAW264.7 macrophages. However, both gallic acid and crude extract enhanced antioxidant enzyme expression and improved acute kidney injury in an LPS-shocked mouse model [100]. The tannin-rich crude extract of *T. bellirica* reduced pulmonary arterial pressure, slowed pulmonary arterial remodeling, increased GSH-Px and SOD activity, decreased malondialdehyde (MDA) levels ($p < 0.05$), and reduced Bax expression in the lung tissues of high-altitude pulmonary hypertension (HAPH) rats. Conversely, the expression levels of Bcl-2, Nrf2, and HO-1 were elevated ($p < 0.05$). In cell experiments, TTR reduced H₂O₂-induced apoptosis and ROS production in PAECs ($p < 0.05$), decreased Bax expression, and increased Bcl-2, Nrf2, and HO-1 expression ($p < 0.05$) [101]. The development of atherosclerosis is closely linked to the inflammatory response initiated by macrophages. Within atherosclerotic plaques, macrophages secrete reactive oxygen species (ROS), matrix metalloproteinases (MMPs), and proinflammatory cytokines [102]. A previous study demonstrated that crude extract of *Terminalia bellirica* (TBE) significantly downregulated the mRNA expression of lectin-like oxidized LDL receptor-1 (LOX-1), interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF- α). Additionally, TBE reduced intracellular ROS production and MMP-9 secretion in THP-1 macrophages [103]. The aqueous-methanolic extract of *T. bellirica* has also been shown to lower blood pressure, potentially by inhibiting calcium release from intracellular stores and blocking calcium influx through membrane calcium channels [104]. The aqueous and ethyl acetate fractions have anticholinergic, Ca²⁺ antagonist, and antispasmodic effects [105].

The pharmacokinetic study of gallic acid from a Triphala formulation containing *T. bellirica* revealed that the plasma concentration was nearly doubled in the group receiving the 4000 mg dose compared with the 2000 mg dose group. The C_{max} values were 70.81 ng/mL (range: 46.26–90.88) and 41.84 ng/mL (range: 32.29–59.54), respectively, in healthy Thai subjects (16 males and 16 females) aged 20–45 years, with body mass indices (BMIs) between 20 and 25 kg/m². Following the oral administration of Triphala, gallic acid was rapidly absorbed, reaching a median t_{max} of 1 h. The study also revealed that the terminal elimination half-life was 1 h for both the 2000 mg and the 4000 mg doses [106]. Owing to its rapid absorption and metabolism, gallic acid has low bioavailability [107]. The LD₅₀ of gallic acid was determined to be greater than 2000 mg/kg in albino mice. A high dose of gallic acid (900 mg/kg/day) administered over 28 days did not result in any significant changes in morphological or behavioral parameters [108].

2.1.6. *Hibiscus sabdariffa* L. (Malvaceae)

Hibiscus sabdariffa L., commonly known as roselle, which is also referred to as red sorrel, originates from India and Malaysia. This tropical plant is widely grown in tropical and subtropical areas around the globe, such as Central and West Africa and Southeast Asia. Scientific research has revealed that *H. sabdariffa* has various pharmacological benefits, including antihypertensive, antihyperlipidemic, anti-inflammatory, antimicrobial, diuretic, uricosuric, and anemia-treating properties [109]. The anthocyanin- and hibiscus acid-rich aqueous extract of *H. sabdariffa* inhibited ACE and had a vasodilatory effect [110]. A study revealed that, out of 121 participants in pilot interventions with high blood pressure (BP) ($\geq 140/90$ mmHg), 61.8% of participants achieved the recommended blood pressure target of $<140/90$ mmHg [111]. In total, 500 mg capsules of *H. sabdariffa* at a concentration of 6 mg/g of anthocyanins, once daily with meals for a duration of four weeks, significantly reduced systolic blood pressure ($p = 0.049$) and triglyceride levels (0.044) in a randomized controlled trial involving 45 participants [112]. Additionally, in a randomized, double-blind, placebo-controlled study among 80 participants, 175 mg of *H. sabdariffa* with a total combination dosage of 500 mg over a 12-week period resulted in a progressive reduction in systolic blood pressure [113].

The vascular effects of hibiscus acid from *Hibiscus sabdariffa* on rat aortic rings were investigated in vitro via myography techniques. Hibiscus acid induced concentration-dependent relaxation of the rat aorta precontracted with either phenylephrine (3 μ M) or KCl (60 mM), independent of the endothelium. The concentration required to achieve 50% relaxation (IC_{50}) in aortas precontracted with phenylephrine (PE) was 0.09 ± 0.01 mg/mL [114]. A previous study reported that hibiscus acid exhibits antihypertensive activity by inhibiting the enzymes α -amylase and α -glucosidase, thereby reducing the absorption of sugars and starches and contributing to weight loss. As a result, hibiscus acid may help prevent metabolic syndromes such as dyslipidemia, arterial hypertension, atherosclerosis, acute myocardial infarction, diabetes, and chronic kidney disease [115]. The antihypertensive effect of *H. sabdariffa* is achieved mainly through mechanisms such as diuresis, vasodilation, regulation of calcium influx, the inhibition of ACE, and the blockade of AT1 receptors [116].

The bioavailability and pharmacokinetics of hibiscus acid, the predominant organic acid in *Hibiscus sabdariffa* beverages, were evaluated in a human clinical study involving 12 volunteers. Hibiscus acid was rapidly absorbed, with a maximum plasma concentration (C_{max}) of 28.5 μ M observed as early as 0.5 h post-intake. Notably, a biphasic absorption pattern was recorded, with additional peaks at 3 and 5 h, indicating potential enterohepatic recirculation. The time to reach maximum concentration (T_{max}) for hibiscus acid was approximately 2.5–2.8 h, which aligns with typical intestinal absorption kinetics. In terms of excretion, hibiscus acid was predominantly eliminated in urine within the 0–6 h window, with a peak occurring between 3 and 6 h. Additionally, its metabolite, hibiscus acid dimethyl ether, showed sustained plasma levels and delayed urinary excretion, peaking at 12 h post-consumption. These findings suggest high bioavailability of hibiscus acid and its derivatives, with implications for prolonged physiological activity and potential health benefits such as anti-inflammatory effects [117].

2.1.7. *Citrus limon* (L.) Osbeck (Family: Rutaceae)

Citrus limon L., which is commonly known as lemon, belongs to the Rutaceae family. Fruit juice (lemon juice) has traditionally been used as a remedy for scurvy, high blood pressure, the common cold, cough, and irregular menstruation. The major bioactive compounds of lemon include flavonoids, phenolic acids, monoterpenoids, coumarins, carboxylic acids, amino acids, and vitamins [118]. A previous study reported that lemon juice can significantly inhibit the activity of angiotensin-1 converting enzyme (ACE) and

hypcholesterolemia in a high-cholesterol diet-fed rat model in a dose-dependent manner. Owing to the high phenolic content (64.5 mg/L) in the lemon juice, the inhibition of ACE activity results in antioxidant scavenging activities and the inhibition of Fe^{2+} and sodium nitroprusside-induced lipid peroxidation in the livers of the rats *in vitro*. In an *in vivo* experiment, the administration of juice significantly reduced total cholesterol in plasma, triglyceride, and LDL-cholesterol levels and increased plasma HDL-cholesterol levels in a high-cholesterol diet-treated rat model [119].

Citric acid is the major ingredient in lemon juice; it can significantly relax the thoracic aorta of spontaneously hypertensive rats and cause vasodilation at a concentration of 40.1 $\mu\text{g/mL}$ (0.21 mmol/L) [120]. Nobiletin, a polymethoxylated flavone obtained from immature citrus peels, induces the phosphorylation of vasodilator-stimulator phosphoprotein (VASP) in human platelet cells via a noncyclic nucleotide-related mechanism (Figure 4) [121]. Studies have shown that nobiletin lowers blood pressure and improves the contractile response to sympathetic nerve stimulation in the mesenteric vascular beds of male Sprague-Dawley rats treated with L-NAME. Nobiletin restored plasma NOx levels and increased the protein expression of endothelial nitric oxide synthase (eNOS), nuclear factor erythroid 2-related factor 2 (Nrf2), and heme oxygenase-1 (HO-1), while significantly reducing the expression of oxidative stress markers ($p < 0.05$). Additionally, nobiletin attenuated the thickening of the aortic wall, cross-sectional area, vascular smooth muscle cell proliferation, and collagen deposition, as well as glomerular extracellular matrix accumulation and renal fibrosis. These effects were achieved by downregulating the expression of matrix metalloproteinases (MMP-2 and MMP-9) and transforming growth factor (TGF) proteins and by upregulating adiponectin receptor 1 in models involving L-NAME and high-fat diet-induced vascular injury [122,123]. A previous study revealed that nobiletin effectively decreased the ventricular systolic pressure and attenuated right ventricular hypertrophy and medial wall thickening in monocrotaline-treated rats. By inhibiting Src/STAT3 activation and pulmonary artery smooth muscle cell proliferation through the downregulation of Pim1 and NFATc2, nobiletin has been shown to have protective effects on pulmonary arterial hypertension in rats (Figure 4) [124,125].

Hesperidin and G-hesperidin, two important bioflavonoids found in citrus fruits, exhibit antihypertensive effects primarily by upregulating the vascular nitric oxide synthase (NOS) pathway. The beneficial impact of these compounds on hypertension is attributed to increased nitric oxide (NO) bioavailability and protection of endothelial function from reactive oxygen species (ROS) through antioxidant mechanisms [126,127]. Additionally, hesperidin significantly reduces blood pressure in spontaneously hypertensive rats by suppressing the renin-angiotensin system (RAS) cascade and decreasing oxidative stress [128].

The pharmacokinetics of citrate, following intravenous administration, were measured in a study aimed at predicting citrate accumulation in humans to assess its therapeutic use. In this study, 12 healthy volunteers received trisodium citrate at a dose of 3.7 mmol/L of plasma flow. Blood samples were collected before infusion, throughout 120 min of infusion, and up to 120 min post-infusion. The plasma citrate levels were quantified via HPLC. The maximum plasma citrate concentration was 0.56 ± 0.45 mmol/L, with a total administered dose of 57.1 ± 10.5 mmol. The total body clearance rate was 686.64 ± 353.60 L/min [129]. Citric acid also plays a critical role in enhancing the bioavailability of certain nutrients and medications by adjusting the pH of formulations. For example, its acidic properties aid in stabilizing and improving the palatability of oral medications, thereby facilitating better absorption and patient compliance [130]. Another compound, nobiletin, which has maximum concentrations in both the plasma and brain, was observed 1 h after a single oral dose of 50 mg/kg. The peak concentrations were 1.78 $\mu\text{g/mL}$ in the plasma and 4.20 $\mu\text{g/mL}$ in the brain. The area under the concentration-time curve (AUC(0-t)) was 7.49 $\mu\text{g}\cdot\text{h/mL}$

in the plasma and 20.66 $\mu\text{g}\cdot\text{h}/\text{mL}$ in the brain. The mean elimination half-lives ($t_{1/2}$) in the plasma and brain are 1.80 h and 11.42 h, respectively [131]. A study reported that the absolute bioavailability of nobiletin was $22.37\% \pm 4.52$ in lean rats after oral administration. The gut microbiota present in rats plays an important role in nobiletin metabolism [132]. An LD_{50} study revealed the safety of nobiletin at 5000 mg/kg [133]. In another study, hesperidin exhibited different pharmacokinetic rates in the different parts of the intestine after oral administration of 709 $\mu\text{mol}/\text{kg}$ in mice [134]. The rates of bioavailability in the duodenum, jejunum, cecum, and colon were reported to be 0.14%, 0.49%, 2.12%, and 1.06%, respectively. Owing to its low solubility in water, the gut microbiota in the gastrointestinal tract helps in absorption, biotransformation, and rapid excretion [135]. Hesperidin showed a median lethal dose (LD_{50}) of 4837.5 mg/kg, and few observed adverse effects in a subchronic toxicity study at 1000 mg/kg in Sprague-Dawley rats [136].

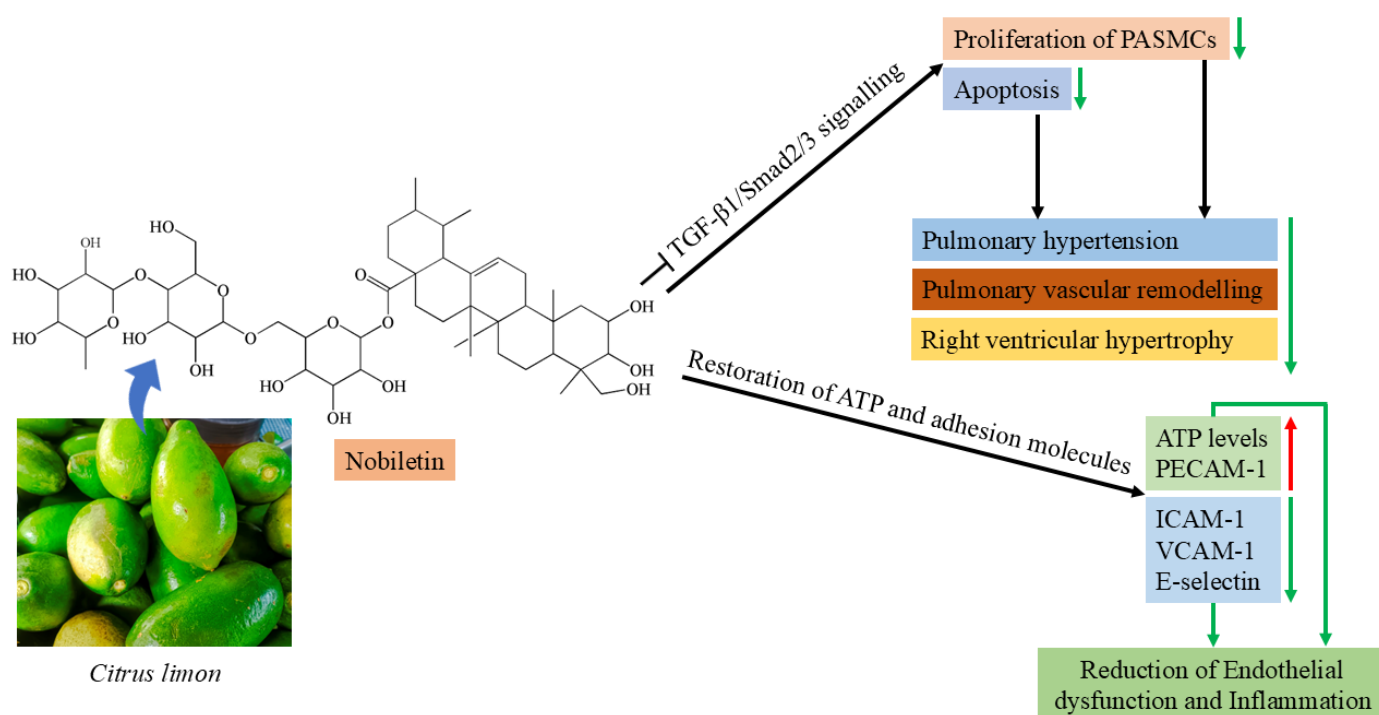


Figure 4. Nobiletin, one of the prominent bioactive compounds from citrus peel, significantly reduced hypertension by blocking of TGF- β 1/Smad2/3 signaling, as well as restoration of ATP and adhesion molecules. (In the figure, green arrows indicate downregulation and red arrows indicate upregulation of the respective molecules or signaling pathways).

2.1.8. *Passiflora edulis* Sims (Family: Passifloraceae)

Passion fruit (*Passiflora edulis*), which is commonly found in tropical and subtropical regions, has numerous health benefits, including antitumour, antihypertensive, antioxidant, antidiabetic, and hypolipidemic properties [137]. At a dose of 50 mg/kg per day, purple passion fruit peel (PFP) extracts significantly reduced systolic blood pressure by 12.3 mmHg ($p < 0.1$) and decreased serum nitric oxide levels by 65% ($p < 0.05$) in spontaneously hypertensive rats. Furthermore, a 4-week randomized, double-blind, placebo-controlled trial was conducted in hypertensive human subjects to evaluate the effects of 400 mg of PFP extract daily compared with a placebo. The trial's primary outcome was measured through blood pressure readings. Compared with the placebo group, participants who received the PFP extract experienced significant reductions in both systolic and diastolic blood pressures of 30.9 ± 6.3 mmHg and 24.6 ± 3.3 mmHg, respectively ($p < 0.001$). No adverse effects were reported by the participants [138]. High-performance

liquid chromatography (HPLC) analysis of the peel extract confirmed the presence of cyanidin 3-O-glucoside, quercetin 3-O-glucoside, and edulilic acid, a novel cyclic acid glucoside unique to *P. edulis* [139]. Sukketsiri et al. (2023) investigated the antioxidant, anti-inflammatory, antilipid, and vascular relaxant activities of seeds and fruit extracts from *P. edulis* [140]. Both extracts exhibited antioxidant activity, inhibited pancreatic lipase and cholesterol esterase, reduced nitric oxide levels during LPS-induced inflammation in RAW264.7 cells, and promoted ex vivo vasorelaxation in rat aortic rings. These effects were attributed to the high content of piceatannol and polyphenolic stilbenes in the seed extract, as well as β -carotene and γ -tocopherol in the fruit extract. The long-term administration of piceatannol increased endothelial nitric oxide synthase (eNOS) protein levels and eNOS mRNA expression in a dose-dependent manner. Additionally, piceatannol enhanced the phosphorylation of eNOS [141].

The pharmacokinetic study of the primary antihypertensive compound piceatannol revealed that the plasma AUC, urine $t_{1/2}$, CL, and Vd were 8.48 ± 2.48 mg·h/mL, 19.88 ± 5.66 h, 2.13 ± 0.92 L/h/kg, and 10.76 ± 2.88 L/kg (mean $\pm$ SEM), respectively, following a single intravenous dose of 10 mg/kg piceatannol in male Sprague-Dawley rats [142]. A previous study revealed that piceatannol, a natural analog of resveratrol, has an oral bioavailability of over 1%, indicating that it is more stable than resveratrol [143].

2.1.9. *Garcinia cowa* Roxb. ex Choisy (Family: Clusiaceae)

Garcinia cowa is an evergreen medium-sized tree, commonly known as cowa fruit/kau thekera, which is widely distributed throughout the Southeast Asian region. Various plant parts, i.e., leaves, fruit, bark, latex and roots, have been used in traditional medicine for the treatment of various diseases, such as fever, indigestion and blood circulation [144]. Recent studies have shown that the leaf of *G. cowa* caused significant relaxation of the aortic rings of rats in a concentration-dependent manner. The vasorelaxant effect of *G. cowa* leaf extract primarily involves the generation of nitric oxide and prostanoids, as well as the activation of ATP-sensitive potassium channels. The phytochemical investigation of the tested crude extract confirmed the presence of kaempferol, vitexin, and isovitexin, which are possible bioactive compounds for vasorelaxant effects [145]. Previous studies confirmed that the compound kaempferol induces vessel relaxation through the activation of the NO–cGMP–PKG signaling pathway, enhancement of bradykinin-induced relaxation, and stimulation of large-conductance Ca^{2+} -activated potassium channels [146]. In contrast, two additional compounds, vitexin and isovitexin, were found to reduce phorbol ester-induced vascular contraction primarily by inhibiting MEK activity and reducing ERK1/2 phosphorylation. This mechanism also leads to the activation of small-conductance Ca^{2+} -activated potassium (SKCa) channels and the upregulation of Kir6.1 ATP-sensitive K^{+} channels [147,148].

In LPS-induced RAW264.7 macrophages, phloroglucinol benzophenones (garcinia-cowones F, H, and I) and xanthenes (cowanol, mangostanin, and cratoxylone) isolated from the leaves of *Garcinia cowa* had inhibitory effects on nitric oxide (NO) production, with IC_{50} values ranging from 5.4 to 18.6 μM , respectively. Nitric oxide is a highly reactive molecule produced in the body through both enzymatic and nonenzymatic pathways. It is acknowledged as a proinflammatory mediator that participates in numerous biological functions and may be pivotal in inflammatory conditions. Many diseases, such as neurodegenerative and cardiovascular disorders, cancer, obesity, and diabetes, are closely linked to inflammation [149].

Pharmacokinetic studies of vitexin were conducted following intravenous and oral administration to mice at doses of 10 mg/kg and 30 mg/kg, respectively. After administration, vitexin was rapidly and widely distributed throughout the body, reaching peak concentrations at approximately 19.14 ± 1.07 min. It was quickly eliminated from the plasma,

with a half-life ($t_{1/2}$) of 29.11 ± 2.31 min, a clearance rate (CL) of 0.89 ± 0.06 L·kg/min, and an oral bioavailability of 3.91% [150]. The plasma concentration of the compound isovitexin sharply decreased from 22.5 µg/mL to 2.77 µg/mL at 1 h after intravenous tail administration at a dose of 2 mg/kg in rats. A pharmacokinetic study reported that isovitexin had a half-life $t_{1/2}$ of 1.05 ± 0.325 h, with a mean residual time (MRT) of 1.229 ± 0.429 h, and the area under the curve (AUC) was 11.39 ± 5.05 µg/mL/h [151]. In an in vitro study, vitexin showed cytotoxicity (IC_{50}) against breast cancer cell lines at a 12 mg/kg concentration [152]. In in vivo, up to 2 g/kg of both vitexin and isovitexin did not result in any cytotoxicity in normoglycemic mice or diabetic rats after up to 14 days of monitoring [153]. Following intravenous administration of kaempferol at doses of 10 and 25 mg/kg, the plasma concentration–time profiles indicated a large volume of distribution (8–12 L/kg) and high clearance (~3 L/h/kg), with a terminal half-life of approximately 3–4 h. When kaempferol is administered orally, it shows relatively rapid absorption, reaching a peak plasma concentration (t_{max}) within approximately 1–2 h. However, its bioavailability (F) remains low at approximately 2%, likely due to extensive first-pass metabolism involving glucuronidation and other pathways in the gut and liver [154].

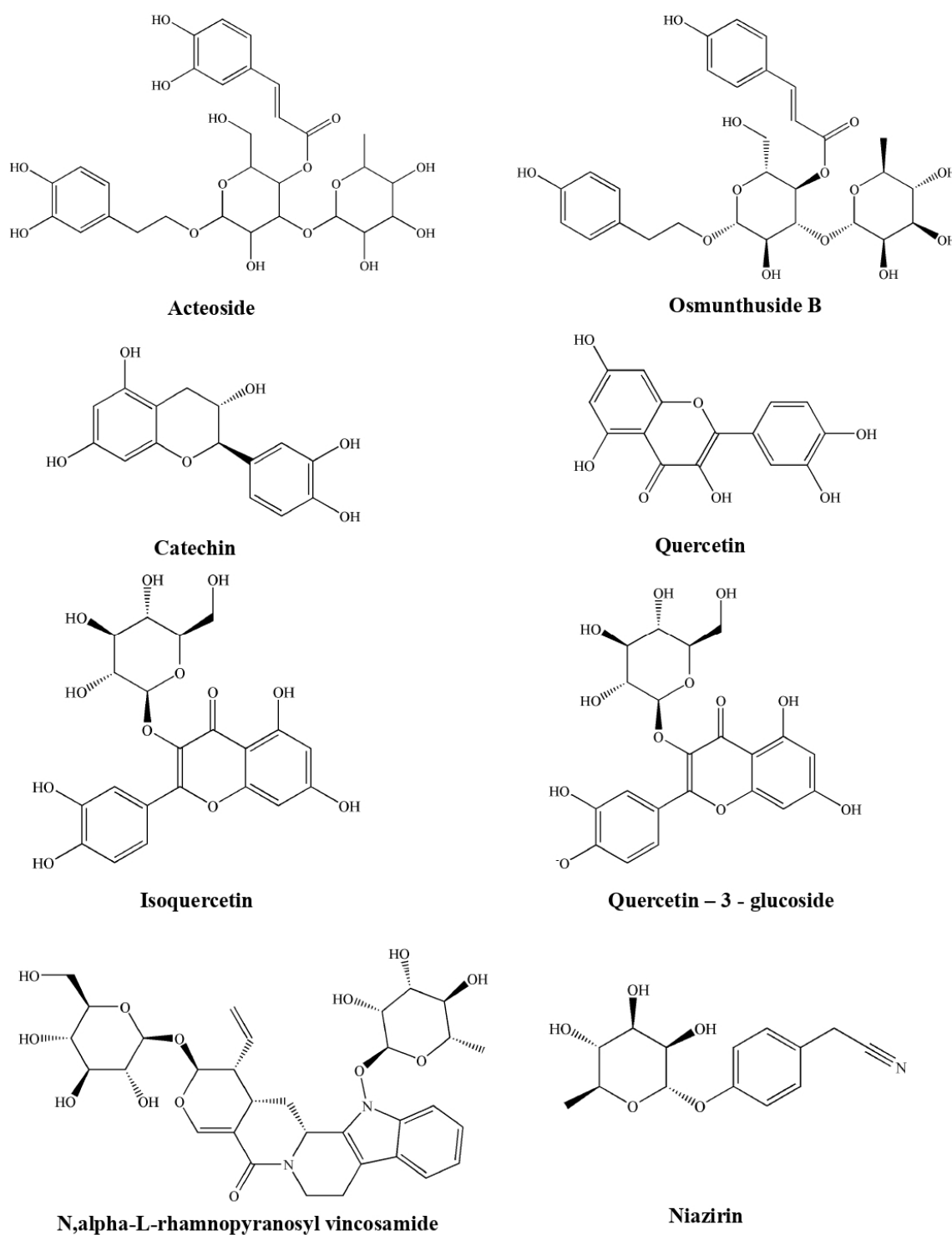
2.1.10. *Solanum torvum* Sw (L.) (Family: Solanaceae)

Solanum torvum is commonly known as Turkey berry and is native to Asia, Africa, the West Indies, and South America. The fruits are edible and are consumed for medicinal purposes to treat hypertension [155]. The ethanolic fruit extract of *Solanum torvum* significantly reduced the systolic blood pressure and the serum glucose, cholesterol, and triglyceride levels. It also ameliorated vascular reactivity to catecholamines and corrected fructose-induced metabolic disturbances. In male albino rats, administration of the extract caused a rightward shift in the cumulative concentration–response curve (CCRC) of angiotensin II (Ang II) in isolated strips of the ascending colon, indicating a reduced contractile response [156]. The aqueous and methanolic extracts of *S. torvum* significantly inhibited platelet aggregation and reduced arterial blood pressure in Wistar rats. Aqueous extracts have been shown to induce antiplatelet aggregation via thrombin and adenosine diphosphate at a concentration of 2 mg/mL via intravenous injection. The methanolic extracts reduced the heart rate at all doses, whereas the aqueous extract only reduced the heart rate at 5 mg/kg. Aqueous extracts reduced blood pressure at doses of 1 and 2 mg/kg without affecting heart rate [157]. Similarly, chronic oral administration of aqueous extracts of *Solanum torvum* fruits significantly reduced arterial hypertension and cardiac hypertrophy in L-NAME-treated rats by increasing urine volume and sodium excretion. In vitro, the extract induced strong, partially endothelium-dependent contraction of the aortic ring [158]. Additionally, the methanolic extract of *S. torvum* fruits exhibited angiotensin-converting enzyme (ACE) inhibitory activity, with an IC_{50} value of 1.2 mg/mL. Bioassay-guided fractionation confirmed the presence of dihydroxycyclopentyl-3-(3,4-dihydroxyphenyl) acrylate, a methyl salicylate glycoside, which had an IC_{50} of 778 µg/mL. In addition, the presence of torvumoside and larciresinol-4, 4-O-β-D- diglucoside potentially contributes to ACE inhibitory activity through their antioxidant activity [159].

2.2. In Silico ADME/T Profiling of Target Plant Bioactive Compounds

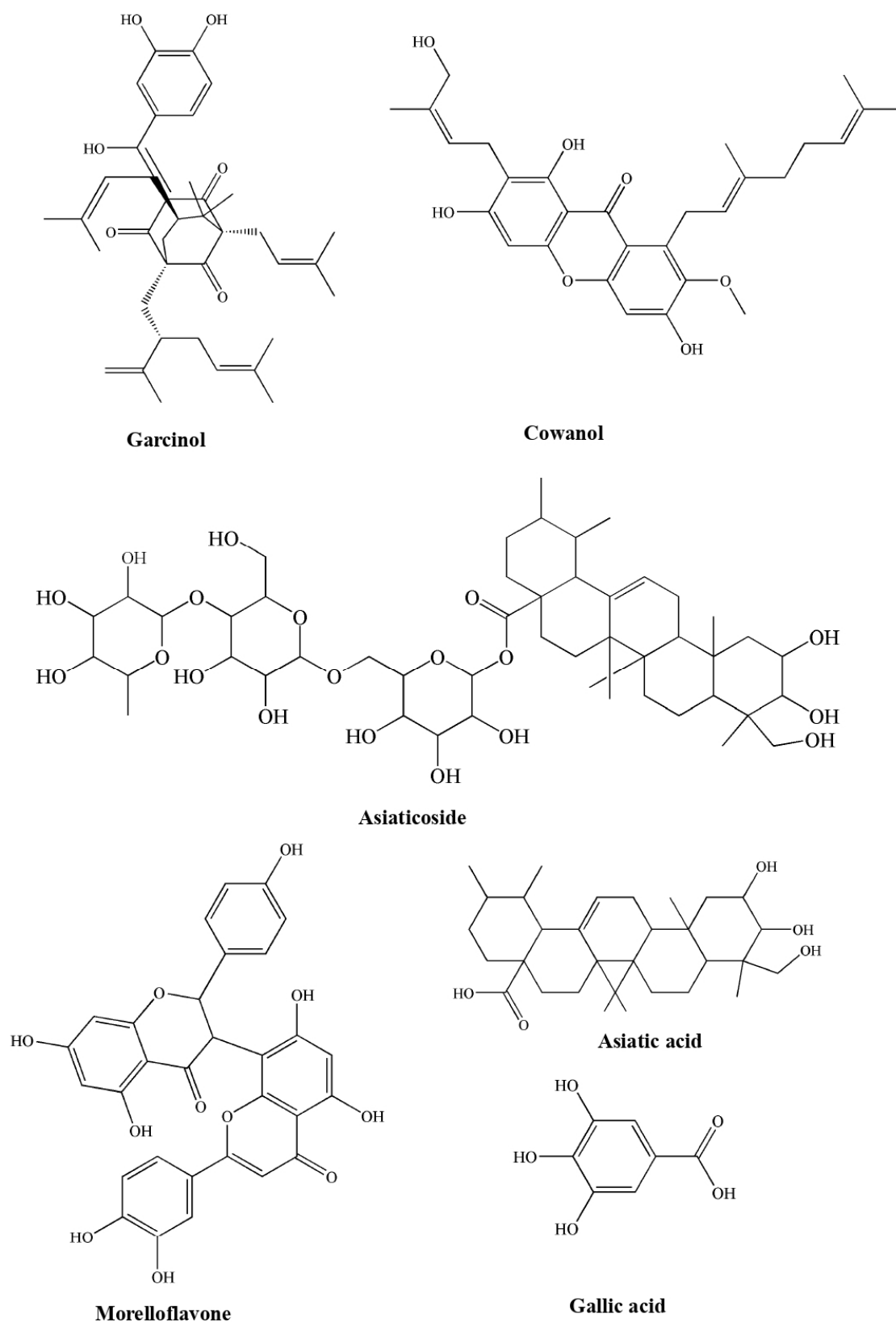
This analysis examines the absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics and drug-likeness of compounds sourced from plants (Figure 5a–d) with antihypertensive effects (Supplementary Tables S1–S6). The physicochemical assessment indicated that most compounds are within the acceptable drug-like range, characterized by a molecular weight under 500 Da, a topological polar surface area below 140 Å², and favorable hydrogen bonding potential. Notably, compounds such as

kaempferol, cratoxylone, piceatannol, and niazirin exhibit optimal physicochemical properties, including low rotatable bond counts and balanced hydrophilic–lipophilic profiles, suggesting good oral bioavailability (Figure 6).



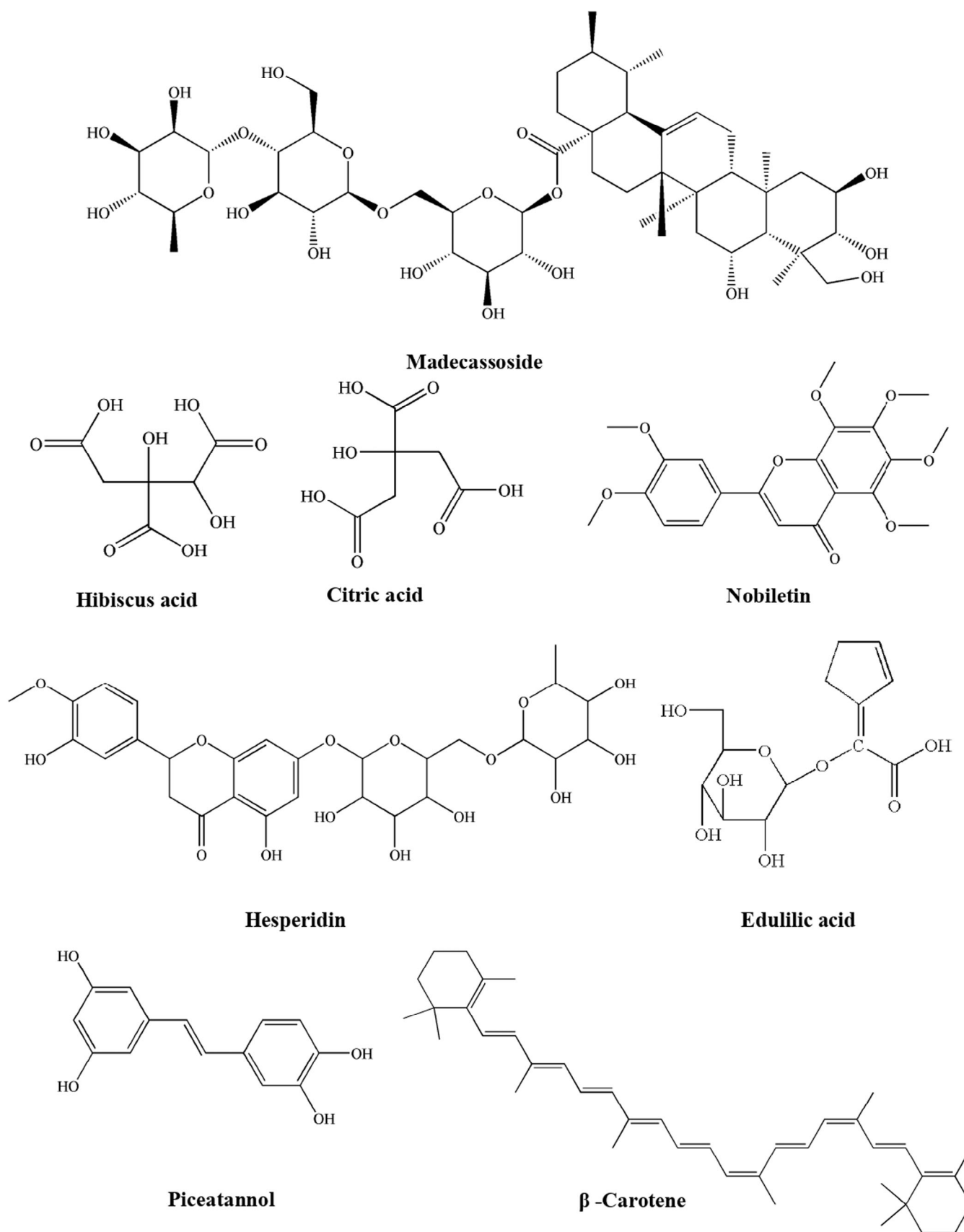
(a)

Figure 5. Cont.



(b)

Figure 5. Cont.



(c)

Figure 5. Cont.

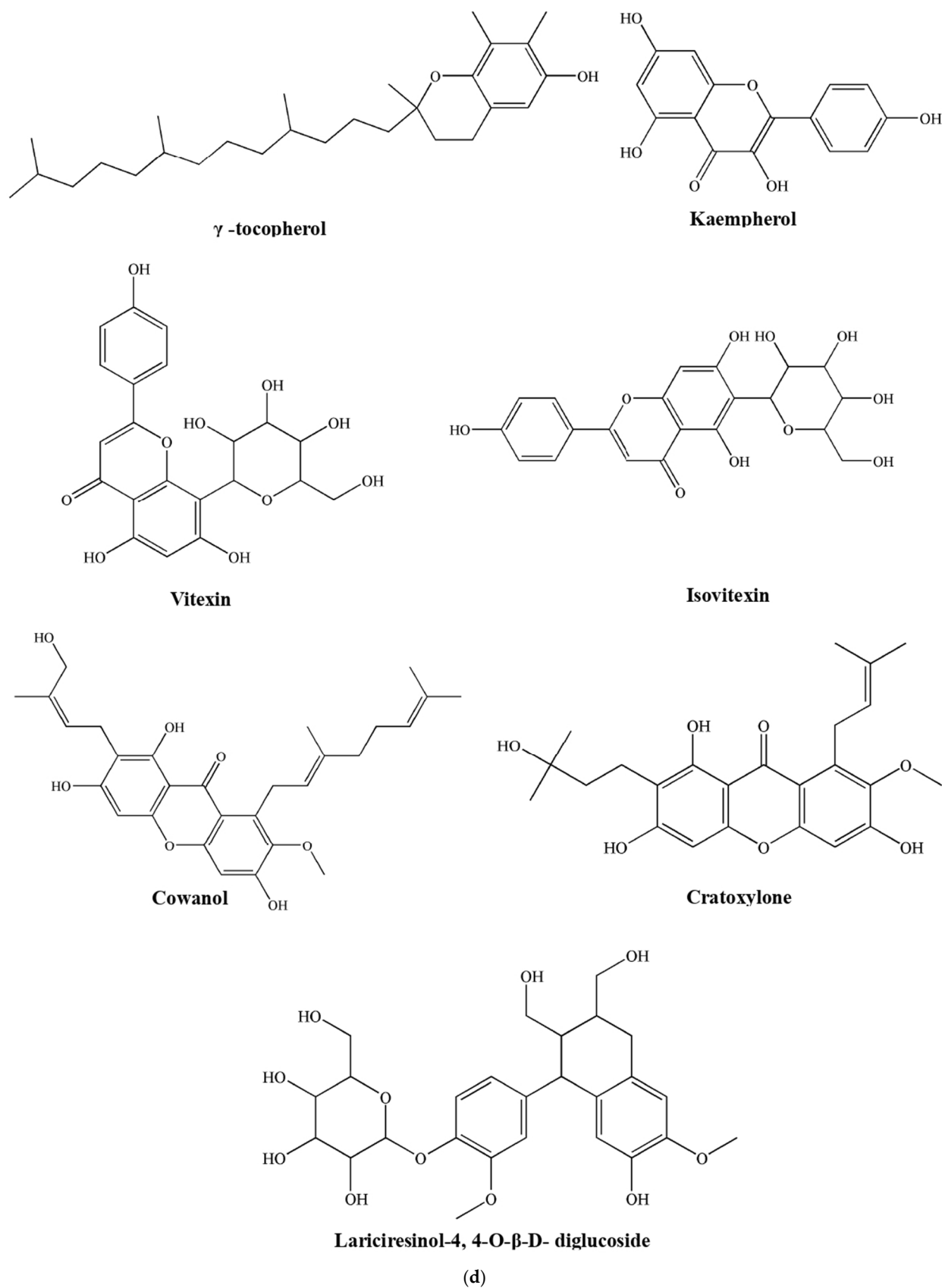


Figure 5. Chemical structures of bioactive compounds from the reported plant species having potent antihypertensive activities (a–d).

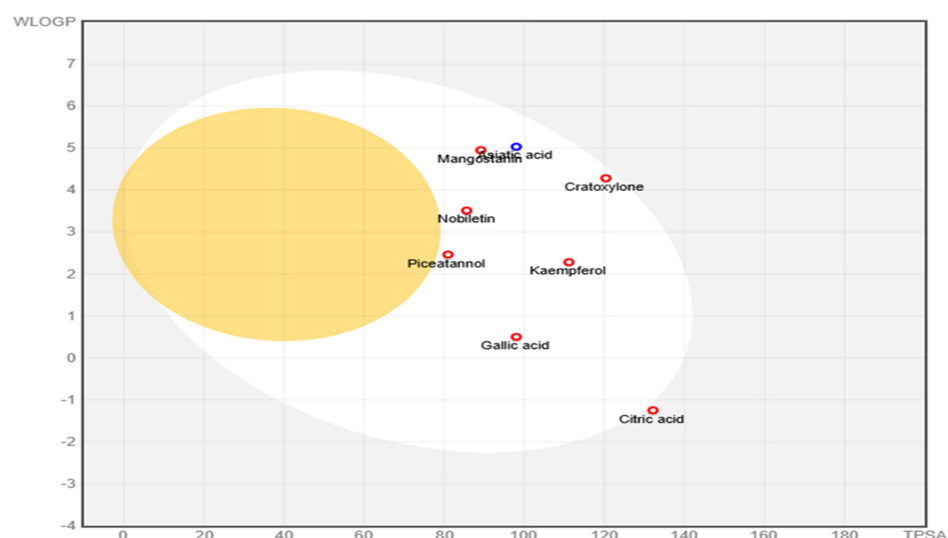


Figure 6. SwissADME BOILED-Egg assessment of compounds. The white zone represents very probable HIA (GI) absorption, whereas the yellow zone shows very likely BBB permeability. The outer gray region consists of compounds that are expected to have poor absorption but no brain penetration.

Lipophilicity analysis, which is based on consensus LogP values, revealed that the majority of these compounds fall within the ideal range of 1–3, with kaempferol (1.58), niazirin (0.32), and piceatannol (2.14) demonstrating a favorable lipophilic balance that minimizes the risk of poor membrane permeability or excessive tissue accumulation. Furthermore, water solubility assessments revealed that compounds such as niazirin, citric acid, hibiscus acid, and osmanthuside are highly soluble, which is beneficial for formulation and oral delivery, whereas garcinol and morelloflavone present solubility challenges that could hinder bioavailability and require advanced formulation techniques. Pharmacokinetic evaluations suggest that several compounds, including kaempferol, cratoxylone, piceatannol, gallic acid, and niazirin, exhibit high gastrointestinal absorption and are not substrates for P-glycoprotein, increasing their suitability for oral administration. Importantly, none of the compounds are predicted to penetrate the blood–brain barrier, a desirable feature of antihypertensive agents, as central nervous system access is generally not preferred for this class of drugs. Kaempferol and nobiletin exhibited inhibition of CYP450 enzymes, particularly CYP3A4 and CYP1A2, which raises concerns about potential drug–drug interactions in combination therapies. Most candidates demonstrated favorable drug-likeness, adhering to established criteria such as the Lipinski, Ghose, Veber, Egan, and Muegge rules, indicating strong oral bioavailability potential. Notably, kaempferol, cratoxylone, niazirin, piceatannol, and nobiletin did not violate these filters and achieved bioavailability scores of 0 or 1, reinforcing their classification as highly drug-like. In contrast, larger polyphenolic compounds such as acteoside, hesperidin, and cyanidin-3-O-glucoside exhibited multiple violations and lower bioavailability scores, suggesting limited oral drug potential in their current forms. The majority of the top-performing compounds presented minimal medicinal chemistry alerts, such as PAINS and Brenk alerts, indicating a low risk of nonspecific binding or false positives in biological assays. The synthetic accessibility scores were generally favorable, ranging from 0 to 2, although more complex molecules such as garcinol received a higher score of 3, indicating challenges in synthesis or scalability. Overall, kaempferol, cratoxylone, piceatannol, niazirin, and nobiletin have emerged as promising candidates for further research because of their balanced ADMET profiles, minimal rule violations, high predicted oral bioavailability, and advantageous medicinal chemistry properties. These findings support their advancement into *in vitro* and *in vivo* studies targeting critical hypertensive mechanisms, such as angiotensin-converting enzyme

(ACE) inhibition, endothelin antagonism, or calcium channel modulation, while also considering formulation enhancement strategies such as nanocarriers or prodrug approaches for compounds with poor solubility yet promising pharmacodynamic profiles.

A thorough *in silico* toxicity (T) assessment of 22 bioactive compounds derived from plants, known for their antihypertensive and antihyperglycemic effects, was conducted via the ProTox-III platform, which yielded significant insights into their therapeutic potential. The evaluation covered various toxicity endpoints, including organ-specific toxicity, ecotoxicity, blood–brain barrier permeability, receptor interactions, activation of stress response pathways, molecular initiating events, and interactions with cytochrome P450 enzymes. Vitexin, isovitexin, isoquercetin, and nobiletin consistently exhibited low toxicity across key parameters, including organ toxicity, mutagenicity, and immunotoxicity. Hibiscus acid, madecassoside, and asiaticoside had high predictive probabilities (over 0.90) for hepatotoxicity and neurotoxicity, raising concerns about the risks of prolonged systemic exposure (Supplementary Table S7). Additionally, garcinol and morelloflavone exhibited cardiotoxicity predictions above 0.85, which is particularly alarming for substances aimed at cardiovascular treatment. From a genotoxicity standpoint, gallic acid, hesperidin, and acteoside presented high mutagenicity scores near 0.98, warranting further investigation through *in vitro* and *in vivo* assays. The high cytotoxicity predictions for kaempferol, piceatannol, and morelloflavone underscore the need for careful assessment of therapeutic windows and dosage. Notably, hesperidin, osmanthuside, and acteoside had high immunotoxicity, suggesting potential adverse effects on immune function. Receptor-binding simulations indicated strong affinities (scores >0.90) for nuclear hormone receptors, including PPAR- γ , estrogen, androgen, and aryl hydrocarbon receptors, suggesting possible endocrine-disrupting effects alongside their therapeutic applications. Furthermore, stress response pathways such as Nrf2/ARE, MMP, HSE, and p53 pathways were activated by many compounds, indicating both antioxidant capabilities and the risk of mitochondrial dysfunction, particularly with hibiscus acid and piceatannol, which are predicted to disrupt the mitochondrial membrane potential.

The ADME/T profiling of these compounds has highlighted both significant advantages and certain obstacles regarding their potential as lead molecules for antihypertensive activity. A comparison with approved drugs from DrugBank, which focus on essential parameters such as intestinal absorption and calculated lipophilicity (ClogP), indicated a considerable overlap in chemical space (Figure 7), underscoring the novel and drug-like characteristics of these natural compounds. Nevertheless, some candidates showed deviations in specific ADMET parameters, including solubility, permeability, or metabolic stability. To address these issues, employing a bioisosteric modification strategy could prove beneficial in optimizing their pharmacokinetic and safety profiles. This targeted approach aims to increase the affinity for the intended targets while reducing undesirable traits, thereby increasing the chances of successful lead development.

2.3. Prospects and Challenges of the Use of Plant Bioactive Compounds in Modern Drug Development

Chemical compounds derived from medicinal plants play crucial roles in treating various health conditions, often resulting in fewer side effects than synthetic drugs do. These plant-based remedies also offer affordable primary healthcare solutions, particularly in regions lacking adequate conventional medical infrastructure, where cultural beliefs and traditional practices guide treatment choices [160]. The presence of multiple phytochemicals in a single plant can lead to synergistic therapeutic effects, benefiting the management of both metabolic and infectious diseases [161]. Emerging biotechnological tools, such as tissue culture techniques, present promising avenues for the large-scale cultivation of potent and endangered medicinal plants [162]. However, the effective isolation and purification of

key bioactive compounds remain significant challenges. Employing advanced extraction methods alongside modern analytical technologies is essential for the efficient and accurate recovery of natural products from plants.

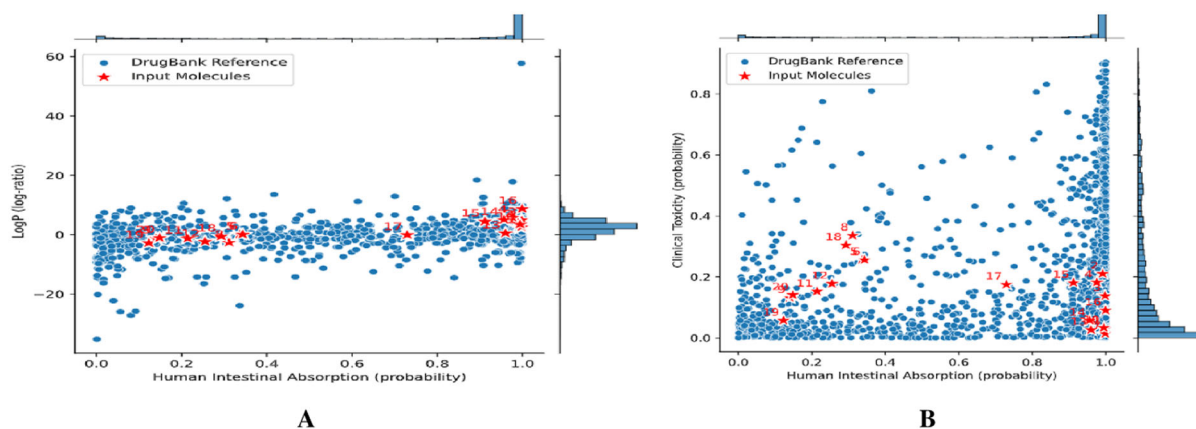


Figure 7. The comparison of the compound library (Input molecules, red star) with the Drugbank library, blue circle (A): ALogP vs. Human intestinal absorption (B): Clinical toxicology vs. Human intestinal absorption.

In this review, we identified a total of 22 significant bioactive compounds (Figure 5a–d) with antihypertensive activity from 10 medicinal plants. However, we were unable to elucidate the chemical structures of certain compounds due to the lack of available information in chemical databases such as PubChem. These include two compounds, namely (E)-2,3-dihydroxycyclopentyl-3-(3',4'-dihydroxyphenyl) acrylate and torvumoside [methyl salicylate 2-O-(2'-O-β-apiofuranosyl, 6'-O-β-xylopyranosyl)-β-glucopyranoside) from *Solanum torvum*, niaziridin from *Moringa oleifera*, edulilic acid from *Passiflora edulis*, and three compounds, namely garciniacowones F, H, and I from *Garcinia cowa*. Moreover, before clinical application, it is important to assess the safety, efficacy, and toxicity of these bioactive compounds to understand their pharmacokinetic behavior in biological systems. As illustrated in Table 2 of this review, many plant-derived compounds presented low IC₅₀ values, indicating strong therapeutic potential while exhibiting high LD₅₀ values (from reported preclinical/clinical literature), suggesting low toxicity, particularly in the context of antihypertensive effects. Nonetheless, a common limitation of these compounds is their poor bioavailability, which often hinders effective site-specific action. To overcome this, nanotechnology-based approaches, such as nanoparticle formulations, may offer a promising strategy to increase bioavailability and ensure targeted therapeutic delivery [163].

In addition, 12 other plant species, *Elsholtzia communis* (Collett & Hemsl.) Dunn, *Cissampelos pareira* L., *Tithonia diversifolia* (Hemsl.) A. Gray, *Fagopyrum esculentum* Moench, *Allium hookeri* Thwaites, *Blumea balsamifera* (L.) DC., *Sarcococca saligna* (D. Don) Müll. Arg., *Catharanthus roseus* (L.) G. Don, *Citrus maxima* (Burm.) Merr., *Mikania micrantha* Kunth, *Cuscuta cassytoides* Nees ex Engelm., and *Bidens pilosa* L., have limited representation in the scientific literature, with only one to two studies available on their antihypertensive activity. To substantiate and establish their potential, there is an urgent need for comprehensive experimental studies and repeated scientific evaluations employing standardized in vitro and in vivo models, along with detailed elucidation of their mechanisms of action and identification of their respective bioactive compounds. Ethnobotany serves as a foundational approach in the discovery of modern drugs, as it is rooted in traditional knowledge and practices. Therefore, proper ethnobotanical documentation, followed by rigorous scientific validation, is crucial for identifying more potent and pharmacologically significant plant-derived compounds with antihypertensive potential from this region.

Table 1. Potent bioactive compounds from the selected plants with their mechanism of action and antihypertensive activity.

Sl. No.	Scientific Name and Family	Parts Used	Bioactive Compound	Experimental Model	Mechanism of Action	Activity	References
1.	<i>Clerodendrum colebrookeanum</i> Walp. (Family: Lamiaceae)	Leaves	Acteoside	In silico study	Inhibit ROCK- I and II, PDE-5	Antihypertensive	[57]
				Rat aorta	NO/cyclic GMP overproduction	Antihypertensive	[58]
				Rat Plasma	Inhibit ACE	Anti-inflammatory	[59]
				LPS-induced mice	Increase NO production, restore sepsis-induced mitochondrial changes, inhibit apoptosis in cardiomyocytes	Anti-inflammatory	[60]
			Osmanthuside	In silico study	Inhibit ROCK-II, PDE-5	Antihypertensive	[57]
2.	<i>Moringa oleifera</i> Lam. (Family: Moringaceae)	Leaves,	Catechin, isoquercetin, quercetin, gallic acid	L-NAME-induced hypertensive rat	Suppress vascular superoxide anion production and oxidative stress reduction	Antihypertensive	[69]
			Quercetin- 3-O glucoside	L-NAME-induced hypertensive rat	Inhibit ACE, systolic blood pressure	Antihypertensive	[73]
			N, α -L-rhamnopyranosyl vincosamide	Isoproterenol (ISO)-induced cardiac toxicity in rats	Lowered cardiac marker	Antioxidant	[74]
			Niaziridin and niazirin	Monocrotaline-induced hypertensive rat	Reduced pulmonary arterial blood pressure	Antioxidant	[75]
			LGF, GLEF	Spontaneously hypertensive rat	Inhibit ACE and renin, reduced systolic and diastolic blood pressure	Antihypertensive	[70]
			IPPAYSK, ILVDR, FFFPK, and LLDPR	In silico study	Inhibit ACE	Antihypertensive	[72]
		Seed	IWHHTFYNELR	In silico study	Inhibit ACE	Antihypertensive	[72]

Table 1. Cont.

Sl. No.	Scientific Name and Family	Parts Used	Bioactive Compound	Experimental Model	Mechanism of Action	Activity	References
3.	<i>Garcinia dulcis</i> (Roxb.) Kurz (Family: Clusiaceae)	Fruit	Camboginol	2-kidney-1-clip hypertensive rat	Activate nitric oxide synthase, prostacyclin signaling pathway, and ATP-activated potassium channel	Vasorelaxant	[81]
			Morelloflavone	2-kidneys-1-clip hypertensive rat	Activate nitric oxide signaling pathway	Diuretic, Vasorelaxant	[82,83]
			Garcinol	LPS-activated THP-1 and Raw 264.7 macrophages	Inhibit TNF- α , IL-8, IL-6, IL-1 β , iNOS, COX-2, and NF- κ B	Anti-inflammatory	[84]
				Male albino Wistar rats	Caspase-3 and Bax	Anti-inflammatory	[85]
4.	<i>Centella asiatica</i> (L.) Urb. (Family: Apiaceae)	Leaves	Asiaticoside	Hypoxia-induced pulmonary hypertension in rats	Inhibit TGF- β 1/Smad2/3 signaling pathway	Anti-inflammatory	[89,90]
				Human umbilical endothelial cells	Reduce VCAM-1, PECAM-1, E-selectin levels	Anti-inflammatory	
			Asiatic acid	2K-1C hypertensive rats	Increased plasma angiotensin II, serum angiotensin ACE activity, restored Ang II-AT ₁ R-gp91 ^{phox} -NF- κ B pathway	Anti-inflammatory	[92]
				L-NAME-induced hypertensive rats	Increase NO bioavailability through upregulation of eNOS protein expression	Vasorelaxant	[93,94]
			Madecassoside	Neonatal rat cardiomyocytes	Inhibit TNF- α production, NF- κ B, phosphorylation of ERK1/2 and p38	Anti-inflammatory	[96]

Table 1. Cont.

Sl. No.	Scientific Name and Family	Parts Used	Bioactive Compound	Experimental Model	Mechanism of Action	Activity	References
5.	<i>Terminalia bellirica</i> (Gaertn.) Roxb. (Family: Combretaceae)	Fruit	Gallic acid	LPS-induced RAW 264.7 macrophage	Inhibit MAPK/NF-κB pathway, activate Akt/AMPK/Nrf2 pathway	Anti-inflammatory and ROS scavenger	[100]
6.	<i>Hibiscus sabdariffa</i> L. (Malvaceae)	Calyx	Hibiscus acid	Rat aorta	Inhibition of Ca ²⁺ influx via voltage-dependent Ca ²⁺ channels	Vasorelaxant	[114]
				α-amylase inhibitory assay	Inhibit α-amylase/α-glucosidase	Vasorelaxant	[115]
7.	<i>Citrus limon</i> (L.) Osbeck (Family: Rutaceae)	Fruit	Citric acid	Spontaneously hypertensive male rats	Vascular muscle relaxant	Vasorelaxant	[120]
				Human platelet cells	Activate VSAP Inhibit NOx and eNOS	Vasorelaxant	[121]
				L-NAME induced hypertensive rats	Inhibit MMP-2 and MMP-9	Vasorelaxant	[122]
			Nobiletin	High-fat-diet fed rats	Upregulation of AdipoR1, Suppression of TGF-β1 in kidney	Vasorelaxant and renal alteration	[123]
				Monocrotaline-induced PAH rats	Inhibit Src/STAT3	Antihypertensive	[124]
				Monocrotaline-induced PAH rats	Inhibit the phosphorylation level of PI3K/Akt/STAT3	Anti-inflammatory	[125]
			Hesperidin, G-Hesperidin	MCF-7 cells	Upregulation of vascular NO synthase	Vasorelaxant,	[126]
				Stroke-prone spontaneously hypertensive rats	ROS scavenger	Antioxidant	[127]
				2K-1C hypertensive rats	Downregulation of renin-angiotensin system	Antihypertensive	[128]

Table 1. Cont.

Sl. No.	Scientific Name and Family	Parts Used	Bioactive Compound	Experimental Model	Mechanism of Action	Activity	References
8.	<i>Passiflora edulis</i> Sims (Family: Passifloraceae)	Fruit	Edulilic acid	Spontaneously induced hypertensive rat	Decrease systolic and diastolic blood pressure	Antihypertensive	[139]
			Piceatannol, beta carotene, gamma tocopherol	LPS-induced RAW 264.7 cells and rat aorta	ROS scavenger, Inhibit pancreatic lipase, cholesterol esterase	Antioxidant, Vasorelaxant	[140]
9.	<i>Garcinia cowa</i> Roxb. ex Choisy (Family: Clusiaceae)	Leaves	Kaempferol	Rat aorta	Activate NO–cGMP–PKG signaling pathway	Vasorelaxant	[146]
			Vitexin	Rat aorta	Inhibit MEK activity, reducing ERK1/2 phosphorylation	Vasorelaxant	[147]
			Isovitexin	L-NAME-induced hypertensive rat	Stimulate NO release Activate SKCa Upregulate Kir 6.1 ATP-sensitive K ⁺ channels	Vasorelaxant	[148]
			Garciniacowones F, H, I, Cowanol, Nagostanin and Cratoxylone	LPS-induced RAW 264.7 cells	Regulation of NO overproduction	Anti-inflammatory	[149]
10.	<i>Solanum torvum</i> Sw (L.) (Family: Solanaceae)	Fruit	Dihydroxycyclopentyl-3-(3,4-dihydroxyphenyl) acrylate, Torvumoside, Lariciresinol-4,4-O-β-D- diglucoside	Bovine plasma	Inhibit ACE activity	Antihypertensive	[159]

Table 2. Safety, efficacy, and toxicity profile of antihypertensive potential bioactive compounds.

Sl. No.	Plant Name	Isolated Compound	IC ₅₀	Bioavailability	Toxicity (LD ₅₀)	Clinical Trial Status	References
1.	<i>Clerodendrum colebrookeanum</i> Walp	Acteoside	0.127 µM	4% in beagle dogs	at >5 g/kg in oral and IP administration in both rats and mice.	Phase 2 and Phase 3 (ClinicalTrials.gov ID NCT02662283)	[164,165]
		Osmanthuside	23.14 ± 0.51 mg/mL	0.17% according to Swiss ADME	LD ₅₀ data not available	NA	[166,167]
2.	<i>Moringa oleifera</i> Lam.	Catechin	44.53 µM	Less than 5% in rats	at 1084 mg/kg via IP administration in rats. Dyspnea-like symptoms occur.	Phase 1 (ClinicalTrials.gov ID NCT03278925)	[168,169]
		Isoquercetin/ Quercetin- 3-O glucoside	79 µg mL ⁻¹	20% in humans	>5 g/kg IP in mice.	Phase 2 (ClinicalTrials.gov ID NCT04474626)	[76,168,170]
		Quercetin	4.48 µM	Less than 10%	484 µg/mL in Zebrafish	Phase 2 (ClinicalTrials.gov ID NCT01708278)	[171–173]
		N, α-L-rhamnopyranosyl vincosamide	19.92 ± 1.19 g/mL	NA	Leaf extract at 2000 mg/kg in rats.	NA	[74,174]
		Niaziridin	NA	NA	NA	NA	
		Niazirin	18.55 uM	46.78–52.61%	3750 mg/kg in mice	NA	[78,175]
3.	<i>Garcinia dulcis</i> (Roxb.) Kurz	Camboginol/ Garcinol	0.1 µM	Moderate oral bioavailability of around 26–36% in Sprague-Dawley rats.	40% Garcinol has a low toxicity profile in rodents	NA	[87,176,177]
		Morelloflavone	0.48 mM	0.17 according to Swiss ADME	No toxicological report	NA	[166,177]

Table 2. Cont.

Sl. No.	Plant Name	Isolated Compound	IC ₅₀	Bioavailability	Toxicity (LD ₅₀)	Clinical Trial Status	References
4.	<i>Centella asiatica</i> (L.) Urb.	Asiaticoside	300 µM	Less than 1% in male Wistar rats.	>2000 g/kg of leaf extract orally (No LD ₅₀ reported for the compound)	Phase 2 and Phase 3 (ClinicalTrials.gov ID NCT06231212)	[178,179]
		Asiatic acid	60 µM	16.25%	Showed cardiotoxicity in zebrafish	Phase 2 and Phase 3 (ClinicalTrials.gov ID NCT06231212)	[179–181]
		Madecassoside	26 µM	Less than 1% in male Wistar rat	No toxicological report	Phase 2 and Phase 3 (ClinicalTrials.gov ID NCT06231212)	[178,182]
5.	<i>Terminalia bellirica</i> (Gaertn.) Roxb	Gallic acid	3.5 µg/mL	Low bioavailability due to fast absorption and metabolism.	4300 gm/kg (IP), 320 mg/kg (IV) in mouse; 5000 mg/kg (Oral) in rabbit	Phase 1 (ClinicalTrials.gov ID NCT04970589)	[107,168]
6.	<i>Hibiscus sabdariffa</i> L	Hibiscus acid	37.15 µg/mL	10% in oral administration in humans.	>5000 mg/kg of calyx extract (IP) in mice. Above 500 mg/kg of <i>H. sabdariffa</i> extract alter the taste of rats.		[117,183]
7.	<i>Citrus limon</i> (L.) Osbeck	Citric acid	0.64 ± 0.04 µM/mL	94.80% in rabbits	5040 mg/kg (Oral) in Mouse and 3000 mg/kg (Oral) in rats.		[184,185]
		Nobiletin	6.12 µM	19.93 ± 3.93% and 46.20 ± 5.03% in oil suspension and emulsion, respectively.	Data are not available		[186–188]
		Hesperdin	16.08 mM	Less than 20%	4837.5 mg/kg (Oral) in rats.		[136,189,190]

Table 2. Cont.

Sl. No.	Plant Name	Isolated Compound	IC ₅₀	Bioavailability	Toxicity (LD ₅₀)	Clinical Trial Status	References
8.	<i>Passiflora edulis</i> Sims	Piceatannol	60 µM	17.70 ± 0.91% after oral administration	217 mg/kg (IP) in mouse	Phase 1 (ClinicalTrials.gov ID NCT06127381)	[168,191,192]
		Beta carotene	7.0 µg/mL	60.7%	>10,000 mg/kg (Oral) in rats.	Phase 4 (ClinicalTrials.gov ID NCT03005496)	[193,194]
9.	<i>Garcinia cowa</i> Roxb. ex Choisy	Kaempferol	178 µM	~2% in rats	No toxic effect seen up to 2000 mg/kg/day in SD rats	Phase 1 (ClinicalTrials.gov ID NCT02191241)	[154,195,196]
		Vitexin	52.80 ± 1.65 µM	Very low bioavailability	1 mg/kg (IP) in mice showed LD ₂₅	Phase 4 (ClinicalTrials.gov ID NCT01647984)	[168,197,198]
		Isovitexin	18.6 ± 1.3 µg/mL	14.58% oral bioavailability in mouse	2.56 mol/kg	NA	[199–201]
		Cowanol	13.4 µM	-	2.778 mol/kg in rat	NA	[149,202]
		Garciniacowone F	11.0 µM	NA	NA	NA	[149]
		Garciniacowone H	7.7 µM	NA	NA	NA	[149]
		Garciniacowone I	5.8 µM	NA	NA	NA	[149]
		Mangostanin/9-Hydroxycalabaxanthone	18.6 µM	NA	NA	NA	[149]
		Cratoxylone	5.4 µM	NA	NA	NA	[149]

Table 2. Cont.

Sl. No.	Plant Name	Isolated Compound	IC ₅₀	Bioavailability	Toxicity (LD ₅₀)	Clinical Trial Status	References
10.	<i>Solanum torvum</i> Sw (L.)	(E)-2,3-dihydroxycyclopentyl-3-(3',4'-dihydroxyphenyl)acrylate	(778.8 g/mL) 2.7 mM	NA	NA	NA	[159]
		Torvumoside (methyl salicylate 2-O-(2'O-β-apiofuranosyl, 6'-O-β-xylopyranosyl)-β-glucopyranoside)	NA	NA	NA	NA	
		Lariciresinol-4, 4-O-β-D- diglucoside	NA	NA	NA	NA	

3. Materials and Methods

3.1. Systematic Review of Hypertension and Medicinal Plant-Related Therapeutic Evidence

In this systematic review, relevant research articles were identified through comprehensive searches in major scientific databases, including PubMed, Google Scholar, ScienceDirect, and Scopus via the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [203]. The introduction provides a concise overview of hypertension, covering its definition, classification, global prevalence, causes, symptoms, and association with cardiovascular diseases. It also discusses current limitations in diagnostic approaches and underscores the potential of affordable, plant-based therapeutic strategies.

Studies evaluating the antihypertensive and hypotensive effects of selected medicinal plants were included on the basis of demonstrated mechanisms of action. These mechanisms include inhibition or reduction in angiotensin-converting enzyme (ACE) activity; elevation of nitric oxide (NO) levels; inhibition of NF- κ B; calcium channel blocking or antagonistic activity; enhancement of flow-mediated dilation (FMD); reduction in proinflammatory cytokines such as TNF- α and IL-6; inhibition of vascular cell adhesion molecule-1 (VCAM-1); suppression of platelet-derived growth factor (PDGF) proliferation; inhibition of lipid peroxidation (LPS); promotion of urinary excretion of potassium (K⁺), sodium (Na⁺), and chloride (Cl⁻) ions; inhibition of angiotensin II; activation of endothelial nitric oxide synthase (eNOS); and scavenging of reactive oxygen species (ROS). Collectively, these factors contribute to vasorelaxant, vasodilatory, anti-inflammatory, anti-proliferative, and antioxidant effects.

A total of 370 articles were initially retrieved. Following the removal of 58 duplicates, further exclusions were made: 16 articles due to insufficient data, 23 for lack of full-text access, 17 non-English publications, 38 studies involving plant combinations instead of single species, and 3 studies lacking in vitro or in vivo models. After applying these criteria, 215 studies were selected for inclusion (Figure 8).

Inclusion criteria are as follows:

- i. The full texts of the articles were published in English.
- ii. Studies reporting antihypertensive activity via in vitro, in vivo, or both approaches via standardized protocols.
- iii. Studies have focused on single plant species, utilizing crude extracts, bioactive fractions, or isolated pure compounds. Pharmacokinetic studies of major compounds regardless of the source plant were also included to provide information on their absorption, distribution, metabolism, excretion, and bioavailability.
- iv. Peer-reviewed studies published up to 2024.

Exclusion criteria are as follows:

- i. Articles available only as abstracts without full text.
- ii. Book chapters or conference proceedings not indexed in PubMed, Google Scholar, Scopus, or ScienceDirect.
- iii. Non-English language publications.
- iv. Studies lacking scientific rigor or proper methodology or not published in peer-reviewed and refereed journals.

Additional data sources are as follows:

The updated and verified names of the plant species mentioned in the study were obtained from the World [204]. Additional data, including IC₅₀ values, LD₅₀ values, and bioavailability information, were obtained from [166,168]. Clinical trial information related to the selected medicinal plants or their active constituents was extracted from [205]. The chemical structures of the bioactive compounds were illustrated via ChemDraw 8.0 software.

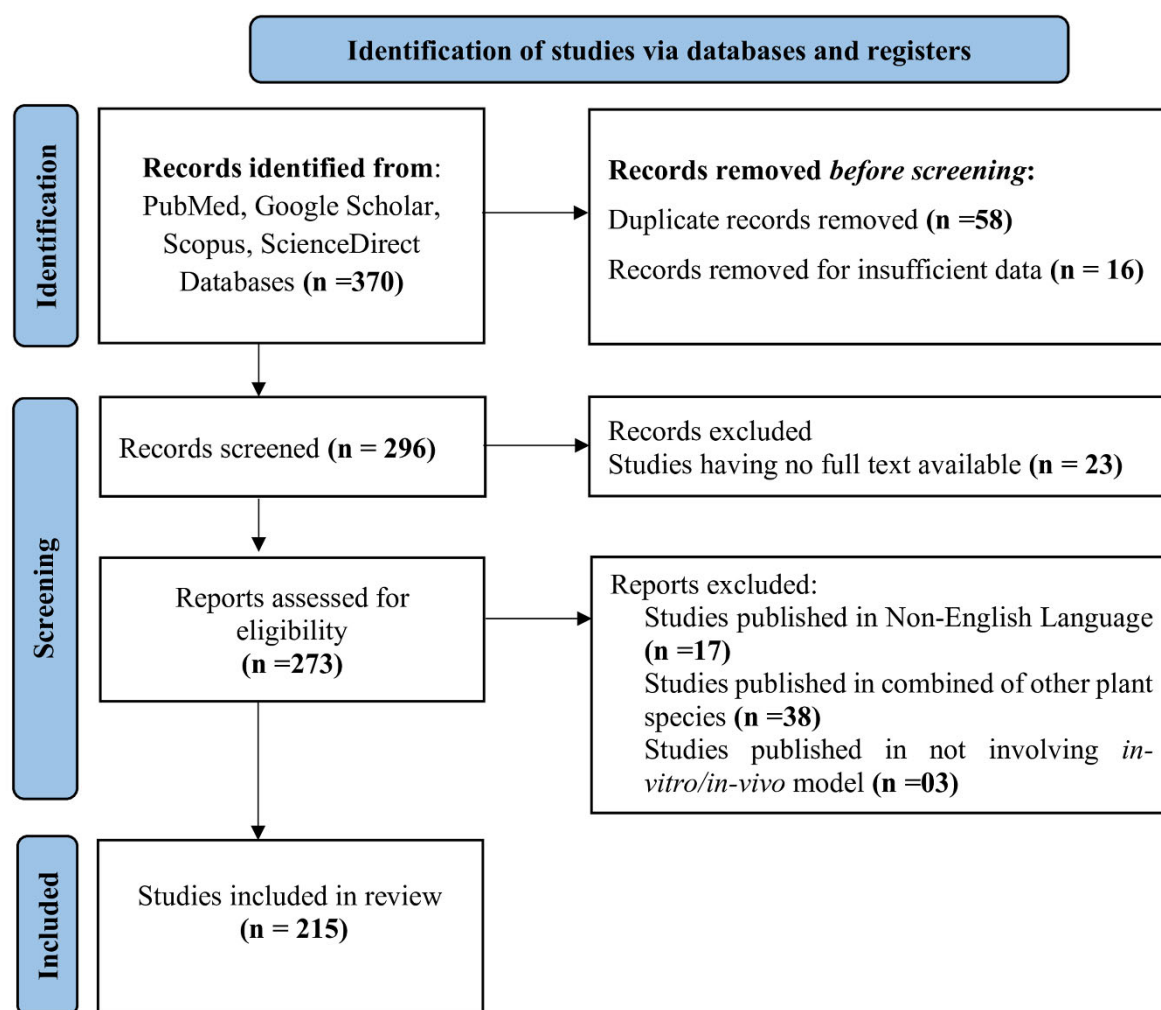


Figure 8. PRISMA flow diagram for the selection process of studies included in this review.

3.2. An In Silico Evaluation of Identified Plant-Based Compounds with Antihypertensive Activity

In recent years, computer-aided drug discovery (CADD) has played a pivotal role in advancing this research, primarily through ligand-based and structure-based approaches [206–208]. Emerging computational techniques such as molecular docking, network pharmacology, metabolomics, and molecular dynamics simulations have been increasingly employed to explore and predict the antihypertensive potential of plant-derived compounds [209–211]. These methodologies enable the identification of active phyto-constituents, their molecular targets, and mechanistic pathways, thereby accelerating the development of novel therapeutics for hypertension.

The assessment of the ADME (Absorption-A, Distribution-D, Metabolism-M, and Excretion-E) and toxicity (T) characteristics of compounds is essential in the early stages of drug discovery, as these characteristics influence the pharmacokinetic profile and safety of potential drug candidates [212]. This study conducted a thorough ADMET and toxicity evaluation of 22 plant-derived compounds known for their antihypertensive effects to determine their drug-likeness and appropriateness for initial drug development. Two compounds, madecassoside and asiaticoside, were omitted from further analysis because of their high molecular weights. ADMET profiling utilizes three sophisticated in silico tools: SwissADME, ProTox 3.0, and ADMET-AI. SwissADME (<https://tox.charite.de/protox3/>, accessed on 15 May 2025) was employed to predict essential physicochemical properties, including lipophilicity, through models such as iLOGP and XLOGP3, as well as pharmacokinetic parameters such as gastrointestinal absorption and

blood–brain barrier permeability, while also assessing drug-likeness via established filters such as those of Lipinski and Ghose. Additionally, synthetic accessibility was evaluated, and any PAINS or Brenk alerts were identified to gauge medicinal chemistry viability [213]. ProTox 3.0, a cutting-edge toxicity prediction platform leveraging molecular similarity and machine learning, was utilized to analyze 61 toxicity endpoints, encompassing acute oral toxicity and organ toxicity [214]. Finally, ADMET-AI was used to compare the input compounds against the Drugbank library, i.e., ALogP and clinical toxicology versus human intestinal absorption [215].

4. Conclusions

Although synthetic antihypertensive drugs are essential for controlling high blood pressure and preventing complications such as heart attack and stroke, they may cause a variety of adverse effects. The use of traditional medicines provides several benefits over synthetic drugs, such as fewer side effects, a holistic approach to health, cultural relevance, sustainability, cost-effectiveness, synergistic effects, personalized treatment, and a lower risk of resistance. These advantages make traditional medicine an important complement or alternative to synthetic drugs, especially in enhancing overall health and well-being. Ethnomedicinal plants with antihypertensive properties present a valuable opportunity for developing new drugs that are natural and potentially safer than synthetic medications. Leveraging the wide range of bioactive compounds and traditional wisdom linked to these plants, researchers can create innovative and efficient treatments for hypertension, thereby addressing a significant global health concern. Establishing the safety, efficacy, and bioavailability of plant-derived bioactive compounds through rigorous preclinical and clinical studies is essential for the development of standardized and effective plant-based therapeutics. Such evidence would strengthen the scientific basis for the potential integration of traditional medicinal knowledge into modern healthcare and facilitate the development of novel antihypertensive drugs.

5. Limitations of the Study

The ADMET and toxicity profiles for 22 bioactive compounds identified in this review were obtained solely from in silico platforms (SwissADME, ProTox 3.0 and ADMET-AI). These predictions are based on similarity algorithms and machine learning models and not experiential evidence and should be validated via in vitro and in vivo studies. Due to the lack of structural data in public chemical databases, the chemical structures of a few compounds in this study, including a dihydroxycyclopentyl acrylate derivative and torvumoside (*Solanum torvum*), niaziridin (*Moringa oleifera*), edulilic acid (*Passiflora edulis*), and garcinia cowones F, H and I (*Garcinia cowa*), could not be completely resolved, restricting their computational evaluation.

However, several promising compounds have poor oral bioavailability, such as asiaticoside (<1% in rats) and kaempferol (~2% in rats), which could be limited in their therapeutic potential unless their bioavailability is enhanced by formulation approaches like drug delivery systems based on the use of nanoparticles. The in silico toxicity screening also predicted safety concerns for a few compounds, such as hepatotoxicity and neurotoxicity (hibiscus acid, madecassoside and asiaticoside), cardiotoxicity (garcinol and morelloflavone), mutagenicity (gallic acid, hesperidin, and acteoside), and possible endocrine-disrupting activity due to the interaction with nuclear hormone receptors. While these predictions do not provide evidence of toxicity, they do indicate the importance of achieving thorough experimental safety testing.

No new experimental or clinical data were generated, and this is a literature review and analysis. Standardized in vitro and in vivo studies are needed to confirm the proposed

antihypertensive mechanisms, detailed pharmacokinetic and bioavailability studies, dose-dependent effects on toxicological studies, and formulation optimization for bioavailability in future studies. But if the preclinical evidence is significant, well-designed clinical trials will be needed to prove the safety and effectiveness of these compounds in humans.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ddc5030043/s1>, Table S1: Physicochemical Property calculation; Table S2: Lipophilicity; Table S3: Water Solubility; Table S4: Pharmacokinetics; Table S5: Drug likeness; Table S6: Medicinal Chemistry; Table S7: Toxicity Prediction of Compounds with Hypertensive activity.

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Abbreviations

ACE	Angiotensin-converting enzyme
ACEIs	Angiotensin-converting enzyme inhibitors
ADMET	Absorption, distribution, metabolism, excretion and toxicity
AHA	American Heart Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BBB	Blood–brain barrier
BMI	Body mass index
BP	Blood pressure
CADD	Computer-aided drug discovery
CCRC	Cumulative concentration-response curve
CHD	Coronary heart disease
COX-2	Cyclooxygenase-2
DBP	Diastolic blood pressure
EDHF	Endothelium-derived hyperpolarizing factor
eNOS	Endothelial nitric oxide synthase
FMD	Flow-mediated dilation
HAPH	High-altitude pulmonary hypertension
HCHF	High-carbohydrate, high-fat

HO-1	Heme oxygenase-1
HR	Heart rate
HUVECs	Human umbilical vein endothelial cells
ICAM-1	Intercellular adhesion molecule-1
IL-1	Interleukin-1
iNOS	Inducible nitric oxide synthase
LDL	Low-density lipoprotein
LOX-1	Lectin-like oxidized LDL receptor-1
LPS	Lipopolysaccharide
MABP	Mean arterial blood pressure
MDA	Malondialdehyde
MMPs	Matrix metalloproteinases
NF- κ B	Nuclear factor kappa B
NFHS	National Family Health Survey
NO	Nitric oxide
NOS	Nitric oxide synthase
Nrf2	Nuclear factor erythroid 2
oxLDL	Oxidized low-density lipoprotein
PDE-5	Phosphodiesterase-5
PDGF	Platelet-derived growth factor
PECAM-1	Platelet endothelial cell adhesion molecule-1
RAAS	Renin–angiotensin–aldosterone system
RAS	Renin-angiotensin system
ROCK-II	Rho-kinase-II
ROS	Reactive oxygen species
RVH	Renovascular hypertension
SBP	Systolic blood pressure
SKCa	Small-conductance Ca^{2+} -activated potassium channel
SOD	Superoxide dismutase
TGF	Transforming growth factor
TNF- α	Tumor necrosis factor-alpha
VASP	Vasodilator-stimulated phosphoprotein
VCAM-1	Vascular cell adhesion molecule-1
VOOC	Voltage-operated calcium channels
WHO	World Health Organization

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