

Natural vasodilators: mechanisms and therapeutic potential in cardiovascular diseases

Aomei Sun¹, Opoku Bonsu Francis¹, Shutong Yan¹, Jing Wang¹, Haoshuang Zhao¹, Ling Leng^{1,2}, Ruiqiao Li¹, Hongtao Liu³, Xiaoxuan Tian^{1,2,*}, Dake Qi^{4,*}, Qilong Wang^{1,2,5,*}

¹Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China; ²State Key Laboratory of Chinese Medicine Modernization, Tianjin, China; ³Key Laboratory of Chinese Medicinal Resource and Chinese Herbal Compound of the Ministry of Education, Hubei University of Chinese Medicine, Wuhan, China; ⁴College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada; ⁵Endocrinology Department, Fourth Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China

Abstract

Natural products with vasodilatory properties are increasingly recognized for treating hypertension, angina, and heart failure owing to their efficacy, accessibility, and favorable safety profiles, rendering them viable therapeutic alternatives. Following a systematic search of the NCBI PubMed and CNKI databases, 227 natural compounds with potent vasodilatory activity were identified. This review delineates the vasodilatory effects of major phytochemical classes—specifically flavonoids, saponins, phenols, and alkaloids—and evaluates preclinical evidence supporting their therapeutic application. Furthermore, potential vasodilatory mechanisms are elucidated, encompassing endothelium-dependent regulation of smooth muscle tone, fluid homeostasis, oxidative stress mitigation, and antagonism of the renin-angiotensin-aldosterone system. These mechanisms clarify the pharmacological basis of natural vasodilators, offering researchers and clinicians enhanced strategies for managing cardiovascular diseases.

Keywords: Natural products, Vasodilation, Vasodilatory factors, Ion Channel, RAAS, Ginsenosides, Berberine, Resveratrol

Graphical Abstract: <https://links.lww.com/AHM/A230>

Introduction

Cardiovascular diseases (CVD) account for more than 35% of global deaths annually. These conditions remain a critical health burden, significantly impairing the quality of life for patients. Over the past three decades, the prevalence of CVD has risen across all age groups, with the associated risks increasing significantly with age^[1–3].

Vasodilatory dysfunction arises from alterations in multiple physiological processes, including vascular injury, aging, hyperglycemia, oxidative stress, inflammation, and hyperlipidemia—all of which are established risk factors for CVD. Vasodilation is co-regulated by vasoactive molecules, the autonomic nervous system, and local metabolic states. Consequently, any stimulus disrupting the homeostatic equilibrium of these regulatory mechanisms may be considered a primary driver of vasodilatory dysfunction and a precursor to various cardiovascular pathologies. Ultimately, vasodilatory dysfunction precipitates ischemia in tissues and organs, serving as a critical pathological driver of hypertension,

coronary heart disease, and heart failure, as well as ischemic stroke and myocardial infarction^[4–5].

Vasodilation is a complex process involving structural interactions between endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), alongside the contribution of vasoactive molecules. These molecules are synthesized and released by ECs to modulate vascular tone. Multiple conventional vasodilators are currently available, each employing distinct mechanisms to achieve three primary treatment objectives: reducing blood pressure, increasing blood flow (eg, nitroglycerin, hydralazine, and minoxidil), and relieving angina. In addition to these strategies, indirect-acting vasodilators, including calcium channel blockers (eg, verapamil, nifedipine, and amlodipine) and renin-angiotensin-aldosterone system (RAAS) antagonists, are utilized to manage hypertension and related conditions.

While conventional vasodilators demonstrate a rapid onset, adverse effects, including hypotension, reflex tachycardia, peripheral edema, electrolyte imbalances, hepatotoxicity, and nephrotoxicity, are common. Prolonged administration of these agents may also precipitate

Aomei Sun and Opoku Bonsu Francis contributed equally to this work.

*Corresponding author. Qilong Wang, E-mail: wangqilong_00@tjutc.edu.cn; Dake Qi, E-mail: dake.qi@umanitoba.ca; Xiaoxuan Tian, E-mail: tian_xiaoxuan@tjutc.edu.cn.

How to cite this article: Sun AM, Francis OB, Yan ST, Wang J, Zhao HS, Leng L, Li RQ, Liu HT, Tian XX, Qi DK, Wang QL. Natural vasodilators: mechanisms and therapeutic potential in cardiovascular diseases. *Acupunct Herb Med* 2026;6(2):155–187. doi: 10.1097/HM9.0000000000000200

Received 16 December 2025 / Accepted 12 April 2026

Copyright © 2026 Tianjin University of Traditional Chinese Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

pharmacological tolerance and rebound phenomena upon discontinuation^[6]. Moreover, interindividual variability in absorption kinetics and potential drug–drug interactions may compromise efficacy and increase adverse reactions, thereby limiting the utility of existing pharmacotherapies. Given these therapeutic constraints, novel treatment options, particularly those derived from natural products, are receiving significant attention.

Natural products are regarded as promising alternatives for the treatment and prevention of CVD^[7–9]. This transition is primarily driven by the capacity of natural products for multi-target and multi-pathway modulation, addressing the constraints associated with conventional pharmacotherapy. Natural compounds are categorized into several primary classes, including alkaloids, saponins, polyphenols, terpenoids, flavonoids, and phenylpropanoids. These diverse compounds have demonstrated significant therapeutic efficacy.

Tetramethylpyrazine, isolated from *Ligusticum sinense* cv. Chuanxiong, is a constituent of traditional Chinese medicine formulated to promote blood circulation and resolve blood stasis. Tetramethylpyrazine also possesses anti-inflammatory and antioxidant properties, both of which modulate vasodilation^[10]. Tanshinone, a bioactive constituent of *Salvia miltiorrhiza* Bunge, demonstrates vasodilatory activity and enhances microcirculation. Ellagic acid, found in *G. tinctoria* extract, protects endothelial function by attenuating the generation of reactive oxygen species (ROS) in high-glucose-induced ECs. These findings underscore the protective effects of natural products on the vascular endothelium and validate the shift toward natural products as viable therapeutic alternatives^[11]. Recent investigations have identified that scopoletin, senkyunolide A, and ligustilide from *Ligusticum chuanxiong* Hort. exert coronary artery dilating effects. Studies have confirmed that scopoletin and senkyunolide A induce endothelium-dependent dilation and modulate vascular tone *via* the AKT serine/threonine kinase 1 (AKT)-endothelial nitric oxide synthase (eNOS)-nitric oxide (NO) pathway. Furthermore, borneol induces vasorelaxation by attenuating Ca²⁺ influx and activating K⁺ channels^[12]. Additionally, puerarin and various flavonoids demonstrate synergistic effects in maintaining vascular endothelial integrity and reducing blood pressure. Notwithstanding these advantages, the chemical complexity of natural compounds complicates the characterization of their therapeutic properties. Consequently, many mechanisms of action remain unelucidated, hindering widespread clinical adoption.

This review screened major databases, including PubMed and CNKI, to extract relevant data on natural compounds, specifically reviewing principal vasodilatory pathways, key traditional Chinese medicine constituents, and their molecular mechanisms. This summary provides a foundation for the development of natural products as potential therapeutic options for CVDs.

Vasodilatory mechanisms and signaling pathways

The regulation of vasodilation is mediated by intricate interactions between endothelial factors, intracellular signaling cascades, the neurohumoral system, and redox homeostasis (Figure 1). Vasoactive factors derived from the endothelium are synthesized through established pathways

and activate downstream cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) or cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling in VSMCs. The modulation of ion channels, particularly Ca²⁺ and K⁺ channels, further regulates cytosolic calcium dynamics, promoting membrane hyperpolarization and vasorelaxation. Simultaneously, systemic regulators, including the RAAS and autonomic neurotransmitters, integrate with endothelial signaling to modulate vascular tone (Figure 2). In pathological states, oxidative stress impairs these pathways by reducing NO bioavailability and compromising endothelial function, thereby shifting the equilibrium toward vasoconstriction. In summary, these interconnected mechanisms constitute the core pathways of vasodilation under physiological and pathological conditions.

Vasodilatory factors

Nitric oxide

NO is a gaseous signaling molecule synthesized by vascular ECs. In ECs, NO is primarily generated from L-arginine by eNOS^[13]. Following synthesis, NO diffuses into adjacent VSMCs and activates soluble guanylyl cyclase (sGC), increasing intracellular cGMP levels. Elevated cGMP subsequently activates PKG, promoting Ca²⁺ efflux, which reduces cytosolic Ca²⁺ concentrations and induces smooth muscle relaxation and vasodilation.

Carbon monoxide

Analogous to NO, the vasodilatory effect of carbon monoxide (CO) is mediated *via* the cGMP-dependent PKG pathway^[14]. Additionally, CO activates K⁺ channels to promote K⁺ efflux and subsequent membrane hyperpolarization, thereby reducing Ca²⁺ influx and facilitating vasodilation^[15]. Recent investigations have highlighted signaling crosstalk between CO and NO: low CO concentrations may enhance vascular protection, whereas excessive CO levels may impair the mitochondrial respiratory chain and exert cytotoxic effects^[16–17].

Hydrogen sulfide

Hydrogen sulfide (H₂S) exerts a vasodilatory effect partly by inhibiting phosphodiesterase (PDE) enzymes, particularly PDE5, thereby increasing cGMP levels in VSMCs and promoting relaxation^[18–19]. H₂S also elevates cGMP and activates PKG while directly modulating K⁺ channels. Specifically, H₂S facilitates post-translational modification of cysteine thiol groups in channel proteins—a process termed persulfidation—which enhances the activity of ATP-sensitive K⁺ (K_{ATP}) channels and large-conductance Ca²⁺-activated K⁺ (BK_{Ca}) channels. The resulting K⁺ efflux and membrane hyperpolarization inhibit voltage-dependent calcium channel activity, attenuate Ca²⁺ influx, and promote smooth muscle relaxation^[20]. Additionally, H₂S inhibits L-type Ca²⁺ channels, further reducing Ca²⁺ influx^[21–22].

Prostacyclin

Prostacyclin (PGI₂) is synthesized in ECs from arachidonic acid (AA) through the enzymatic cascade of

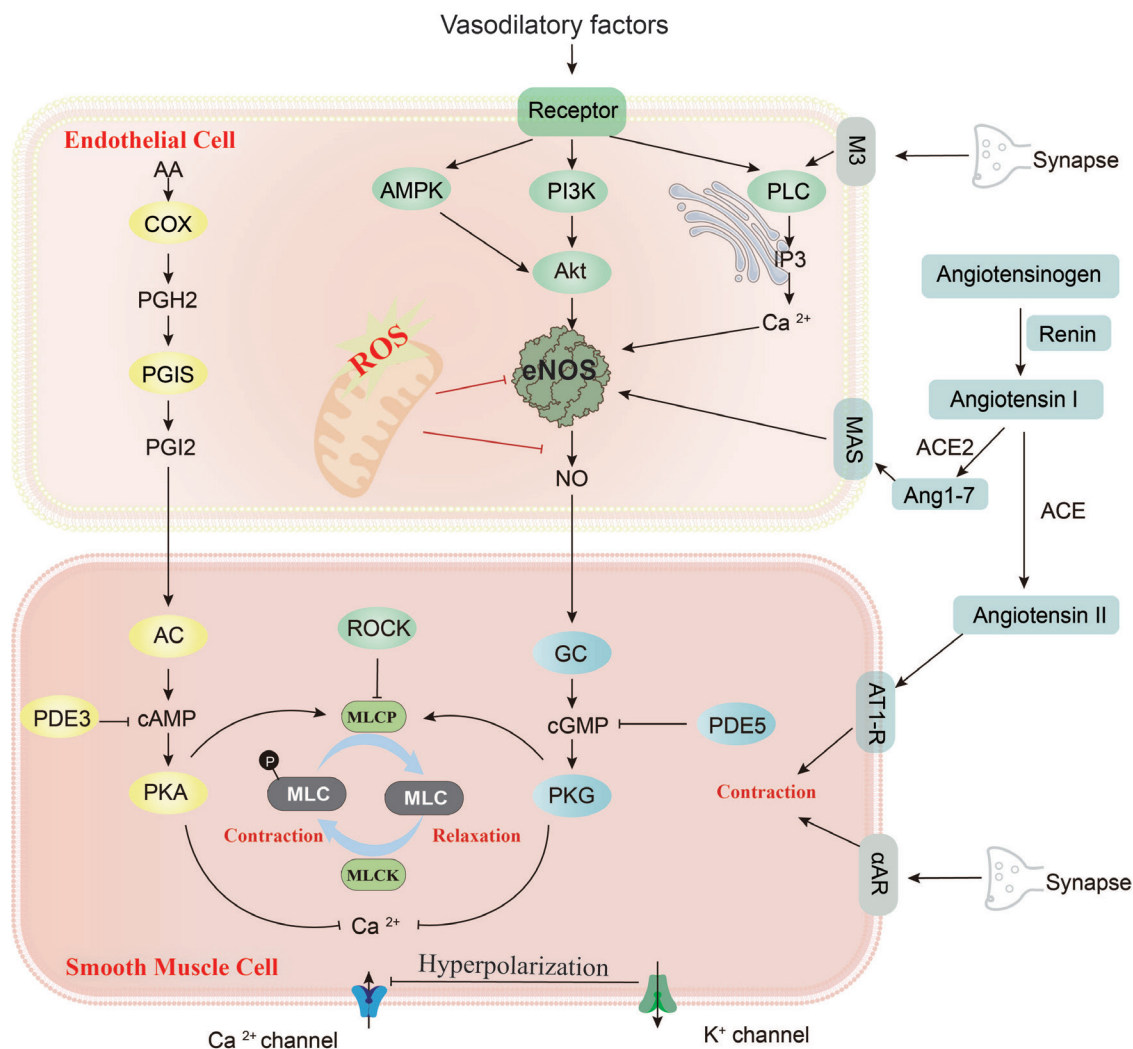


Figure 1. Overview of key physiological systems and cellular mechanisms regulating vascular tone and vasodilation. Vascular tone is regulated through integrated interactions across several systems: (1) Endothelial cells synthesize diverse vasoactive factors, including NO, PGI₂, and EDHF, which promote vasodilation by acting on underlying VSMCs. (2) VSMCs modulate vessel caliber in response to these endothelial factors *via* alterations in intracellular calcium concentration and membrane potential, governed by ion channel (Ca²⁺, K⁺) activity. (3) The RAAS influences vascular tone through Ang-II, which promotes vasoconstriction and serves as a target for achieving vasodilation *via* ACE2 antagonism. (4) The autonomic nervous system regulates vascular tone through sympathetic pathways (α-adrenergic receptors mediating vasoconstriction; β-adrenergic receptors mediating vasodilation) and parasympathetic pathways. (5) ROS impair endothelial function and reduce NO bioavailability, negatively affecting vasodilation. AA, Arachidonic acid; AC, Adenylate cyclase; ACE, Angiotensin-converting enzyme; AMPK, AMP-activated protein kinase; Ang-II, Angiotensin II; AT1R, Angiotensin II type 1 receptor; cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; COX, Cyclooxygenase; eNOS, Endothelial nitric oxide synthase; GC, Guanylyl cyclase; IP3, Inositol 1,4,5-trisphosphate; MAS, Membrane-associated G-protein coupled receptor; MLC, Myosin light chain; MLCK, Myosin light chain kinase; MLCP, Myosin light chain phosphatase; NO, Nitric oxide; PDE, Phosphodiesterase; PGH₂, Prostaglandin H₂; PGIS, Prostacyclin synthase; PGI₂, Prostacyclin; PI3K, Phosphatidylinositol 3-kinases; PKA, Protein kinase A; PKG, Protein kinase G; PLC, Phospholipase C; RAAS, Renin-angiotensin-aldosterone system; ROS, Reactive oxygen species; EDHF, Endothelium-derived hyperpolarizing factor; VSMCs, Vascular smooth muscle cells.

cyclooxygenase (COX) and prostacyclin synthase. Once generated, PGI₂ diffuses into adjacent VSMCs and binds to the prostacyclin (IP) receptor. This receptor is coupled to Gs proteins, which activate adenylate cyclase (AC), increasing intracellular cAMP levels and subsequently activating PKA. Activated PKA reduces cytosolic Ca²⁺ concentrations, promoting smooth muscle relaxation and vasodilation^[23].

Endothelium-derived hyperpolarizing factor

Epoxyeicosatrienoic acids

Epoxyeicosatrienoic acids (EETs) are AA metabolites produced by cytochrome P450 enzymes. EETs released from ECs induce smooth muscle hyperpolarization and

relaxation *via* two primary mechanisms. First, EETs activate transient receptor potential vanilloid 4 (TRPV4) channels on VSMCs^[24]; TRPV4-mediated Ca²⁺ influx then activates BK_{Ca} channels^[25]. Second, EETs increase intracellular cAMP levels and activate PKA; notably, PKA inhibitors partially block EET-induced vasodilation^[26].

Hydrogen peroxide

Hydrogen peroxide (H₂O₂) modulate multiple ion channels to regulate vascular tone. In small human coronary arteries, H₂O₂-induced vasodilation is primarily promoted by PKG dimerization and BK_{Ca} channel activation^[27]. Furthermore, H₂O₂ enhances the 4-aminopyridine (4-AP)-sensitive voltage-gated K⁺ current, leading to VSMC hyperpolarization and vasodilation^[27].

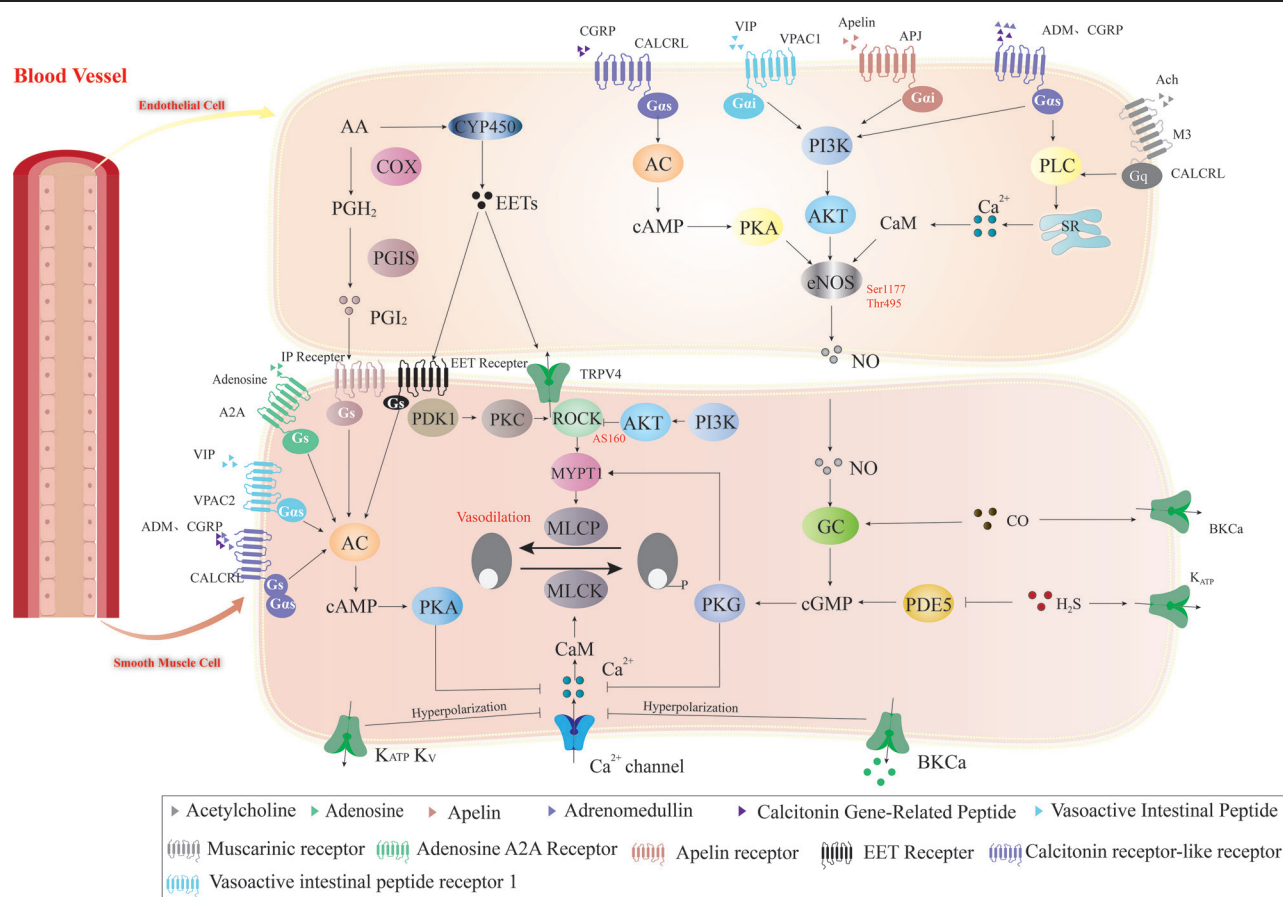


Figure 2. Major vasodilatory factors and mechanisms regulating vascular tone. This diagram illustrates the principal molecular mechanisms by which diverse vasodilatory factors—such as acetylcholine, adenosine, apelin, adrenomedullin, CGRP, and VIP—induce vascular relaxation. In endothelial cells, these ligands bind to their respective receptors (eg, muscarinic M3 receptor, adenosine A₂A receptor, apelin receptor, and calcitonin receptor-like receptor), activating intracellular signaling cascades that stimulate the synthesis of vasodilators, including NO, PGI₂, and EETs. These mediators diffuse into VSMCs and trigger multiple relaxation pathways, notably the NO-cGMP-PKG and cAMP-PKA axes, along with ion channel-mediated hyperpolarization. AA, Arachidonic acid; AC, Adenylate cyclase; ACE, Angiotensin-converting enzyme; Ang-II, Angiotensin II; AT1R, Angiotensin II type 1 receptor; cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; CGRP, Calcitonin gene-related peptide; COX, Cyclooxygenase; EET, Epoxyeicosatrienoic acids; eNOS, Endothelial nitric oxide synthase; GC, Guanylyl cyclase; IP3, Inositol 1,4,5-trisphosphate; MLC, Myosin light chain; MLCK, Myosin light chain kinase; MLCP, Myosin light chain phosphatase; NO, Nitric oxide; PDE, Phosphodiesterase; PGI₂, Prostacyclin; PI3K, Phosphatidylinositol 3-kinases; PKA, Protein kinase A; PKG, Protein kinase G; PLC, Phospholipase C; RAAS, Renin-angiotensin-aldosterone system; ROS, Reactive oxygen species; EDHF, Endothelium-derived hyperpolarizing factor; VIP, Vasoactive intestinal peptide; VSMCs, Vascular smooth muscle cell.

Adenosine

Adenosine is crucial for regulating coronary microcirculation *via* adenosine receptor activation. Adenosine activates the adenosine A₂B receptor (A₂BR) on ECs, promoting eNOS activity, increasing the production and release of NO, and promoting vasodilation^[28]. Additionally, adenosine activates the adenosine A₂A receptor (A₂AR), stimulating AC through G protein-coupled mechanisms and increasing intracellular cAMP. Elevated cAMP activates PKA, which phosphorylates BK_{Ca} channels; this phosphorylation enhances BK_{Ca} channel opening and promotes smooth muscle relaxation^[29–30].

Active peptides

Apelin

Endogenous apelin exerts vasodilatory effects through paracrine and autocrine mechanisms. The apelin receptor (APJ) is a G protein-coupled receptor. Apelin binds to APJ and activates G_{ai}, which subsequently triggers phosphatidylinositol 3-kinase (PI3K)-AKT signaling. Activation

of the PI3K-AKT axis stimulates eNOS, promoting vasodilation^[31]. In diabetic mouse models, apelin enhances the phosphorylation of Ser473-AKT and Ser1177-eNOS, thereby contributing to NO production^[32–33].

Vasoactive intestinal peptide

Vasoactive intestinal peptide (VIP) induces vasodilation primarily through vasoactive intestinal peptide receptor type 1 (VPAC1) and type 2 (VPAC2)^[34]. VPAC1 is predominantly expressed on ECs, where VIP stimulation activates Gs proteins and downstream signaling—including PI3K-AKT—to promote eNOS activation and NO release. Conversely, VPAC2 is primarily localized on VSMCs. Upon binding, VIP couples with Gs proteins to activate AC, increasing intracellular cAMP and subsequently activating PKA.

Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) modulates vascular smooth muscle tone *via* receptors located on ECs and VSMCs^[35]. In isolated ECs, CGRP induces cAMP

production to stimulate NO synthesis^[36–37]. Evidence also suggests CGRP activates the phospholipase C (PLC) pathway, increasing intracellular Ca^{2+} and enhancing eNOS activity^[36,38]. On VSMCs, CGRP directly activates the cAMP-PKA pathway, facilitating smooth muscle relaxation and opening K_{ATP} channels to promote K^+ efflux and reduce Ca^{2+} influx, further promoting vasodilation^[39–40].

Adrenomedullin

Adrenomedullin (ADM) is an endogenous peptide hormone that maintains vascular homeostasis through endothelium-dependent and endothelium-independent mechanisms^[41]. Upon binding to the calcitonin receptor-like receptor (CLR) complex on ECs, ADM activates PI3K-AKT signaling^[41] and the PLC-IP₃- Ca^{2+} pathway, increasing intracellular Ca^{2+} levels. This rise in Ca^{2+} levels enhances eNOS activity and promotes NO release^[42]. On VSMCs, ADM increases intracellular cAMP and activates PKA, inducing endothelium-independent vasodilation^[43–44].

Ion channels

Vasodilation involves the integrated regulation of multiple ion channels that control VSMC relaxation and contraction. Research focuses primarily on calcium and potassium channels.

Intracellular Ca^{2+} originates from extracellular influx through the plasma membrane and release from the endoplasmic or sarcoplasmic reticulum^[45–46]. The plasma membrane of VSMCs contains three major types of Ca^{2+} channels^[46–47]: voltage-operated calcium channels (VOCs), receptor-operated calcium channels (ROCs), and store-operated calcium channels (SOCs). Electrophysiological studies using whole-cell patch-clamping on isolated rat mesenteric artery VSMCs have identified two VOC subtypes: transient (T-type) and sustained (L-type)^[48]. Among these, the L-type channel is the predominant subtype expressed in vascular tissue. Upon stimulation with depolarizing agents such as KCl, L-type channels are readily activated, leading to substantial extracellular Ca^{2+} influx and consequent vasoconstriction^[47]. ROCs, in contrast, are activated by agonist–receptor interactions rather than changes in membrane potential. Their activation is closely associated with the formation of inositol phosphates. For example, stimulation with phenylephrine (PE) activates ROCs, which in turn facilitate VOC opening, allowing further Ca^{2+} influx, membrane depolarization^[49], and vascular contraction. Additionally, inositol 1,4,5-trisphosphate (IP₃) mediates Ca^{2+} release from the sarcoplasmic reticulum *via* activation of ryanodine receptors (RyRs), further augmenting intracellular Ca^{2+} levels^[49]. In ECs, elevated intracellular Ca^{2+} activates eNOS, enhancing NO production and promoting vasodilation^[45]. In VSMCs, increased Ca^{2+} activates myosin light chain kinase (MLCK), leading to myosin light chain (MLC) phosphorylation, actin–myosin cross-bridge cycling, and vascular contraction^[50].

K^+ channel activation in VSMCs facilitates K^+ efflux, resulting in membrane hyperpolarization. This event

suppresses voltage-gated Ca^{2+} channel (VGCC) opening, lowering intracellular Ca^{2+} and inducing vasorelaxation^[47–48]. Four principal classes of K^+ channels have been identified in the vasculature: voltage-gated K^+ channels (Kv), BK_{Ca} , K_{ATP} , and inwardly rectifying K^+ channels (Kir). Kv channels are activated by membrane depolarization, allowing K^+ efflux and subsequent hyperpolarization. Their activity contributes to the maintenance of the resting membrane potential and limits depolarization-induced Ca^{2+} influx, thus preventing excessive vasoconstriction^[51]. BK_{Ca} channels are activated by elevations in intracellular Ca^{2+} , providing a negative feedback mechanism by coupling Ca^{2+} signaling to hyperpolarization and vasodilation^[48]. K_{ATP} channels, on the other hand, are sensitive to the metabolic state of the cell; reduced intracellular ATP promotes channel opening, thereby linking energy homeostasis to vascular tone regulation^[52]. Kir channels are predominantly expressed in small-diameter cerebral arterioles, where they are susceptible to extracellular K^+ fluctuations. Electrophysiological analyses have demonstrated that Kir activity is essential for maintaining the resting membrane potential and contributes to vasodilatory responses in both cerebral and coronary arteries^[53].

Renin-angiotensin-aldosterone system

Beyond endothelial and ion channel-mediated mechanisms, RAAS plays a pivotal role in determining vascular tone. This system is initiated by renin secretion, which catalyzes the conversion of angiotensinogen to angiotensin I (Ang-I). Ang-I is hydrolyzed by angiotensin-converting enzyme (ACE) to generate angiotensin II (Ang-II)^[54], a potent vasoconstrictor. Ang-II exerts its primary pressor effects *via* the angiotensin II type 1 receptor (AT1R), which enhances neurotransmitter release from sympathetic nerve terminals. Activation of presynaptic AT1Rs on sympathetic vasoconstrictor fibers augments norepinephrine secretion, thereby promoting vasoconstriction^[55]. In contrast, binding of Ang-II to AT2R triggers the release of bradykinin, which activates eNOS, leading to increased NO production and elevated cGMP levels, culminating in vasorelaxation^[56–57]. Furthermore, ACE2 catalyzes the conversion of Ang-II into angiotensin-(1–7) [Ang-(1–7)], a bioactive peptide with vasodilatory properties. Ang-(1–7) exerts its effects through activation of the Mas receptor, which stimulates the PI3K-Akt pathway, enhances eNOS activation, and promotes NO release, contributing to vascular relaxation^[54].

Neurological regulation

The autonomic nervous system provides integrated control over vascular tone. The sympathetic nervous system regulates vascular tone primarily through norepinephrine-mediated activation of α_1 -adrenergic receptors on VSMCs, leading to Ca^{2+} influx and contraction. In addition, α_1 -AR signaling enhances Ca^{2+} sensitivity through two distinct pathways: the DAG-PKC axis, which facilitates Ca^{2+} entry and myofilament responsiveness, and the Ras homolog gene family member A (RhoA)-Rho-associated coiled-coil kinase (ROCK) pathway, which inhibits MLCP to

sustain MLC phosphorylation. Conversely, stimulation of β_2 -adrenergic receptors engage the Gs/AC/cAMP/PKA pathway, facilitating vasodilation, particularly in skeletal muscle vasculature. Parasympathetic regulation involves acetylcholine (ACh) released from parasympathetic nerve endings. ACh binds to M_3 muscarinic receptors on ECs, thereby activating the PLC-IP₃-Ca²⁺ signaling cascade^[58–59]. Elevated cytosolic Ca²⁺ binds to calmodulin (CaM), activating eNOS and generating NO.

Oxidative stress

Under oxidative stress, eNOS undergoes a metabolic shift from NO synthesis to the production of oxygen radicals (O₂⁻), which reduces NO bioavailability. Oxygen radicals react with H⁺ to form H₂O₂ and with NO to form peroxynitrite (ONOO⁻)^[60]. The resulting products, O₂⁻, H₂O₂, and ONOO⁻, enhance endothelial dysfunction through direct uncoupling and inactivation of eNOS^[61]. Recent findings have shown that oxidative stress, a process involving the oxidation of biological molecules, can increase the concentration of Ca²⁺ within cells, leading to excessive contraction of VSMCs. This phenomenon is attributed to the activation of stromal interacting molecule 1 (STIM1), a calcium receptor, by oxidative stress. Additionally, ROS directly compromises the functionality of calcium channels and disrupts the balance between vasodilation and vasoconstriction^[62].

Relevant pathways of vasodilation

PLC-IP₃-Ca²⁺ pathway

Upon receptor activation by agonists such as ACh or bradykinin, PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂) to generate diacylglycerol (DAG) and IP₃. IP₃ binds to receptors on the endoplasmic reticulum, triggering Ca²⁺ release into the cytosol. The PLC-IP₃-Ca²⁺ signaling pathway exerts dual and context-dependent effects in vascular tissues^[63]. In ECs, the rise in cytosolic Ca²⁺ binds to CaM, which activates eNOS, thereby promoting vasorelaxation. Conversely, in VSMCs, elevated intracellular Ca²⁺ primarily activates MLCK, which phosphorylates the MLC and facilitates actin–myosin cross-bridge cycling, ultimately leading to vascular contraction^[64].

PI3K-AKT-eNOS pathway

Vasoactive factors including insulin, estrogen, apelin, and Ang-(1–7) activate PI3K-AKT signaling^[65–66]. PI3K catalyzes the conversion of PIP₂ to PIP₃, which recruits and activates AKT at the plasma membrane. Activated AKT phosphorylates eNOS at Ser1177, enhancing NO production. In VSMCs, PI3K-AKT signaling antagonizes the RhoA-ROCK-myosin phosphatase target subunit 1 (MYPT1) axis and promotes MLCP activity^[67]. Furthermore, activated AKT inhibits ROCK, leading to decreased MYPT1 phosphorylation and enhanced MLCP activity, which favors MLC dephosphorylation and smooth muscle relaxation^[68].

Soluble guanylyl cyclase-cGMP-PKG

Upon entry into VSMCs, NO binds to and activates sGC. sGC catalyzes cGMP generation, which binds to and

activates PKG. PKG activates calcium pump proteins on the sarcoplasmic reticulum membrane through phosphorylation^[69]. This process promotes the recycling of intracellular Ca²⁺ back into the sarcoplasmic reticulum and reduces the concentration of Ca²⁺. In addition to this effect, PKG also promotes the opening of BK_{Ca} channels on the cell membranes of VSMCs. The result of these processes is the efflux of K⁺, the hyperpolarization of cell membranes, which further reduces the concentration of Ca²⁺. PKG also binds to and phosphorylates MYPT1, the regulatory subunit of MLCP, to activate MLCP, which further reduces MLC phosphorylation and promotes vasodilation.

Adenylate cyclase-cAMP-PKA

The AC-cAMP-PKA pathway is typically triggered by prostaglandin activation, which stimulates AC *via* G proteins to convert ATP to cAMP. cAMP activates PKA, which phosphorylates K_{ATP} and Kv channels, resulting in K⁺ efflux, cell membrane hyperpolarization, and low intracellular calcium ion concentration, thus inhibiting smooth muscle contraction and causing vasodilation^[70]. Moreover, PKA directly phosphorylates MLCK, inhibits its activity, reduces the phosphorylation of MLC, attenuates the interaction between myosin and actin, and promotes vasodilation.

PDE inhibition

PDEs perform critical regulatory functions in vasodilatory pathways. PDE4 and PDE5 are the primary enzymes regulating cAMP- and cGMP-mediated vasodilation, respectively. These enzymes hydrolyze the 3' cyclic phosphate bond of cAMP and cGMP, thereby reducing their intracellular concentrations and exerting a negative regulatory effect on the sGC-cGMP pathway^[69]. Consequently, the inhibition of cGMP hydrolysis enhances activity within the cGMP signaling pathway, promoting vasodilation.

Myosin light chain kinase-MLCP

Vascular smooth muscle contraction is regulated by the phosphorylation of MLC, which is governed by the balance between MLCK and MLCP. Ca²⁺-CaM activates MLCK to phosphorylate MLC at Ser19, promoting actin–myosin interaction and contraction. Conversely, MLCP dephosphorylates MLC to induce relaxation^[71]. The cAMP-PKA and cGMP-PKG pathways facilitate vasorelaxation by directly or indirectly activating MLCP through phosphorylation of MYPT1. In contrast, activated RhoA stimulates ROCK, which phosphorylates the MLCP regulatory subunit MYPT1, thereby inhibiting MLCP activity and enhancing MLC phosphorylation^[68].

Vasodilatory effect and mechanism of active ingredients in natural medicines

A comprehensive literature search was performed in PubMed and CNKI databases using the keywords “natural products” and “vasodilation” to identify studies

published between 2000 and 2025. Review articles were excluded, and the remaining studies were screened for relevance (Figure 3). Key experimental data were extracted, including animal models, vascular types, dosage, and underlying mechanisms of vasodilatory activity. The collected studies were further categorized into natural product classes, such as flavonoids, saponins, and alkaloids.

Flavonoids

From our extensive literature search, we found that 58 flavonoid compounds have been reported to exert vasodilatory effects through multiple mechanisms (Table 1). These mechanisms include antioxidant actions, such as ROS scavenging, and the modulation of endothelial signaling pathways. Flavonoids can activate the PLC-Ca²⁺-eNOS and PI3K-AKT-eNOS cascades to enhance NO production, inhibit protein kinase C (PKC), and regulate potassium and calcium channels to maintain intracellular Ca²⁺ homeostasis (Figure 4).

Quercetin, a dietary flavonoid abundant in fruits and vegetables, reduces blood pressure in hypertensive models. Its vasodilatory effect is more pronounced in the aorta and iliac arteries of spontaneously hypertensive rats (SHR) than in normotensive Wistar-Kyoto (WKY) rats, primarily due to its capacity to reduce systemic oxidative stress and preserve the activity of endothelium-derived and exogenous NO^[110,123].

Luteolin is a primary active constituent in wild chrysanthemum extract, responsible for its anti-inflammatory

and vasodilatory effects. It dose-dependently inhibits NO production and the expression of inducible nitric oxide synthase (iNOS) in inflammatory macrophages^[130]. Other studies indicate that it reduces ROS levels, inhibits hydroxyl radical formation, and enhances superoxide dismutase (SOD) activity while stimulating the eNOS-NO-sGC pathway. Chronic administration of luteolin to rats with diabetes improves their endothelium-dependent vasodilatory function^[116]. Luteolin also reduces intracellular Ca²⁺ concentrations in VSMCs and dilates blood vessels by activating BK_{Ca} and K_{ATP} channels^[83].

Chrysin and naringenin, isolated from common fruits, vegetables, and honey, can also activate vascular smooth muscle K_v channels^[117], altering membrane electrophysiological activity and inducing vasodilation. Compounds rich in apigenin can activate TRPV4 channels overexpressed in human embryonic kidney cells, promote endothelium-derived hyperpolarizing factor (EDHF) release, and induce membrane hyperpolarization^[84]. Additionally, grape polyphenols isolated from Bordeaux wines can activate purinergic P2Y1 and P2Y2 receptors on ECs, promoting NO production and activating the NO-GC-cGMP pathway. These polyphenols also inhibit outer membrane ATPase activity to encourage the release of vasodilatory factors (NO, PGI₂, EDHF, etc.), leading to smooth muscle relaxation and vasodilation^[131].

Saponins

Numerous saponins, particularly those derived from traditional Chinese medicinal herbs such as ginseng,

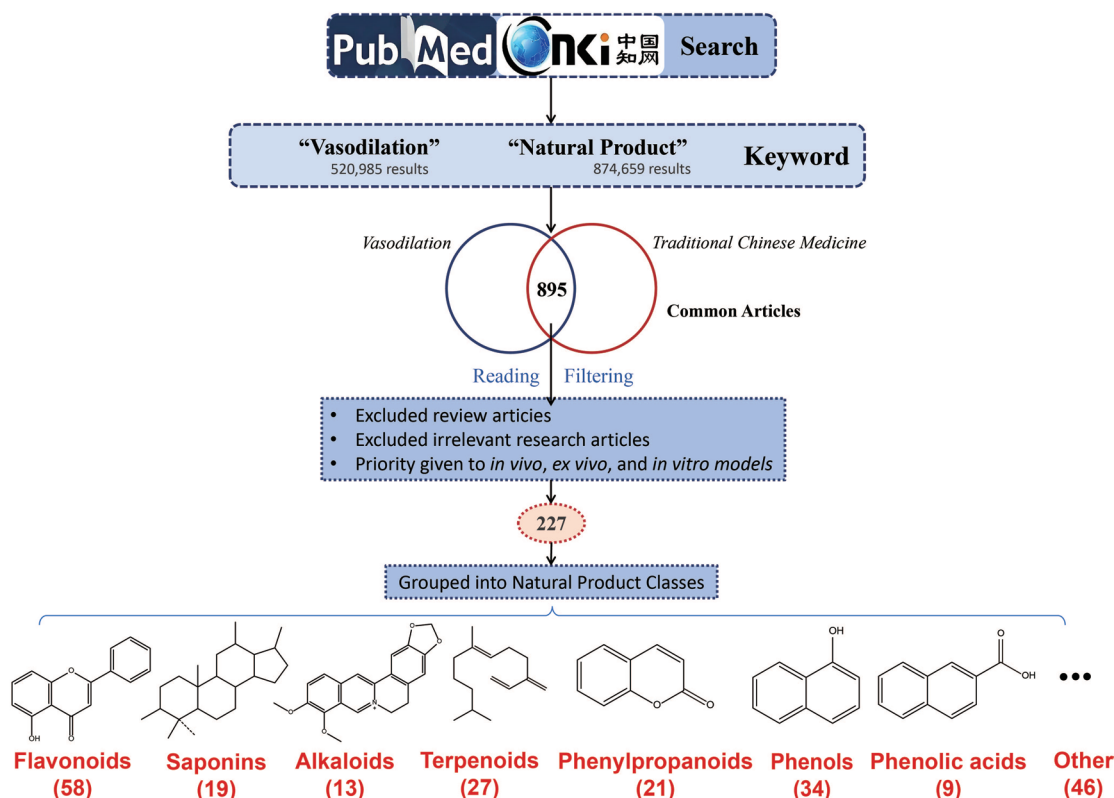


Figure 3. Flowchart of literature search strategy and classification of natural products with vasodilatory activity. Literature was searched in PubMed and CNKI using "Vasodilation" and "Natural Product" as keywords. After excluding reviews and irrelevant studies (prioritizing *in vivo*, *ex vivo*, and *in vitro* models), 227 eligible articles remained. The identified natural products were categorized into classes: Flavonoids (58), Saponins (19), Alkaloids (13), Terpenoids (27), Phenylpropanoids (21), Phenols (34), Phenolic acids (9), and others (46), with representative structures shown for each.

Table 1
Related pathways and mechanisms of flavonoids with vasodilatory effects

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
3,3',4'-Trihydroxyflavone ^[72]	–	Thoracic aorta	SD rat	0.1–100 µM	PE	NO signaling, Ca ²⁺ modulation
3,4-Dihydroxyflavonol ^[73]	–	Thoracic aorta	SD rat	0.1–100 µM	–	Scavenge superoxide free radicals, protect endothelial NO, and maintain NO bioavailability; inhibition of extracellular Ca ²⁺ influx
3'-Hydroxy-5,6,7,4'-tetramethoxyflavone ^[74]	<i>Orthosiphon aristatus</i> (Blume) Miq.	Thoracic aorta	SD rat	0.03–2.20 µM	PE, KCl	NO-sGC-cGMP, PGI ₂ , Ca ²⁺ , Kv, muscarinic and β-adrenergic receptor
5,6,2',3',4'-Pentamethoxyflavone ^[75]	<i>Casimiroa edulis</i> La Llave and Lex., <i>Casimiroa pubescens</i> Ramirez	Caudal ring	Wistar rat	0.1–100 µM	PE	M ₃ muscarinic receptor activation, NO-cGMP signaling
4-Hydroxybenzaldehyde ^[76]	<i>Gastrodia elata</i> Bl.	Thoracic aorta	SD rat	1–3,000 µM	PE, KCl	VDCC inhibition, Ca ²⁺ modulation
α-Naphthoflavone ^[77]	–	Thoracic aorta	Wistar rat	0.1–100 µM	PE	Ca ²⁺ -eNOS-NO-sGC-cGMP signaling; inhibition of VDCC, ROCC, and intracellular Ca ²⁺ stores
β-Naphthoflavone ^[77]	–	Thoracic aorta	Wistar rat	0.1–100 µM	PE	Ca ²⁺ modulation; NOS-NO-cGMP signaling, P450 metabolite (5,6-EET) production
Acacetin ^[78]	–	Mesenteric artery	SHR	0.3–30 µM	5-HT	AKT-eNOS activation, mitigation of excessive ROS
Alpinetin ^[79]	<i>Alpinia Roxb.</i> ; <i>Ficus katsumadai</i> Hayata; <i>Amomum subulatum</i> Roxb.; <i>Scutellaria rivularis</i> Wall. ex Benth.	Superior mesenteric artery	SD rat	0–100 µM	PE, endothelin I, U46619	NO signaling, VGCC inhibition, intracellular Ca ²⁺ modulation, PKC inhibition
Amentoflavone ^[80]	<i>Selaginella tamariscina</i> (P. Beauv.) Spring	Thoracic aorta	SD rat	0.01–10 µM	PE	NOS-NO-sGC-cGMP-PKG-Ca ²⁺ signaling, attenuation of contractile element sensitivity to Ca ²⁺ , KCa and VGCC activation
Apigenin ^[81]	<i>Apium graveolens</i> var. dulce (Mill.) DC.	Thoracic aorta	SD rat	1–12.5 µM	PE, high K ⁺	NO-cGMP signaling, ROCC inhibition, PKC and VGCC modulation
Apigenin ^[82]	<i>Chrysanthemum morifolium</i> Morat.	The mesenteric artery	SD rat	1–100 µM	KCl, PE	TRPV4-EDHF-mediated hyperpolarization, glutathione reductase and SOD activation
Apigenin ^[83]	–	Thoracic aorta	Wistar rat	3–100 µM	KCl	NO signaling, BK _{Ca} activation
Apigenin ^[84]	–	The mesenteric artery	SD rat	0.1–100 µM	PE	Selective TRPV4 stimulation, increased intracellular Ca ²⁺ , EDHF-mediated vasodilation, enhanced eNOS activity
Apigenin ^[85]	<i>Chrysanthemum × morifolium</i> (Ramat.) Hemsl.	Thoracic aorta	SD rat	0.5–72 µM	PE	eNOS-NO-sGC-cGMP signaling, antioxidant activity, attenuation of NO reduction
Ayanin ^[86]	<i>Croton schiedeana</i> Schtidl.	Thoracic ring	Wistar rat	1–1,000 µM	PE, KCl	NO-sGC-cGMP signaling
Baicalin ^[87]	<i>Scutellaria baicalensis</i> Georgi	Superior mesenteric artery	SD rat	30 µM	U46619	NO signaling
Biochanin A ^[88]	–	Coronary artery	Goat	0.1–100 µM	KCl	K _{ATP} and PKA activation; estrogen receptor, Kv, and Ca _v 1.2 channel modulation

(Continued)

Table 1

(Continued)

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
Calycosin ^[69]	<i>Astragalus membranaceus</i> (Fisch.) Bunge	Thoracic aorta	SD rat	1–100 µM	PE, KCL	VOC and ROC inhibition
Cardamonin ^[70]	–	The mesenteric artery	SD rat	1–100 µM	PE, endothelin I, U46619	NO signaling, VDCC inhibition, suppression of intracellular Ca ²⁺ release, PKC inhibition, direct VSMC relaxation
Chrysin ^[63]	–	Thoracic aorta	Wistar rat	3–100 µM	KCl	K ⁺ channel activation
Chrysin ^[90]	–	Thoracic aorta	Wistar rat	1–100 µM	NE, PE	NO-cGMP-Ca ²⁺ signaling, prevention of O ₂ ⁻ -induced eNOS inactivation
Chrysin ^[91]	–	Thoracic aorta	SD rat	0.1–100 mM	PE, KCL	NO-sGC-cGMP cascade, muscarinic and β-adrenergic receptor stimulation, Kv and Ca ²⁺ (VOCC and IP ₃ R) modulation
Chrysin ^[92]	–	Thoracic aorta	Wistar rat	1–100 µM	PE, U46619	PI3K-eNOS-NO-cGMP signaling
Chrysin ^[73]	–	Thoracic aorta	Rat	0.1–100 µM	High K ⁺	ROS scavenging, inhibition of intracellular ion flux
Daidzein ^[93]	<i>Pueraria lobata</i> (Willd.) Ohwi	Basilar artery	SD rat	20–200 µM	U46619	K ⁺ , BK _{Ca}
Daidzin ^[93]	<i>Pueraria lobata</i> (Willd.) Ohwi	Basilar artery	SD rat	1–1,680 µM	U46619	K ⁺ , BK _{Ca}
Dihydrospinochalcone-A ^[94]	<i>Lonchocarpus xuui</i> Lundell	Thoracic ring	Spontaneously hypertensive rats	1–300 µM	NE	eNOS-NO-sGC-PKG, K ⁺
Dioclein (5,2',5'-trihydroxy-6-7-dimethoxyflavanone) ^[95]	<i>Dioclea grandiflora</i> Mart. ex Benth.	Thoracic aorta	SD rat	30 SIRT1-dependent PGC-1α 3,000 µM	NE, KCL	Intracellular calcium pool, reduce the sensitivity of contractile elements to Ca ²⁺ , PKC, VOCCs
Diosmetin ^[96]	<i>Citrus limon</i> L.; <i>Olea europaea</i> L.	Coronary artery	Pig	0.001–10 µM	u46620, KCL	Kv, PKC, Ca ²⁺
Eupatorin ^[97]	<i>Orthosiphon stamineus</i> Benth.	Thoracic ring	SD rat	0.04–2.29 µM	PE, KCL	NO-sGC-cGMP, PGI ₂ , KCa, Kv, Kir, Ca ²⁺ , muscarinic receptor and β-adrenergic receptors, IP ₃
Farrerol ^[98]	<i>Rhododendron dauricum</i> L.	Thoracic ring	SD rat	1–100 µM	PE, KCL	ROCC, blocking ryanodine receptors, VDCC
Fisetin ^[72]	–	Thoracic aorta	SD rat	0.1–100 µM	KPSS, PE	Intracellular Ca ²⁺ , NO
Fisetin ^[73]	–	Thoracic aorta	Rat	0.1–100 µM	High K ⁺	Scavenging oxygen-free radicals and inhibiting extracellular Ca ²⁺
Floranol ^[99]	<i>Dioclea grandiflora</i> Mart. ex Benth.	Thoracic aorta	SD rat	1–300 µM	PE	Scavenging oxygen-free radicals
Formononetin ^[100]	<i>Trifolium pratense</i> L.	Thoracic aorta	SD rat	1–301 µM	NE, KCL	NO-cGMP, Ca ²⁺ , K ⁺
Genistein ^[101]	–	Thoracic aorta	Wistar rat	0.001–10 µM	PE	eNOS-NO-GC-cGMP, PPARγ, NO, estrogen receptor
Hematoxylin ^[102]	<i>Caesalpinia sappan</i> L.	Thoracic aorta	SD rat	0–100 µM	PE	NO, cGMP

(Continued)

Table 1
(Continued)

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
Hesperetin ^[63]	–	Thoracic aorta	Wistar rat	3–100 μ M	KCl	KCa, K_{ATP}
Hesperetin ^[103]	<i>Poncirus trifoliata</i> (L.) Raf.	Coronary artery	pig	0.1 SIRT1-dependent PGC-1 α 100 μ M	U46619	NO-cGMP
Hesperetin ^[104]	–	Thoracic aorta	Wistar rat	10–300 μ M	NE, KCl	PDE1 and PDE4, cAMP and cGMP
Homoplantagin ^[105]	<i>Salvia plebeia</i> R.Br.	Thoracic aorta	SD rat	0.1–10 μ M	KCl, PE	NO and p-eNOS, SOCE-Ca ²⁺ , ERS
Hyperin ^[106]	–	Basilar artery	SD rat	10–1,000 μ M	U46619, KCl	Endothelial relaxation factor, PKC, BK _{Ca} , KCa
Hyperoside ^[107]	–	Thoracic aorta	SD rat	0.3–100 μ M	U46619, KCl	NO, PGI ₂ , EDHF
Icarin ^[108]	<i>Epimedium</i>	Thoracic aorta	Beagle	3.75–30 μ M	KCl, PGF2a	eNOS, NO-cGMP, PDE
Irisin ^[109]	–	Thoracic aorta	Wistar rat	0.001–1 μ M	PE, KCl	Kv, K_{ATP} , SKCa, BK _{Ca} , IKCa, Kir, NO
Isocordoin ^[94]	<i>Lonchocarpus xuii</i> Lundell	Thoracic aorta	Wistar, SHR	1–300 μ M	NA	–
Isorhamnetin ^[110]	–	The mesenteric artery, iliac artery, aorta	SHR	1–31.62 μ M	PE	Removal of superoxide, NO, direct relaxation of smooth muscle
Isorhamnetin-3-glucuronide ^[110]	–	Thoracic aorta	SD rat	1–30 μ M	PE, KCl	Protected the activity of endothelial NO and exogenous NO under high oxidative stress. Prevention of endothelial dysfunction caused by oxide dismutase inhibitors DETCA and ET-1
Kaempferol ^[111]	<i>Carthamus tinctorius</i> L.	Coronary artery	Pig	1 nM–100 μ M	U46619, KCl	Inhibition of lipoxigenase, PKC, PDEs, MLCK
Kaempferol ^[112]	<i>Phyllanthus acidus</i> (L.) Skeels	Thoracic aorta	Wistar rat	10–100 mg/kg	PE, KCl	Stimulation of sGC, K_{ATP} and KCa
Luteolin ^[73]	–	Thoracic aorta	Rat	0.1–100 μ M	High K ⁺	Superoxide radical, Ca ²⁺
Luteolin ^[113]	–	Thoracic aorta	Rat	4.5–36 μ M	PE, KCl	Ca ²⁺ , K ⁺
Luteolin ^[83]	–	Thoracic aorta	Wistar rat	3–100 μ M	KCl	KCa, K_{ATP}
Luteolin ^[114]	<i>Coreopsis tinctoria</i> Nutt.	Thoracic aorta	Wistar rat	5.6–560 μ M	PE, KCl	Ca ²⁺
Luteolin ^[115]	–	Thoracic aorta	SD rat	10–100 μ M	PE, KCl	eNOS-NO
Luteolin ^[116]	<i>Chrysanthemum × morifolium</i> (Ramat.) Hemsl.	Thoracic aorta	SD rat	0.1–100 μ M	PE	Reducing oxidative stress, NO
Luteolin ^[82]	<i>Chrysanthemum × morifolium</i> (Ramat.) Hemsl.	Thoracic aorta	SD rat	1–50 μ M	PE, KCl	Superoxide anion, IKCa, SKCa, EDHF
Naringenin ^[117]	–	Thoracic aorta	Wistar rat	1–300 μ M	PE, KCl	PDE1, PDE4, PDE5-cGMP, cAMP, Ca ²⁺

(Continued)

Table 1
(Continued)

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
Naringenin ^[118]	–	Thoracic aorta	Wistar rat	0.1–100 µM	PE, endothelin-1, U46619, KCL	K_v
Narirutin ^[118]	–	Thoracic aorta	SD rat	0.1–100 µM	PE, endothelin-1, U46619, KCL	Phosphodiesterase-cAMP-PKA-eNOS-NO, prostacyclin, K_v
Nobiletin ^[119]	<i>Citrus × depressa</i> Hayata	Thoracic aorta	SD rat	0.001–10 µM	PE	Ca^{2+} -eNOS-NO
Orientin ^[120]	<i>Phyllostachys nigra</i> (Lodd. ex Lindl.) Munro	Thoracic aorta	New Zealand rabbit	0.1–30 mM	PE, NE, KCL	NO-sGC-cGMP, VDCC, ROCC
Pinocembrin ^[121]	<i>Cistanche tubulosa</i> Hook. fil.	Thoracic aorta	SD rat	30–300 µM	PE, KCL	NO-cGMP, K^+ , Ca^{2+}
Poncirin ^[103]	<i>Poncirus trifoliata</i> (L.) Raf.	Thoracic aorta	Pig	0.1–100 µM	U46619	NO
Procyanidin B2 ^[122]	–	HIMA segments	human	0.001–3 µM	PE	NO, prostacycline-NO, BK_{Ca} , K_{ATP} , K_v , IKCa, IP3 receptors
Puerarin ^[93]	<i>Pueraria lobata</i> (Willd.) Ohwi	Thoracic aorta	SD rat	10–1,680 µM	U46619	NO, EDRFs, K^+ , Ca^{2+} , K_{ATP}
Quercetin 3,3'4"-7-tetramethyl ^[86]	–	Thoracic aorta	Wistar rat	1–1,000 µM	PE, KCL	NO/cGMP
Quercetin 3,7-dimethyl ether ^[86]	<i>Croton schiedeanus</i> Schlecht	Thoracic aorta	Wistar rat	1–1,000 µM	PE, KCL	NO/cGMP, α -adrenergic receptor
Quercetin ^[72]	–	Thoracic aorta	SD rat	0.1–100 µM	KPSS, PE	Ca^{2+} , NO
Quercetin ^[114]	<i>Coreopsis tinctoria</i> Nutt.	Thoracic aorta	Wistar rat	5.6–560 µM	PE, KCL	Ca^{2+}
Quercetin ^[123]	–	Thoracic aorta	SHR	0.1–100 µM	PE, KCL, NE	O_2^- -NO interaction, direct VSMC relaxation
Quercetin ^[86]	<i>Croton schiedeanus</i> Schlecht	Thoracic aorta	Wistar rat	1–1,000 µM	PE, KCL	NO-cGMP signaling
Quercetin ^[124]	–	Thoracic aorta	Wistar rat	0.1–100 µM	PE, K^+	Ca^{2+} -eNOS signaling, antioxidant activity, PKC inhibition
Quercetin-3-glucuronide ^[110]	–	Thoracic aorta	SD rat	1–30 µM	PE, KCL	ET-1 antagonism, mitigation of oxidative stress-induced NO reduction
Rhofolin ^[83]	–	Thoracic aorta	Wistar rat	3–100 µM	KCl	–
Rutin ^[125]	–	Thoracic aorta	SD rat	10–160 µM	PE	NO-sGC-cGMP signaling
Rutin ^[126]	–	Thoracic aorta	SD rat	10–161 µM	PE	eNOS and PGI_2 activation, K_{ATP} modulation
Scutellarin ^[127]	<i>Erigeron breviscapus</i> (Vaniot) Hand.-Mazz.	Thoracic aorta	Wistar rat	3–100 µM	NE	Inhibition of Ca^{2+} influx, VDCC modulation
Scutellarin ^[128]	<i>Erigeron breviscapus</i> (Vaniot) Hand.-Mazz.	Thoracic aorta	SD rat	10–1,000 µM	U46619	cGMP-PKG and PKG-VASP signaling, eNOS activation
Tetramethylpyrazine ^[129]	–	Thoracic aorta	SD rat	1–1,000 µM	PE	SIRT1-dependent PGC-1 α pathway, mitochondrial biogenesis, NO signaling

AKT, Protein kinase B; BK_{Ca} , Large-conductance Ca^{2+} -activated K^+ channels; cGMP, Cyclic guanosine monophosphate; DETCA, Diethyldithiocarbamate; EDHF, Endothelium-derived hyperpolarizing factor; eNOS, Endothelial nitric oxide synthase; ET-1, Endothelin-1; HIMA, Human internal mammary artery; K_{ATP} , ATP-sensitive K^+ channels; Kir, Inwardly rectifying K^+ channels; NO, Nitric oxide; NOS, nitric oxide synthase; PE, Phenylephrine; PGI_2 , Prostacyclin; PKC, Protein kinase C; PKG, Receptor-operated calcium channel; ROS, Reactive oxygen species; SD, Sprague-Dawley; sGC, Soluble guanylyl cyclase; SHR, Spontaneously hypertensive rats; SOD, Superoxide dismutase; TRPV4, Transient receptor potential vanilloid 4; VDCC, Voltage-dependent calcium channel; VGCC, Voltage-gated Ca^{2+} channel; VOCC, Voltage-operated calcium channel; VSMC, Vascular smooth muscle cells; 5-HT, 5-Hydroxytryptamine. "–" indicates that the cited literature does not mention this content.

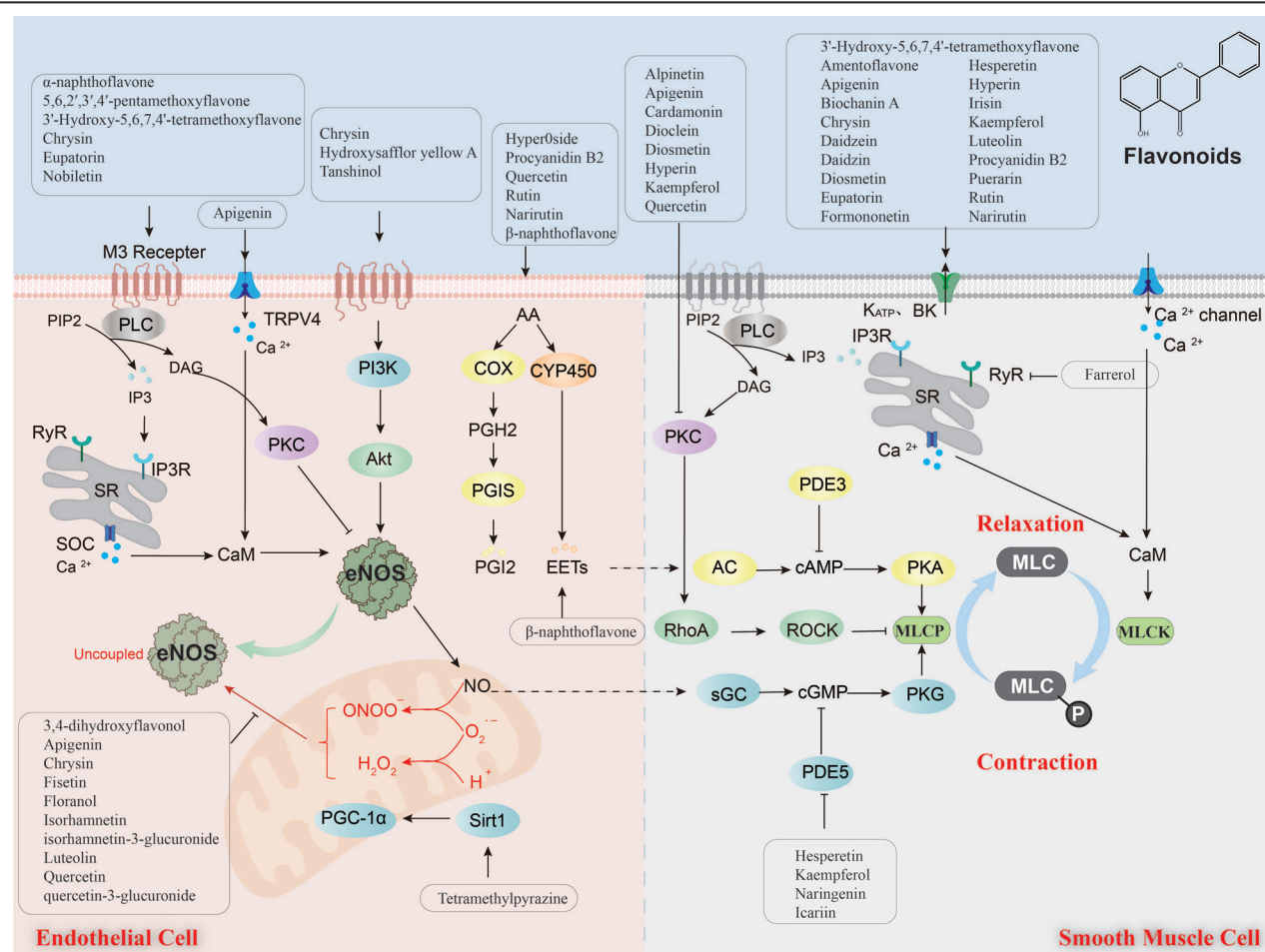


Figure 4. Mechanisms of vasodilation induced by flavonoids. In endothelial cells, flavonoids activate eNOS-NO, COX-PGI₂, and CYP450-EETs pathways, modulate Ca²⁺ signaling, and attenuate oxidative stress to enhance NO bioavailability. In smooth muscle cells, flavonoids inhibit Ca²⁺ influx, regulate cAMP-PKA and cGMP-PKG signaling, and reduce MLC phosphorylation, resulting in vascular relaxation. AA, Arachidonic acid; AC, Adenylate cyclase; ACE, Angiotensin-converting enzyme; Ang-II, Angiotensin II; AT1R, Angiotensin II type 1 receptor; cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; CGRP, Calcitonin gene-related peptide; COX, Cyclooxygenase; EET, Epoxyeicosatrienoic acids; eNOS, Endothelial nitric oxide synthase; GC, Guanylyl cyclase; IP3, Inositol 1,4,5-trisphosphate; MLC, Myosin light chain; MLCK, Myosin light chain kinase; MLCP, Myosin light chain phosphatase; NO, Nitric oxide; PDE, Phosphodiesterase; PGI₂, Prostacyclin; PI3K, Phosphatidylinositol 3-kinases; PKA, Protein kinase A; PKG, Protein kinase G; PLC, Phospholipase C; RAAS, Renin-angiotensin-aldosterone system; ROS, Reactive oxygen species; EDHF, Endothelium-derived hyperpolarizing factor; VIP, Vasoactive intestinal peptide; VSMCs, Vascular smooth muscle cell.

astragalus, and *Panax notoginseng*, exert vasodilatory activity through endothelium-dependent and endothelium-independent mechanisms (Table 2). Recent studies indicate that saponins modulate vascular tone by activating classical endothelial signaling pathways, including the NO-cGMP and PGI₂-cAMP cascades, and by stimulating EDHF responses. Similarly, saponins act directly on VSMCs by inhibiting VDCCs, enhancing K⁺ channel opening, and regulating enzymes such as RhoA and PDEs (Figure 5).

Panax notoginseng (Burk.) F. H. Chen, a traditional herbal medicine, is widely used to treat cardiovascular and cerebrovascular diseases. Its primary bioactive constituents include ginsenosides Rg1, Rb1, Re, Rd, and notoginsenoside R1^[139]. Although their mechanisms vary, two primary pathways mediate most vasodilatory effects: (i) an endothelium-independent pathway involving the inhibition of VSMC Ca²⁺ channels, and (ii) an endothelium-dependent pathway in which the release of NO and PGI₂ activates downstream signaling cascades to induce relaxation.

Among these saponins, ginsenoside Rg3 is a key mediator of endothelium-dependent vasorelaxation. Its endothelium-dependent action is primarily attributed to the activation of the eNOS-cGMP-PKG pathway, leading to enhanced NO production. In contrast, its endothelium-independent mechanism involves the inhibition of L-type Ca²⁺ channels and the activation of K⁺ channels, which induce membrane hyperpolarization and reduce intracellular Ca²⁺ levels^[141,149]. Notably, the stereoisomers of Rg3 demonstrate distinct biological activities. The configuration of the hydroxyl group at the C-20 position critically determines the capacity to modulate Ca²⁺ channels and induce vasodilation. Specifically, 20(S)-Rg3 effectively targets ion channels in VSMCs even in the absence of endothelium, showing stronger relaxation under multiple contractile stimuli, whereas 20(R)-Rg3 exerts weaker Ca²⁺ channel inhibition and limited activity after endothelium removal, suggesting less favorable interactions with ion channel binding sites^[134]. Beyond ion channel regulation, Rg3 also inhibits PDE activity, thereby amplifying cGMP signaling and enhancing vasodilatory responses^[142].

Table 2
Related pathways and mechanisms of natural saponins with vasodilatory effects

Compounds	Natural medicine	Vascular type	Species	Dosage	Vasoconstrictor	Mechanisms
Progesterone ^[132]	—	Thoracic aorta	WKY rats and SHR rats	0.3–300 μ M	PE	Ca ²⁺
20 (S)-Protopanaxadiol ^[133]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Wistar rats	21.5–108.5 μ M	KCl and PE	VDCC, ROCC, K ⁺
20 (R)-Ginsenoside Rg3 ^[134]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Pig	1–300 mM	KCl	high K ⁺ and 5-HT receptor activation
20 (S)-Ginsenoside Rg3 ^[134]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Pig	1–300 mM	KCl	Inhibited L-type Ca ²⁺ channel, high K ⁺ and 5-HT receptor activation
Astragaloside IV ^[135]	<i>Astragalus membranaceus</i> (Fisch.) Bunge	Thoracic aorta	SD rats	1–10,000 μ M	KCL	PI3K-Akt-eNOS
Astragaloside IV ^[136]	<i>Astragalus membranaceus</i> (Fisch.) Bunge	Thoracic aorta	Wistar rats	1.3–130 μ M	PE	NO-cGMP pathway and by extracellular calcium blockade
Bacopaside I ^[137]	<i>Bacopa monnieri</i> (L.) Wettst.	Mesenteric artery	Wistar rats	0.1–100 μ M	PE	Blockade of Ca ²⁺ influx and its release from SR
Bacoside A ^[137]	<i>Bacopa monnieri</i> (L.) Wettst.	Mesenteric artery	Wistar rats	0.1–100 μ M	PE	Blockade of Ca ²⁺ influx and its release from SR
Dioscin ^[138]	—	Thoracic aorta	SD rats	0.1–3.2 mM	KCL and PE	VDCC
Ginsenoside Rb1 ^[139]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Wistar rats	0.01–10 μ M	PE	NO-sGC
Ginsenoside Re ^[139]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Wistar rats	0.01–10 μ M	PE	NO-sGC
Ginsenoside Rg1 ^[139]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Wistar rats	0.01–10 μ M	PE	NO-sGC
Ginsenoside Rg2 ^[140]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Wistar rats	10–10,000 μ M	Norepinephrine	NO-cGMP
Ginsenoside Rg3 ^[141]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	SD rats	1–100 μ M	KCl	Ca ²⁺ , K ⁺
Ginsenoside Rg3 ^[142]	<i>Panax ginseng</i> C. A. Mey.	Corpus cavernosum	Canine	1–1,000 μ g/mL	PE	Inhibit PDEs
Ginsenosides ^[143]	<i>Panax ginseng</i> C.A.Mey.	Thoracic aorta	rats	50 μ g/mL	PE	Ca ²⁺ , K ⁺
Gitogenin ^[144]	<i>Tribulus longipetalus</i> Viv.	Thoracic aorta	Wistar rats		PE	—
Isosteviol ^[145]	<i>Stevia rebaudiana</i> (Bertonii) Bertonii	Thoracic aorta	Wistar rats	0.01–10 μ M	KCl	Related to the opening of SKCa and K _{ATP} channels
Notoginsenoside Ft1 ^[146]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Mesenteric artery	SD rats	0.01–10 μ M	KCl and PE	NO, GR, Erb
Notoginsenoside R1 ^[139]	<i>Panax notoginseng</i> (Burkill) F.H.Chen ex C.H.Chow	Thoracic aorta	Wistar rats	0.01–10 μ M	PE	NO-sGC
Jujuboside B ^[147]	<i>Ziziphus jujuba</i> Mill. var.	Thoracic aorta	SD rats	10 μ M	PE	Activated eNOS and phosphorylated eNOS, TRPC
Diosgenin ^[148]	—	Mesenteric artery	Wistar rats	2–2,000 μ M	PE	Activate BK _{Ca} channels

BKCa, Large-conductance Ca²⁺-activated K⁺ channels; cGMP, Cyclic guanosine monophosphate; eNOS, Endothelial nitric oxide synthase; Erb, Estrogen receptor β ; GR, Glucocorticoid receptor; K_{ATP}, ATP-sensitive K⁺ channels; NO, Nitric oxide; PDE, Phosphodiesterase; PE, Phenylephrine; PI3K, Phosphatidylinositol 3-kinases; ROCC, Receptor-operated calcium channel; SD, Sprague-Dawley; sGC, Soluble guanylyl cyclase; SHR, Spontaneously hypertensive rats; SKCa, Small-conductance Ca²⁺-activated K⁺ channel; SR, Sarcoplasmic reticulum; TRPC, Transient receptor potential channel; VDCC, Voltage-dependent calcium channel; WKY, Wistar-Kyoto; 5-HT, 5-Hydroxytryptamine. "—" indicates that the cited literature does not mention this content.

Saponins from *Panax notoginseng* (Burk.) F. H. Chen and related ginsenosides share a steroidal backbone, which enables interaction with steroid hormone receptors, such as glucocorticoid, estrogen, androgen, progesterone, and mineralocorticoid receptors. For example, notoginsenoside Ft1 exerts an endothelium-dependent vasodilatory effect by stimulating glucocorticoid

receptors (GRs) and estrogen receptor β (ER β) in rat mesenteric arteries. This receptor activation triggers the PI3K-AKT and ERK1/2 pathways, leading to eNOS phosphorylation, enhanced NO release, and sGC activation in VSMCs, ultimately resulting in vasorelaxation^[146]. Additionally, astragaloside IV, a major saponin from *Astragalus membranaceus* (Fisch.) Bunge, regulates

the PI3K-AKT-eNOS signaling axis through AKT phosphorylation at Ser473 and eNOS dephosphorylation at Thr495, resulting in increased NO bioavailability and endothelium-dependent vasodilation^[135].

Other saponins act through ion channel regulation and calcium signaling. For instance, jujuboside B induces endothelium-dependent vasodilation through a distinct mechanism. Zhao et al. demonstrated that jujuboside B enhances extracellular Ca^{2+} influx *via* endothelial transient receptor potential channel (TRPC), promotes eNOS phosphorylation, and increases NO production, thereby contributing to vascular relaxation^[147]. Figure 5 illustrates the proposed mechanisms underlying the vasodilatory effects of saponin compounds.

Phenylpropanoids

The vasoactive properties of phenylpropanoids have been extensively studied to elucidate their mechanisms of action. Several phenylpropanoids demonstrate consistent

antioxidant, anti-inflammatory, and vasorelaxant activities. Phenylpropanoids with vasodilatory effects are shown in Table 3.

Gomisin A, an active component of Schisandra berries, can induce a non-endothelium-dependent vasodilation primarily by inhibiting the RhoA-Rho-kinase pathway to dilate blood vessels^[150,156]. (-) Cubebin promotes vasodilation in rat aorta through the NO/cGMP pathway without the involvement of prostacyclin. (+/-) Preruptorin A is a pair of enantiomers with limited prior research. Xu et al.^[162] found that although the two compounds have different potencies, both exert a significant relaxing effect on isolated rat aortic rings *via* NO catalyzed by eNOS. In Brazilian folk medicine, extracts from pepper are used as a remedy to lower blood pressure. Moreover, Raimundo et al.^[155] found that eudesmin, a lignan isolated from hexane extracts of pepper leaves, induces relaxation in rat aortic vessels by triggering the release of NO and prostaglandins through histamine receptors present in ECs. Zhang et al.^[159] found that

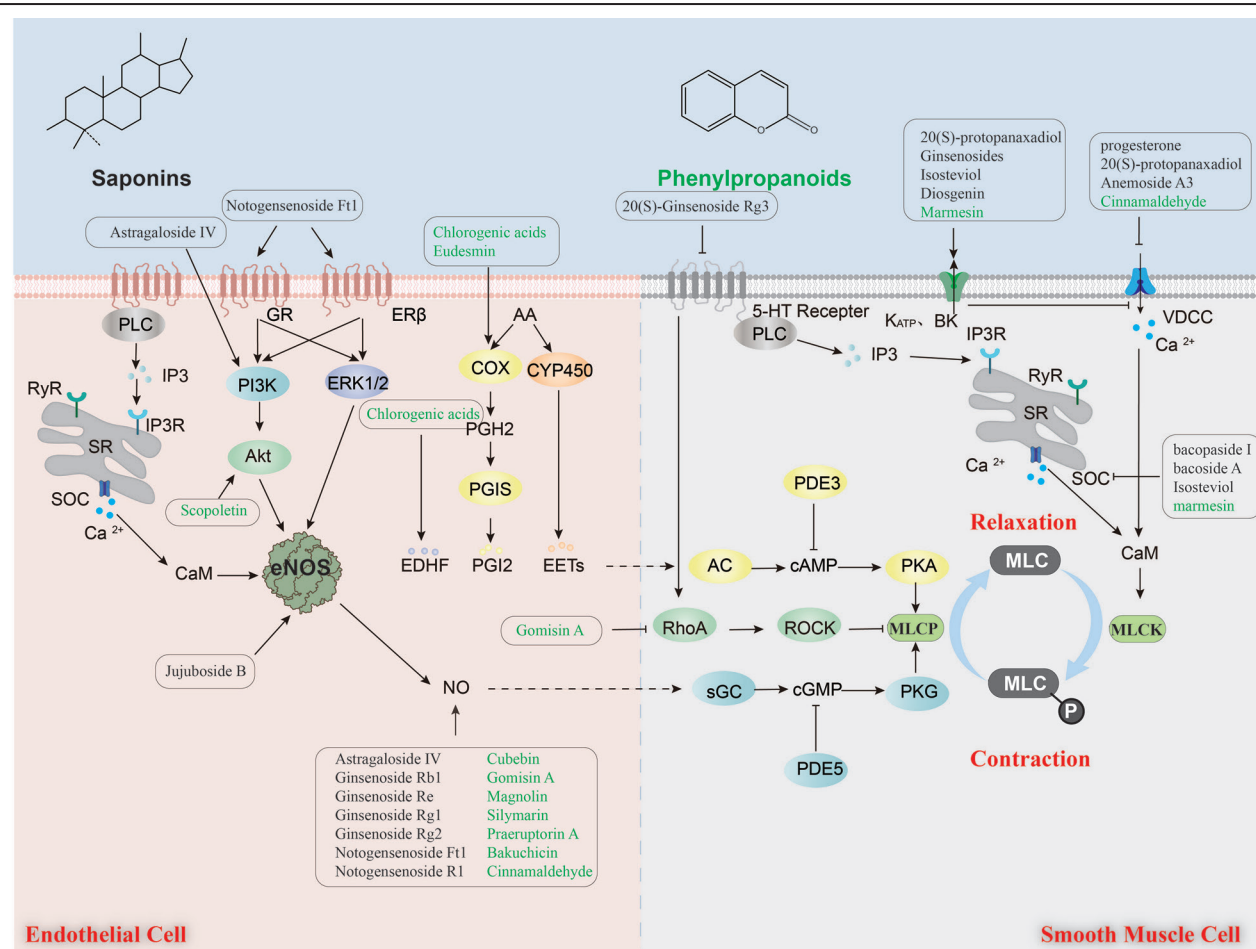


Figure 5. Mechanisms of vasodilation induced by saponins (black font) and phenylpropanoids (green font) in ECs and VSMCs. In endothelial cells, saponins and phenylpropanoids activate eNOS-NO, COX-PGI₂, and CYP450-EETs pathways to produce vasodilatory mediators. In smooth muscle cells, compounds inhibit Ca^{2+} influx, modulate cAMP/PKA and cGMP/PKG signaling, and reduce MLC phosphorylation, resulting in vascular relaxation. AA, Arachidonic acid; AC, Adenylate cyclase; ACE, Angiotensin-converting enzyme; Ang-II, Angiotensin II; AT1R, Angiotensin II type 1 receptor; cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; CGRP, Calcitonin gene-related peptide; COX, Cyclooxygenase; EET, Epoxyeicosatrienoic acids; eNOS, Endothelial nitric oxide synthase; GC, Guanylyl cyclase; IP3, Inositol 1,4,5-trisphosphate; MLC, Myosin light chain; MLCK, Myosin light chain kinase; MLCP, Myosin light chain phosphatase; NO, Nitric oxide; PDE, Phosphodiesterase; PGI₂, Prostacyclin; PI3K, Phosphatidylinositol 3-kinases; PKA, Protein kinase A; PKG, Protein kinase G; PLC, Phospholipase C; RAAS, Renin-angiotensin-aldosterone system; ROS, Reactive oxygen species; EDHF, Endothelium-derived hyperpolarizing factor; VIP, Vasoactive intestinal peptide; VSMCs, Vascular smooth muscle cell.

Table 3**Related pathways and mechanisms of natural phenylpropanoids with vasodilatory effects**

Compounds	Natural medicine	Vascular type	The species investigated	Dosage	Vasoconstrictor	Mechanisms
Cubebin ^[150]	<i>Piper cubeba</i> L.fil.	Thoracic aorta	Wistar rats		PE	NO-cGMP
Cinnamaldehyde ^[151]	<i>Cinnamomum zeylanicum</i> Blume, <i>Cinnamomum cassia</i> (L.) J.Presl	Coronary artery rings	Porcine	0.1–0.32 µM	U4, KCl	Ca ²⁺
Cinnamaldehyde ^[152]	<i>Cinnamomum cassia</i> (L.) J.Presl	Aorta rings	SD rats	0.1–100 µg/mL	PE	Ca ²⁺
Cinnamaldehyde ^[153]	<i>Cinnamomum cassia</i> (L.) J.Presl	Aortic rings	Wistar rats	0.1–3,000 µM	KCl	Ca ²⁺
Cinnamaldehyde ^[154]	<i>Cinnamomum cassia</i> (L.) J.Presl	Thoracic aorta	Wistar rats	1–1,000 µM	KCl, NE	NO, Ca ²⁺
Eudesmin ^[155]	<i>Piper cubeba</i> L.fil.	Thoracic aorta	SD rats	30–35 µg/mL	PE	NO, PGI ₂ , histamine receptor
Gomisin A ^[156]	<i>Schisandra chinensis</i> (Turcz.) Baill.	Thoracic aorta	SD rats	0.1–1 mM	NaF, U46619	Inhibition of RhoA-Rho-kinase pathway
Gomisin A ^[157]	<i>Schisandra chinensis</i> (Turcz.) Baill.	Thoracic aorta	SD rats	1–300 µM	PE	Activating NO pathway, and partially dephosphorylation of MLC
Hypophyllanthin ^[158]	<i>Phyllanthus niruri</i> L.	Thoracic aorta	Wistar rats	100 µM	PE	Blockade of Ca ²⁺ entry into VMSCs
Magnolin ^[159]	<i>Magnoliaceae</i> Juss.	Thoracic aorta	SD rats	0.1–1,000 µM	PE	eNOS-NO
Phyllanthin ^[158]	<i>Phyllanthus niruri</i> L.	Thoracic aorta	Wistar rats	100 µM	PE	Blockade of Ca ²⁺ entry into VMSCs
Prinsepiol-4-O-beta-D-glucopyranoside ^[160]	<i>Valeriana prionophylla</i> Standl.	Thoracic aorta	Wistar rats	1–100 µM	PE	–
Silymarin ^[161]	<i>Silybum marianum</i> (L.) Gaertn.	Thoracic aorta	Wistar rats	50 mg/L	PE	NO-Ca ²⁺
(-)-Praeruptorin A ^[162]	<i>Peucedanum praeruptorum</i> Dunn	Thoracic aorta	SD rats	1–30 µM, 3–100 µM	KCL, PE	Blocking Ca ²⁺ channels
(+)-Praeruptorin A ^[162]	<i>Peucedanum praeruptorum</i> Dunn	Thoracic aorta	SD rats	1–100 µM	KCL and PE	Blocking Ca ²⁺ channels, NO-cGMP
8-Geranyloxypsoralen	<i>Casimiroa edulis</i> Llave et Lex	Caudal arterial	Wistar rats	0.1–100 µM	PE	–
Bakuchicin ^[163]	<i>Psoralea corylifolia</i> L.	Thoracic aorta	SD rats	0.1–100 µM	PE	NO-cGMP, Ca ²⁺
Herniarin ^[75]	<i>Casimiroa edulis</i> Llave et Lex	Caudal arterial	Wistar rats	0.3–300 µM	PE	–
Imperatorin ^[75]	<i>Casimiroa edulis</i> Llave et Lex	Caudal arterial	Wistar rats	0.3–300 µM	PE	O ₂ ²⁻ in the regulation of arterial tone
Mammea A/AA cycloF ^[164]	<i>Clusiaceae</i>	Thoracic aorta	MS rats	0.32–32 µM	U46619	NO-cGMP
Marmesin ^[165]	<i>Angelica citriodora</i> Hance	Thoracic aorta	SD rats	25–100 µg/mL	KCL, PE	Inhibition of L-type VDCC, ROCC, opening KCa, and calcium ion release in the block inhibits the increase of calcium ion concentration in VSMC
Scopoletin ^[12]	<i>Scopolia japonica</i> maxim.	Coronary artery	SD rats	0.1–1,000 µM	U46619	Increased eNOS and Akt phosphorylation

cGMP, Cyclic guanosine monophosphate; eNOS, Endothelial nitric oxide synthase; PE, Phenylephrine; PGI₂, Prostacyclin; MLC, Myosin light chain; MS, Male Swiss; NE, Norepinephrine; NO, Nitric oxide; ROCC, Receptor-operated calcium channel; SD, Sprague-Dawley; VDCC, Voltage-dependent calcium channel; VSMC, Vascular smooth muscle cells.

magnolol may induce endothelium-dependent vasodilation by activating eNOS, with no apparent renal toxicity. Figure 5 illustrates the proposed mechanisms underlying the vasodilatory effects of phenylpropanoid compounds.

Terpenoids

Terpenoids modulate vascular regulation through various biological activities, including vasorelaxation, oxidative stress reduction, suppression of pro-inflammatory cytokine expression, and free radical scavenging. Table 4 and Figure 6 summarize the terpenoid compounds with vasodilatory activity and their underlying mechanisms of action.

1,8-Cineole, a monoterpene extracted from the essential oil of *Alpinia zerumbet* (Pers.) B.L.Burtt & R.M.Sm., inhibits the contraction of rat aorta induced by PE. Its vasodilatory mechanisms, including activation of the NO-cGMP pathway, antioxidant effects, inhibition of Ca^{2+} influx, K^+ channel activation, and anti-inflammatory effects, have been extensively reported^[168]. Borneol, a crystalline compound extracted from borneol essential oil, is a component of the emergency heart medicine “Suxiao Jiuxin Pill,” which can induce non-endothelial-dependent vasodilation in rat coronary arteries. In addition to borneol, marrubin, another pharmacologically active terpenoid, has been shown to exert a vasorelaxant effect mediated through endothelial-dependent and endothelial-independent pathways. The endothelium-dependent pathway primarily achieves this through activation of the NO-cGMP signaling pathway and preservation of EC function, while the endothelium-independent pathway involves K^+ channel opening and Ca^{2+} antagonism^[183]. Aristolone from *Nardostachys jatamansi* (D.Don) DC. acts on both VSMCs and ECs through K_{ATP} channel activation and the PDK1-AKT-eNOS signaling pathway, thus achieving vasodilation^[170]. Essential oil extract from *Pectis brevipedunculata* (Gardner) Sch.Bip., a type of Brazilian walnut, has been shown to promote endothelial integrity and strong vasodilation in damaged aortas. Ursolic acid and uvaol are two non-polar compounds isolated from *Prunus serotina* Ehrh. Experimental results indicate that these two triterpenoids increase the production of NO and H_2S in aortic tissue, while molecular docking studies suggest that both can bind to endothelial NOS and CSE with high affinity for residues that form the stabilizing structure of the active sites of both enzymes. These findings suggest that the vasodilatory mechanisms of these compounds involve the activation of the NO-cGMP and H_2S - K_{ATP} pathways, possibly through direct activation of NOS and CSE^[181].

Alkaloids

Current evidence indicates that most alkaloids exert vasodilatory effects predominantly through dual mechanisms or endothelium-independent pathways (Figure 6).

Neferine, a traditional bioactive compound, has attracted significant interest in antihypertensive research due to its favorable safety profile. Its vasodilatory effects involve both an endothelium-dependent pathway, primarily *via* the eNOS-NO-sGC cascade, and endothelium-independent mechanisms, including the modulation

of Ca^{2+} channel activity and the inhibition of Ca^{2+} release from the sarcoplasmic reticulum^[184]. Similarly, the vasodilatory action of cassiarin A is only partially attenuated by endothelial removal or pharmacological inhibition with the NO synthase blocker L-NAME and the sGC inhibitor ODQ. These findings suggest that cassiarin A exerts both endothelium-dependent and endothelium-independent effects, closely associated with the NO-cGMP axis and BKCa channel activity^[185]. Berberine has also been reported to induce vasorelaxation through dual mechanisms. Its endothelium-dependent action is similar to that of cassiarin A, whereas its endothelium-independent effects involve the activation of multiple K^+ channels (including BK_{Ca}, Kv, and Kir), the inhibition of intracellular Ca^{2+} release, and direct relaxation of vascular smooth muscle. These combined properties highlight its therapeutic potential for patients with conditions such as congestive heart failure^[186].

In contrast, other alkaloids act primarily through endothelium-independent mechanisms. For instance, tiliacoronine 12'-O-acetate induces vasodilation by promoting Ca^{2+} release *via* ryanodine receptors and IP_3R ^[187]. 8-Oxo-9-dihydromakomakine, isolated from *Aristolochia chilensis*, exerts significant vasorelaxant effects in hypertension and myocardial ischemia models by inhibiting extracellular Ca^{2+} influx in VSMCs *via* endothelium-independent mechanisms^[188]. Similarly, alkaloids—including fumigaclavine C, sinomenine, mesaconitine, and isocorynoxine—exert vasorelaxant effects primarily through endothelium-independent mechanisms, characterized by the inhibition of L-type Ca^{2+} channels, the activation of K_{ATP} channels, and the suppression of Ca^{2+} release from intracellular stores^[189–191]. Notably, isocorynoxine also activates Kv channels, further enhancing its vasodilatory effect^[192]. Table 5 examines the detailed molecular mechanisms through which key terpenoids mediate their vasorelaxant effects.

Phenols

Phenolic compounds have multiple mechanisms of action in vasodilation, primarily through pathways involving cAMP, NO, K^+ , Ca^{2+} , etc (Figure 7).

Resveratrol, a phenolic compound isolated from rhubarb (*Rheum rhabarbarum*), has been reported to exhibit beneficial effects, including anti-allergic properties, antioxidant activity, suppression of vasoconstriction, and prevention of diabetes. To investigate its vasodilatory mechanism, Yoo et al.^[180] isolated the thoracic aorta of SD rats and pre-contracted it with deoxyadrenaline. Additionally, the experiment involved removing the endothelium and using L-NAME (a non-selective NO synthase inhibitor) to investigate whether its effects were endothelium-dependent. They found that the vasodilatory effect of resveratrol was NO-mediated and endothelium-dependent^[180].

Senejoux et al.^[197] conducted *in vitro* and *in vivo* experiments using Wistar rat thoracic aortic rings and SHR. The study found that apocynin has acute antihypertensive effects and exhibits both NO-mediated endothelium-dependent and Ca^{2+} -inhibited non-endothelium-dependent effects during vasodilation^[197]. Apple procyanidins, which can inhibit cancer cell growth, resist tumor damage, and prevent obesity, have garnered

Table 4**Related pathways and mechanisms of natural terpenoids with vasodilatory effects**

Compounds	Natural medicine	Vascular type	The species investigated	Dosage	Vasoconstrictor	Mechanisms
Marrubiin ^[166]	<i>Phlomis bracteosa</i> L.	Thoracic aorta	SD rat	1–1,000 µg/mL	KCL, PE	Ca ²⁺ , NO
Sclareol ^[167]	<i>Salvia sclarea</i> L.	Thoracic aorta	Normotensive/ hypertensive rats	10 ⁻⁴ –100 µM	PE	NO-cGMP
1,8-Cineole ^[168]	<i>Alpinia zerumbet</i> (Pers.) B.L.Burt and R.M.Sm.	Thoracic aorta	Wistar rat	0.01–3,000 mg/ mL	PE	NO-cGMP, Ca ²⁺
15-Dien-19-oic acid ^[169]	<i>Viguiera arenaria</i> Baker	Thoracic aorta	Wistar rat	10–100 µM	KCL, PE	Ca ²⁺ , NO
Aristolone ^[170]	<i>Nardostachys jatamansi</i> (D.Don) DC.	Thoracic aorta and mesenteric arterial rings	Hypertensive rats	0–200 µM	U46619	K _{ATP} , PDK1-Akt-eNOS
Betulinic acid ^[171]	<i>Ziziphus jujuba</i> Mill. var.	Thoracic aorta	SD rat	0.01–100 µM	PE	eNOS, NO
Betulinic acid ^[172]	<i>Ziziphus jujuba</i> Mill. var.	Thoracic aorta	Hypertensive rats	0.1–100 µM	PE	eNOS, NO
Betulinic acid ^[172]	—	Thoracic aorta	SD rat	0.1–100 µM	PE	eNOS-NO-cGMP
Citral ^[173]	<i>Pectis brevipedunculata</i> (Gardner) Sch.Bip.	Thoracic aorta	Wistar Kyoto	10–10,000 µM	PE	Ca ²⁺
Ent-18-hydroxy- trachyloban-3-one ^[174]	<i>Croton zambesicus</i> Müll. Arg.	Thoracic aorta	Wistar rat	1–3 µM	KCL, noradrenaline	Ca ²⁺ , NO-cGMP
Erythrodil ^[175]	—	Thoracic aorta	Wistar rat	0.1–100 µM	KCL, PE	Ca ²⁺ , NO
Gentiopicroside ^[176]	<i>Gentiana straminea</i> Maxim., <i>Gentiana</i> <i>macrophylla</i> Pall.	Thoracic aorta	SD rats	5–320 µM	KCL	PI3K-Akt-Rho kinase signaling pathway, Ca ²⁺ , K ⁺
Geraniol ^[177]	—	Thoracic aorta	Wistar rats	10–300 µM	PE	Ca ²⁺
Kaurenoic acid ^[178]	<i>Viguiera robusta</i> Gardner	Thoracic aorta	Wistar rat	50, 100 µM	KCL, PE	Ca ²⁺ , NO-cGMP
Kaurenoic acid ^[179]	<i>Viguiera robusta</i> Gardner	Thoracic aorta	Wistar rat	1–450 nM/L	KCL, PE	Ca ²⁺ , NO-cGMP, K ⁺
Ligustilide ^[12]	—	Coronary artery	SD rat	0.1–1,000 µM	U4	—
Nardosinone ^[12]	<i>Nardostachys jatamansi</i> (D.Don) DC.	Coronary artery	SD rat	0.1–1,000 µM	U4	—
Oleanolic acid ^[175]	—	Thoracic aorta	Wistar rat	0.1–100 µM	KCL, PE	COX, NO
Phlomeoic acid ^[166]	<i>Phlomis bracteosa</i> L.	Thoracic aorta	SD rat	1.0–1,000 µg/mL	KCl, PE	Ca ²⁺ , NO
Piceatannol ^[180]	<i>Rheum undulatum</i> L.	Thoracic aorta	SD rat	1–30 µM	PE	NO-cGMP
Pimaradienoic acid ^[178]	<i>Viguiera arenaria</i> Baker	Thoracic aorta	Wistar rat	50, 100 µM	KCl, PE	Ca ²⁺ , NO
Ursolic acid ^[181]	<i>Prunus serotina</i> Ehrh.	Thoracic aorta	Wistar rat	1.0–1,000 µg/mL	PE	NO-cGMP, H ₂ S-K _{ATP}
Uvaol ^[181]	<i>Prunus serotina</i> Ehrh.	Thoracic aorta	Wistar rat	1.0–1,000 µg/mL	PE	NO-cGMP, H ₂ S-K _{ATP}
Zerumbone ^[182]	<i>Zingiber zerumbet</i> (L.) Roscoe ex Sm.	Thoracic aorta	Wistar rat	0–1,000 µM	KCl, PE	Ca ²⁺
Borneol ^[12]	—	Coronary artery ring	Rat	0.1–1,000 µM	U46619	Kir, KCa, Kv
Kanshone A ^[12]	—	Coronary artery ring	Rat	0.1–1,000 µM	U46619	eNOS-NO-sGC- cGMP
Kanshone H ^[12]	—	Coronary artery ring	Rat	0.1–1,000 µM	U46619	—
Sedanolid ^[12]	—	Coronary artery ring	Rat	0.1–1,000 µM	U46619	—
Senkyunolide A ^[12]	—	Coronary artery ring	Rat	0.1–1,000 µM	U46619	eNOS-NO-sGC- cGMP
Senkyunolide H ^[12]	—	Coronary artery ring	Rat	0.1–1,000 µM	U46619	—

cGMP, Cyclic guanosine monophosphate; COX, Cyclooxygenase; eNOS, Endothelial nitric oxide synthase; K_{ATP}, ATP-sensitive K⁺ channels; Kir, Inwardly rectifying K⁺ channels; NO, Nitric oxide; PDK1, 3-Phosphoinositide-dependent kinase 1; PE, Phenylephrine; PI3K, Phosphatidylinositol 3-kinases; SD, Sprague-Dawley; sGC, Soluble guanylyl cyclase. "—" indicates that the cited literature does not mention this content.

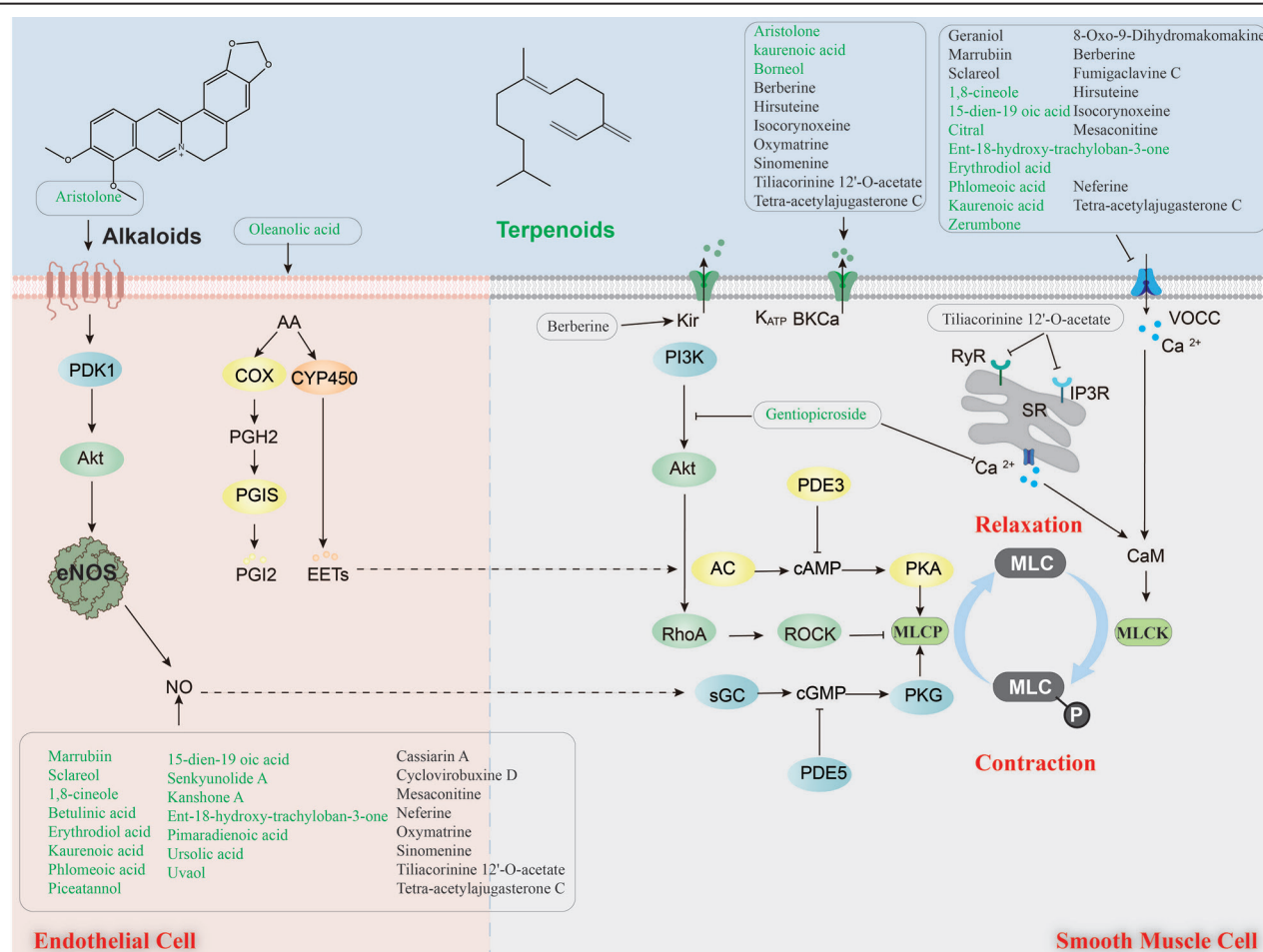


Figure 6. Mechanisms of vasodilation induced by alkaloids (black font) and terpenoids (green font) in ECs and VSMCs. In endothelial cells, alkaloids activate the PDK1-Akt-eNOS-NO pathway, while terpenoids regulate the COX-PGI₂ and CYP450-EETs pathways to produce vasodilatory mediators. In smooth muscle cells, these compounds inhibit Ca²⁺ influx, activate K⁺ channels, and modulate cAMP-PKA and cGMP-PKG signaling, reducing MLC phosphorylation to induce vascular relaxation. AA, Arachidonic acid; AC, Adenylate cyclase; ACE, Angiotensin-converting enzyme; Ang-II, Angiotensin II; AT1R, Angiotensin II type 1 receptor; cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; CGRP, Calcitonin gene-related peptide; COX, Cyclooxygenase; EC, Endothelial cell; EET, Epoxyeicosatrienoic acids; eNOS, Endothelial nitric oxide synthase; GC, Guanylyl cyclase; IP3, Inositol 1,4,5-trisphosphate; MLC, Myosin light chain; MLCK, Myosin light chain kinase; MLCP, Myosin light chain phosphatase; NO, Nitric oxide; PDE, Phosphodiesterase; PGI₂, Prostacyclin; PI3K, Phosphatidylinositol 3-kinases; PKA, Protein kinase A; PKG, Protein kinase G; PLC, Phospholipase C; RAAS, Renin-angiotensin-aldosterone system; ROS, Reactive oxygen species; EDHF, Endothelium-derived hyperpolarizing factor; VIP, Vasoactive intestinal peptide; VSMCs, Vascular smooth muscle cell.

widespread attention in vascular research. To investigate their mechanism of regulating vascular function, researchers induced thoracic aortic vasoconstriction in SD rats using 1.0 mM PE or 70 mM KCl, then added the sample solution cumulatively. The results confirmed that the vasodilation induced by the compound is associated with endothelium-dependent hyperpolarization primarily involving the cGMP production pathway. Conversely, it can cause hyperpolarization through the activation of multiple K⁺ channels *via* non-endothelial-dependent mechanisms^[198]. Similarly, compounds such as brasilin, curcumin, and gingerol achieve vasodilation through both endothelial and non-endothelial-dependent mechanisms. This seemingly paradoxical property of some phenolic compounds highlights their diverse mechanistic profiles and therapeutic potential, depending on the desired outcome^[102,199]. In contrast, gingerol reduces VSMC proliferation and inhibits neointimal formation by inhibiting the activation of p38 mitogen-activated protein kinase (p38 MAPK)^[200]. Regarding carvacrol, research suggests it

may involve the release of calcium from the sarcoplasmic reticulum and calcium-sensitive transduction pathways regulating the contraction system, as well as the modulation of vasodilation through non-endothelial-dependent inhibition of Ca²⁺ influx^[201]. While carvacrol induces vasodilation regardless of endothelial presence, the effect is significantly enhanced in the presence of the endothelium. By excluding the involvement of the NO pathway, the AA cascade, and TRPC, voltage-gated Kv channels were the key pathways through which carvacrol exerts its vasodilatory effects^[202].

The NO pathway appears to be closely related to endothelium-dependent vasodilation. Epigallocatechin gallate, a bioactive polyphenol, can inhibit gluconeogenesis in hepatocytes and activate the eNOS pathway in a PI3-kinase-dependent manner. It requires ECs to produce NO to exert its vasodilatory effect^[203]. Ion channels are also intimately associated with non-endothelial dependence. Petasin exerts its effects by directly inhibiting the activity of L-type voltage-dependent calcium channels

Table 5
Related pathways and mechanisms of natural alkaloids with vasodilatory effects

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
8-Oxo-9-Dihydromakomakine ^[188]	<i>Aristolelia chilensis</i> (Molina) Stuntz	Thoracic aorta	SD rats	0.001–100 μ M	PE	Ca ²⁺
Berberine ^[186]	<i>Coptis chinensis</i> Franch.	Mesenteric arteries	SD rats	1–30 μ M	PE	K ⁺ , Ca ²⁺
Cassiarin A ^[185]	<i>Cassia siamea</i> Lam.	Mesenteric arteries	Wistar rats	10 nM–100 mM	PE	NO-cGMP
Cyclovirobuxine D ^[193]	<i>Buxus sinica</i> var. <i>parvifolia</i> M.Cheng	Thoracic aorta	Wistar rats	10–600 μ M	KCl	NO-cGMP
Fumigaclavine C ^[190]	<i>Aspergillus fumigatus</i> Fresen.	Thoracic aorta	SD rats	1–100 μ M	PE, KCl	Ca ²⁺
Hirsuteine ^[194]	<i>Uncariae Ramulus et Uncus</i>	Thoracic aorta	Wistar rats	0.1–100 μ M	NE	–
Isocorynoxine ^[192]	<i>Uncaria rhynchophylla</i> (Miq.) Miq.	Mesenteric arteries	SD rats	0.01–100 μ M	PE, KCl	Ca ²⁺ , Kv
Mesaconitine ^[191]	<i>Aconitum napellus</i> L.	Thoracic aorta	Wistar rats	10–300 μ M	PE	Ca ²⁺ , NO
Neferine ^[184]	<i>Nelumbo nucifera</i> Gaertn.	Thoracic aorta	Wistar rats	10 ^{–6} –100 μ M	PE, KCl	eNOS-NO-sGC, Ca ²⁺
Oxymatrine ^[195]	<i>Sophora flavescens</i> Aiton	Thoracic aorta	SD rats	0.9–34.2 mM	PE, KCl	NO-cGMP, BK _{Ca} , Kir
Sinomenine ^[189]	<i>Sinomenium acutum</i> (Thunb.) Rehder and E.H.Wilson	Thoracic aorta	Wistar rats, SHR	0.1–10 mM	PE, KCl	K _{ATP}
Tiliacoronine 12'-O-acetate ^[187]	<i>Tiliacora triandra</i> (Colebr.) Diels	Thoracic aorta	Wistar rats, SHR	10 ^{–9} –316 μ M	PE	eNOS-NO-sGC, Ca ²⁺ , Kv
Tetra-acetyljugasterone C ^[196]	<i>Vitex cienkowskii</i> Kotschy and Peyr.	Thoracic aorta	Rats	0.01–100 μ M	PE, KCl	NO-cGMP-cGKI, K ⁺ , Ca ²⁺

BK_{Ca}, Large-conductance Ca²⁺-activated K⁺ channels; cGKI, cGMP-dependent protein kinase I; cGMP, Cyclic guanosine monophosphate; eNOS, Endothelial nitric oxide synthase; K_{ATP}, ATP-sensitive K⁺ channels; Kir, Inwardly rectifying K⁺ channels; NE, Norepinephrine; NO, Nitric oxide; PE, Phenylephrine; SD, Sprague-Dawley; sGC, Soluble guanylyl cyclase. "–" indicates that the cited literature does not mention this content.

in vascular smooth muscle, explaining its vasodilatory effects. Additionally, petasin exhibits more pronounced effects in the vasculature of SHR rats, suggesting its potential therapeutic utility in hypertension management^[204]. Hexahydrocurcumin possesses stronger antioxidant capacity than its parent compound, curcumin. Studies have found that HHC can inhibit the influx of extracellular Ca²⁺ through VOCCs and ROCCs. Moohammadaree et al.^[205] were interested in the pharmacological mechanisms of HHC in treating hypertension and conducted in-depth studies, further confirming the role of HHC in vasodilation for the treatment of CVDs. Table 6 summarizes the phenol compounds with vasodilatory activity and their underlying mechanisms of action.

Phenolic acids

The vascular modulatory effects of phenolic acids have been extensively investigated. Conventional vasodilators used for treating CVDs with vascular underpinnings achieve their therapeutic goals by modulating key physiological states, including muscular tone, ionic channels, endogenous metabolites, neurohormonal signaling, oxidative states, and inflammatory microenvironments, etc. Moreover, phenolic acids from natural products also exhibit comparable regulatory functions in vascular tissues. Table 7 and Figure 7 summarize the phenolic acid compounds with vasodilatory activity and their underlying mechanisms of action.

Notably, gallic acid induces endothelium-dependent vasodilation by causing eNOS phosphorylation and opening potassium channels, as well as non-endothelium-dependent vasodilation by blocking L-type Ca²⁺ channels and inhibiting Ca²⁺ influx^[218]. Leeya et al.^[112] found that 4-hydroxybenzoic acid and caffeic acid isolated from the leaf extract of *Phyllanthus acidus* (L.) Skeels exhibited hypotensive activity in anaesthetized female Wistar rats, while inducing vasodilation in thoracic aortic rings by directly acting on the blood vessels to cause vasodilatation, as well as indirectly by stimulating the release of NO from the vascular endothelium. *In vitro* studies by Matsui et al.^[215] revealed that their newly isolated antihypertensive compound, (+)-osbeckic acid from tartary buckwheat, can activate the NO-cGMP endothelium-dependent pathway. At doses ranging from 0.5 to 2.5 mg/mL, (+)-osbeckic acid significantly relaxed the thoracic aortic rings of SD rats. This discovery not only demonstrates the antihypertensive potential of (+)-osbeckic acid but also positions phenolic compounds as antihypertensive and vasoactive compounds capable of inducing endothelium-dependent vasodilation. This dual pharmacological activity of phenolic compounds is exhibited by many other similar compounds, making them an interesting niche for therapeutic alternatives.

Other studies have found that salidroside A extracted from *Salvia miltiorrhiza* Bunge can promote angiogenesis in the myocardium of rats with ischemia, thereby increasing perfusion and improving myocardial

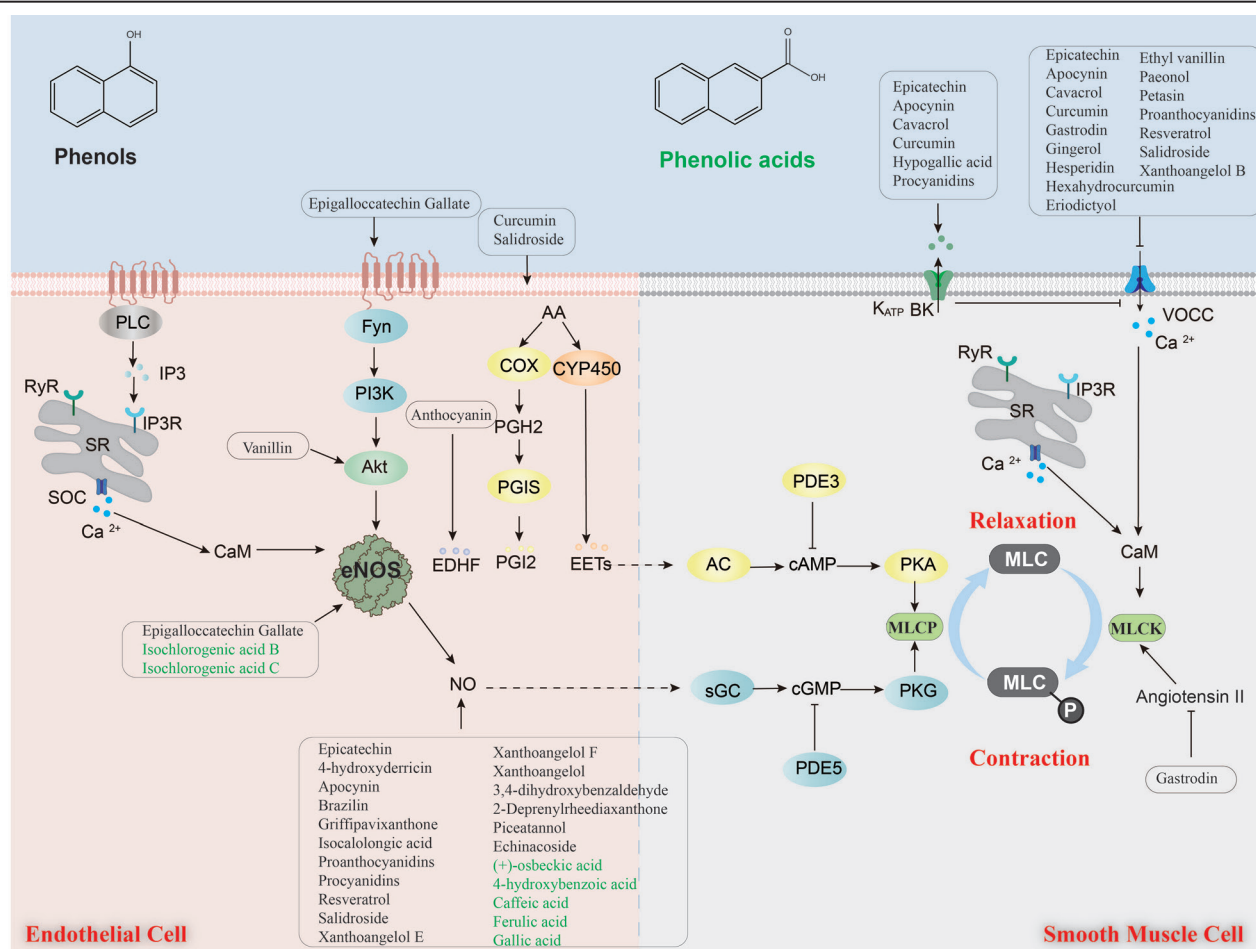


Figure 7. Mechanisms of vasodilation induced by phenolic (black font) compounds and phenolic acids (green font) in ECs and VSMCs. In endothelial cells, phenolic and phenolic acids activate the Fyn-Pi3K-Akt-eNOS-NO pathway, regulate COX-PGI₂ and CYP450-EETs signaling, and modulate Ca²⁺ dynamics to produce vasodilatory mediators. In smooth muscle cells, they inhibit Ca²⁺ influx, activate K⁺ channels, and modulate cAMP-PKA and cGMP-PKG pathways, reducing MLC phosphorylation to induce vascular relaxation. AA, Arachidonic acid; AC, Adenylate cyclase; ACE, Angiotensin-converting enzyme; Ang-II, Angiotensin II; AT1R, Angiotensin II type 1 receptor; cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; CGRP, Calcitonin gene-related peptide; COX, Cyclooxygenase; EC, Endothelial cell; EET, Epoxyeicosatrienoic acids; eNOS, Endothelial nitric oxide synthase; GC, Guanylyl cyclase; IP3, Inositol 1,4,5-trisphosphate; MLC, Myosin light chain; MLCK, Myosin light chain kinase; MLCP, Myosin light chain phosphatase; NO, Nitric oxide; PDE, Phosphodiesterase; PGI₂, Prostacyclin; PI3K, Phosphatidylinositol 3-kinase; PKA, Protein kinase A; PKG, Protein kinase G; PLC, Phospholipase C; RAAS, Renin-angiotensin-aldosterone system; ROS, Reactive oxygen species; EDHE, Endothelium-derived hyperpolarizing factor; VIP, Vasoactive intestinal peptide; VSMCs, Vascular smooth muscle cell.

ischemia^[219]. Tanshinone Ila, also isolated from *Salvia miltiorrhiza* Bunge, regulates vascular tone and vasodilation. The former is achieved *via* decreasing cyclic strain and tumor necrosis factor- α (TNF- α)-induced endothelin-1 (ET-1) production, while vasodilation is achieved by increasing NO production through elevated eNOS levels.

Phenolic acids also confer protective effects on the cardiovascular system by scavenging oxygen-free radicals, regulating calcium balance, protecting mitochondria, and modulating inflammatory cytokines^[220–221]. These findings further confirm the multifaceted mechanisms of phenolic acid compounds in vasodilation.

ACE, a key component of the RAAS, converts inactive precursor Ang-I into the active vasoconstrictor hormone, Ang-II. In an *in vitro* study, caffeic acid and ellagic acid were shown to inhibit ACE activity, thus preventing the conversion of Ang-I to Ang-II, leading to vasodilation and reduced blood pressure^[222].

Dysregulated inflammatory responses complicate the pathogenesis of many CVDs with vascular etiologies. By alleviating the saturated inflammatory microenvironment, therapeutic agents can restore the balance of pro-inflammatory and anti-inflammatory factors. Many phenolic acid compounds exhibit anti-inflammatory effects by inhibiting pro-inflammatory signaling pathways, key protein expression, and the activity of inflammation-related enzymes. In both *in vivo* and *in vitro* studies, chlorogenic acid suppressed the expression of key pro-inflammatory cytokines, including interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6), within lipopolysaccharide (LPS)-activated RAW 264.7 cells. Aside from inhibiting these cytokines, it also hinders the nuclear factor-kappa B (NF- κ B) signaling pathway, resulting in decreased NO production. Similarly, rosmarinic acid and ellagic acid inhibit TNF- α convertase, resulting in the inhibition of TNF- α production and reduced inflammatory responses^[223].

Table 6
Related pathways and mechanisms of natural phenols with vasodilatory effects

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
2-Deprenylrheediaxanthone ^[164]	<i>Clusiaceae</i>	Thoracic aorta	Male Swiss mice	0.32–32 μ M	U4	NO-cGMP
(-) Epicatechin ^[206]	<i>Jasminum sambac</i> (L.) Aiton	Mesenteric arteries	SD rats	10–300 μ M	PE, U46619	NO
(-) Epicatechin ^[207]	–	Internal mammary artery	Humans	0.1–500 μ M	PE	Kv, BK _{Ca} , K _{ATP} , Ca ²⁺
4-Hydroxyderricin ^[208]	<i>Angelica keiskei</i> (Miq.) Koidz.	Thoracic aorta	Wistar rat	10–100 μ g/mL	PE	NO
Anthocyanins/Flavylum ^[131]	–	Thoracic aorta	Wistar rats	0.0001–100 μ g/L	NE	ATP-P2Y1-P2Y2-NO, NO-GC-cGMP, PGI ₂ , EDHF
Apocynin ^[197]	<i>Picrorhiza kurroa</i> Royle ex Benth.	Thoracic aorta	Wistar rats/SHR	0.03–10 mM	PE	NO, Ca ²⁺ , K _{ATP}
Brazilin ^[102]	<i>Caesalpinia sappan</i> L.	Thoracic aorta	SD rats	1–100 μ M	PE	NO, cGMP
Carvacrol ^[201]	<i>Thymus vulgaris</i> L., <i>Origanum compactum</i> Benth., <i>Acalypha phleoides</i> Cav., <i>Species Lippia sidoides</i> Cham.	Thoracic aorta	Wistar rats	1–1,000 μ M	PE, KCl	Ca ²⁺
Carvacrol ^[202]	–	Thoracic aorta	Wistar rats	0.1–100 μ M	KCl	K ⁺
Chlorogenic acid ^[209]	<i>Eucommia</i> Oliv.	Thoracic aorta	Wistar rats	0.0001–100 μ M	PE	Increasing NOS, COX, and EDHF signaling pathways
Curcumin ^[199]	<i>Curcuma longa</i> L.	Mesenteric arteries	SD rats	0.01–100 μ M	PE, KCl	PGI ₂ , K ⁺ , Ca ²⁺
Echinacoside ^[210]	<i>Cistanche tubulosa</i> (Schenk) Wight	Thoracic aorta	SD rats	30–300 μ M	KCl, PE	NO-cGMP
Epigallocatechin Gallate ^[203]	–	Mesenteric vascular beds	Wistar rat	1–100 μ M	Norepinephrine	eNOS, phosphatidylinositol 3-kinase, Fyn kinase
Eriodictyol ^[211]	<i>Satureja obovata</i> Lag.	Thoracic aorta	Wistar rats	10–100 μ M	KCl, NE	Ca ²⁺
Gastrodin ^[212]	<i>Gastrodia elata</i> Bl.	Abdominal aorta	c57bl/6 mice	0.25–1.5 mg/mL	NE	Ca ²⁺ , MLCK/p-MLC2
Gingerol ^[200]	<i>Zingiber officinale</i> Roscoe	Carotid arteries, Thoracic aorta	SD rats	50–400 mM	PE	p38 MAPK, Ca ²⁺
Griffipavixanthone ^[164]	<i>Clusiaceae</i>	Thoracic aorta	Swiss mice	0.32–32 μ M	U4	NO-cGMP
Hexahydrocurcumin ^[205]	<i>Curcuma longa</i> L.	Thoracic aorta	Wistar rats	1 nM–1 mM	PE, KCl	Ca ²⁺ , VOCC
Hypogallic acid ^[112]	<i>Phyllanthus acidus</i> (L.) Skeels	Thoracic aorta	Wistar rats	1–10 mg/kg	PE	K _{ATP}
Isocalolongic acid ^[164]	<i>Calophyllum caledonicum</i> Vieill.	Thoracic aorta	Male Swiss mice (6–8 weeks)	0.25–25 mM	U46619	NO
Paeonol ^[213]	<i>Paeonia</i> $\times$ <i>suffruticosa</i> Andrews., <i>Cynanchum paniculatum</i> (Bunge) Kitag.	Renal artery, coronary artery	Hyperlipidemic model rats	0.251–10 mM	KCl	Ca ²⁺
Petasin ^[204]	<i>Petasites formosanus</i> Kitam.	Thoracic aorta	SD rat, Wistar rat, SHR	0.01–100 μ M	KCl	VOCC
Proanthocyanidins ^[214]	–	Mesenteric arterial bed, mesenteric artery	Wistar rats	1–100 μ g/mL	PE	NO-cGMP, Ca ²⁺

(Continued)

Table 6
(Continued)

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
Procyanidins ^[198]	<i>Malus pumila</i> Mill.	Thoracic aorta	SD rats	0.3–100 mg/mL	PE, KCl	NO-cGMP, K ⁺
Protocatechuic acid ^[215]	<i>Fagopyrum tataricum</i> (L.) Gaertn.	Thoracic aorta	SD rats	0.5–2.5 mg/mL	PE	–
Resveratrol ^[180]	<i>Rheum rhabarbarum</i> L.	Thoracic aorta	SD rats	1–30 μ M	PE	–
Salidroside ^[216]	<i>Rhodiola rosea</i> L.	Thoracic aorta	SD rat	10 ^{–5} –10 μ M	PE	COX-PGI ₂ , VDCC, ROCC
Thymol ^[201]	<i>Thymus vulgaris</i> L., <i>Origanum compactum</i> Benth., <i>Acalypha phleoides</i> Cav., <i>Species Lippia sidoides</i> Cham.	Thoracic aorta	Wistar rats, SHR	1–1,000 μ M	PE, KCl	–
Panthoangelol B ^[208]	<i>Angelica keiskei</i> (Miq.) Koidz.	Thoracic aorta	Wistar rats	10–100 μ g/mL	PE	Ca ²⁺
Xanthoangelol E ^[208]	<i>Angelica keiskei</i> (Miq.) Koidz.	Thoracic aorta	Wistar rats	10–100 μ g/mL	PE	EDRF-NO
Xanthoangelol F ^[208]	<i>Angelica keiskei</i> (Miq.) Koidz.	Thoracic aorta	Wistar rats	10–100 μ g/mL	PE	EDRF-NO
Xanthoangelol ^[208]	<i>Angelica keiskei</i> (Miq.) Koidz.	Thoracic aorta	Wistar rats	10–100 μ g/mL	PE	EDRF-NO
3,4-Dihydroxybenzaldehyde ^[76]	<i>Gastrodia elata</i> Bl.	Thoracic aorta	SD rats	0.1–10 μ M	PE	NO-cGMP
Piceatannol ^[180]	<i>Rheum rhabarbarum</i> L.	Thoracic aorta	SD rats	1–30 μ M	PE	NO
Vanillin ^[217]	–	Porcine coronary and basilar arteries	Pigs	1–10,000 μ M	U4, KCl	L-Type Ca ²⁺ Channels
Vanillin ^[12]	–	Porcine coronary	SD rats	0.1–1,000 μ M	U4	Akt-eNOS-NO
Vanillyl alcohol ^[217]	–	Porcine coronary and basilar arteries	Pigs	1–10,000 μ M	U4, KCl	L-Type Ca ²⁺ channels

BK_{Ca}, Large-conductance Ca²⁺-activated K⁺ channels; cGMP, Cyclic guanosine monophosphate; COX, Cyclooxygenase; EDHF, Endothelium-derived hyperpolarizing factor; EDRF, Endothelium-derived relaxing factor; eNOS, Endothelial nitric oxide synthase; GC, Guanylyl cyclase; K_{ATP}, ATP-sensitive K⁺ channels; MAPK, mitogen-activated protein kinase; MLC, Myosin light chain; MLCK, Myosin light chain kinase; NE, Norepinephrine; NO, Nitric oxide; NOS, nitric oxide synthase; PE, Phenylephrine; PGI₂, Prostacyclin; SHR, Spontaneously hypertensive rats; ROCC, Receptor-operated calcium channel; SD, Sprague-Dawley; VDCC, Voltage-dependent calcium channel; VOCC, Voltage-operated calcium channel. "–" indicates that the cited literature does not mention this content.

Other classes

The vascular modulatory repertoire of natural products extends beyond the confines of the classes of compounds described earlier. Gentiopicroside, an active glycoside common in herbs from the Gentianaceae family, can induce dose-dependent relaxation in intact and endothelium-denuded aortic rings *via* activation of K⁺ channels and inhibition of Ca²⁺ channels by suppressing the PI3K-Akt-Rho-kinase signaling pathway^[176]. Carnosine is an antioxidant dipeptide commonly found in dietary meat and endogenously produced from the amino acids L-histidine and beta-alanine. Both *in vitro* and *in vivo* studies have confirmed that it improves vascular oxidative states by decreasing ROS production and attenuating calcification in VSMC. A summary of the literature investigating the vasodilation effect of other classes of natural products is shown in Table 8.

Clinical applications

To evaluate the translational potential of the vasorelaxant compounds summarized in this review, a systematic search

of ClinicalTrials.gov was conducted using each compound name in combination with cardiovascular, endothelial, or vascular-related keywords (eg, “hypertension,” “endothelial dysfunction,” “cardiovascular disease”). Registered interventional studies with human participants were screened to identify clinical evaluation status, phases, and indications.

Data retrieved from ClinicalTrials.gov and summarized in Table 9 indicate that a considerable number of the natural compounds discussed in this review have advanced into Phase I–IV clinical trials. These trials primarily target cardiovascular-related conditions, including hypertension, atherosclerosis, ischemic stroke, heart failure, and endothelial dysfunction, thereby providing translational support for their vascular protective potential. For instance, puerarin has progressed to Phase II clinical evaluation for CVD risk factors, reflecting its recognized systemic vascular activity. Similarly, berberine, which has entered Phase IV studies for hypertension and endothelial dysfunction, represents a compound with accumulated post-marketing or late-stage clinical data supporting its cardiovascular application.

Table 7
Related pathways and mechanisms of natural phenolic acids with vasodilatory effects

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
ε-Viniferin ^[180]	<i>Rheum rhabarbarum</i> L.	Thoracic aorta	SD rats	1–30 μM	PE	–
(+)-Osbeckic acid ^[215]	<i>Fagopyrum tataricum</i> (L.) Gaertn.	Thoracic aorta	SD rats	0.5–2.5 mg/mL	PE	NO-cGMP
4-Hydroxybenzoic acid ^[112]	<i>Phyllanthus acidus</i> (L.) Skeels	Thoracic aorta	Wistar rats	1–10 mg/kg	PE	sGC pathway
Caffeic acid ^[112]	<i>Phyllanthus acidus</i> (L.) Skeels	Thoracic aorta	Wistar rats	1–10 mg/kg	PE	sGC pathway
Ethyl vanillin ^[217]	–	Porcine coronary arteries, porcine basilar arteries	Porcine	1–10,000 μM	U46619, KCl	Ca ²⁺
Ferulic acid ^[129]	–	Thoracic aorta	SD rats	0.1–1,000 μM	PE	–
Gallic acid ^[218]	–	Thoracic aorta	Wistar rats	0.3–10 mM	PE	NO/cGMP ^[218]
Isochlorogenic acid B ^[12]	–	Coronary arteries	SD rats	0.1–1,000 μM	U46619	NOS3 ^[12]
Isochlorogenic acid C ^[12]	–	Coronary arteries	SD rats	0.1–1,000 μM	U46619	NOS3 ^[12]

cGMP, Cyclic guanosine monophosphate; NO, Nitric oxide; PE, Phenylephrine; SD, Sprague-Dawley; sGC, Soluble guanylyl cyclase. “–” indicates that the cited literature does not mention this content.

In addition to clinical progression, issues related to physicochemical stability, bioavailability, and safety profiles are critical for translational development^[253]. Notably, only a subset of vasodilatory natural compounds identified in preclinical studies have advanced to clinical evaluation, with oral administration being the predominant delivery route. Therefore, while substantial experimental evidence supports their vascular activity, further systematic studies addressing long-term safety, dose optimization, stability enhancement, and controlled clinical validation are necessary to establish clear practical clinical significance.

Discussion

Accumulating experimental evidence indicates that primary phytochemical classes—specifically flavonoids, saponins, alkaloids, terpenoids, and phenols—exert potent vasodilatory effects. Current findings suggest that these natural compounds modulate vascular tone *via* integrated, multi-target signaling pathways; common mechanisms include anti-inflammatory and antioxidant activities, enhanced NO production, and ion channel regulation. This review delineates the therapeutic potential of natural vasodilators, elucidates their mechanisms of action, and proposes methodological strategies to enhance translational research value. By characterizing the interaction between phytochemicals and regulatory molecules, this review addresses the gap between experimental observations and established physiological mechanisms. This analysis clarifies how natural products may be utilized to manage CVDs requiring therapeutic vasodilation.

Regarding the analyzed flavonoids, primary mechanisms include the eNOS-NO-sGC-cGMP signaling axis, ion channel (Ca²⁺ and K⁺) modulation, and free radical scavenging. Increased cytosolic Ca²⁺ concentration represents the convergence point for diverse signaling pathways that trigger VSMC contraction. Therefore,

bioactive molecules that inhibit this rate-limiting step may facilitate vasodilation. A rise in cytosolic Ca²⁺ directly activates downstream signaling, ultimately modulating Ca²⁺ levels. Consequently, natural products such as tanshinone IIA and ligustilide, which modulate eNOS expression and inhibit Ca²⁺ channels, present unique opportunities for developing novel vasodilatory therapies. Through the development of multi-component formulations, natural products remain promising resources for innovative therapies, serving as either standalone treatments or adjuvants to conventional vasodilators.

The translational relevance of these molecular findings is corroborated by the clinical status of several representative phytochemicals. Various compounds discussed in this review, including flavonoids, saponins, alkaloids, and phenolic derivatives, have progressed to approved clinical use or entered Phase I–IV clinical trials for cardiovascular indications. These registered trials primarily target conditions such as hypertension, atherosclerosis, ischemic stroke, and endothelial dysfunction, providing a clinical context for the observed vasorelaxant effects. Notably, parenteral formulations predominate in late-phase clinical trials, likely reflecting strategies to mitigate the limited oral bioavailability and metabolic instability characteristic of natural compounds. In addition to their vasorelaxant potential, the stability, potential toxicity, and possible interactions of natural products with conventional antihypertensive drugs must be rigorously evaluated to ensure clinical applicability.

Despite these developments, most clinically utilized natural products are prescribed based on broad cardiovascular benefits rather than mechanism-oriented precision strategies derived from vascular signaling research. Early-phase trials largely emphasize safety and general cardioprotection, whereas endothelial-specific functional endpoints, pharmacokinetic optimization, and long-term toxicity assessments remain insufficiently characterized.

Table 8
Related pathways and mechanisms of other categories with vasodilatory effects

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
1-Nitro-2-phenylethane ^[224]	–	Thoracic aorta	Wistar rats	0.1–100 µg/mL	PE, KCl	Ca ²⁺
3-(3, 4-Dihydroxyphenyl)-2-hydroxypropanoate ^[225]	<i>Salvia miltiorrhiza</i> Bunge	Intestinal artery	SD rats	0.0001–30 µM	NE	Ca ²⁺
4,4'-Dihydroxydiphenyl methane ^[76]	<i>Gastrodia elata</i> Bl	Thoracic aorta	SD rats	0.3–3 mM	PE	Ca ²⁺
4-Hydroxy-3-(3-methyl-2-butenyl) acetophenone ^[226]	<i>Senecio nutans</i> Sch.Bip.	Thoracic aorta	SD rats	10 µM	PE	Ca ²⁺
5-Acetyl-6-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran ^[226]	<i>Senecio nutans</i> Sch.Bip.	Thoracic aorta	SD rats	10 µM	PE	Ca ²⁺
5-Hydroxymethyl-2-furoic acid ^[215]	<i>Fagopyrum tataricum</i> (L.) Gaertn.	Thoracic aorta	SD rats	0.5–2.5 mg/mL	PE	–
Adenosine ^[227]	–	Thoracic aorta	Wistar rats	0.1–300 mM	KCl, PE	Na ⁺ /K ⁺ -ATPase, K _{ATP} , A2A receptor
Adenosine ^[112]	<i>Phyllanthus acidus</i> (L.) Skeels	Thoracic aorta	Wistar rats	0.03–0.3 mg/kg	PE	K _{ATP} , A2A receptor
Arachidonic acid ^[228]	–	Thoracic aorta	New Zealand White rabbits	0.1–100 µM	PE	SKCa
Carnosine ^[229]	–	Descending thoracic aortic rings	SD rats	0.625–20 mM	U4	cGMP
Crambescin C1 ^[230]	<i>Crambe</i> L.	Aortic rings	Wistar rats	0.1–10 µM	PE	eNOS, iNOS
Piceatannol ^[180]	<i>Rheum rhubarbarum</i> L.	Thoracic aorta	SD rats	0–30 µM	PE	NO
Resveratrol ^[180]	<i>Rheum rhubarbarum</i> L.	Thoracic aorta	SD rats	0–30 µM	NO	NO
Sodium bisulfite and Sodium sulfite ^[231]	–	Thoracic aorta	Wistar rats	2–8 mM		Ca ²⁺ , PGI ₂
Docosahexaenoic ^[232]	–	Thoracic aorta	SHR	1–100 µM	KCl	Ca ²⁺ , K _{ATP}
Ethyl rosmarinat ^[233]	<i>Hyptis suaveolens</i> (L.) Poit.	Thoracic aorta	Wistar rats	0.1–3 mM	PE	Ca ²⁺
3-(1,3-Dioxoisindolin-2-yl) benzyl nitrate ^[234]	–	Thoracic aorta	Male Wistar rats	0.1–1,000 µM	PE	NO-eNOS
Heparin ^[235]	–	Thoracic aorta	Male Wistar rats	10–1,000 µM	NE	NO
Isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate ^[225]	<i>Salvia miltiorrhiza</i> Bunge	Mesenteric artery	Male SD rats	0.001–10 µM	NE	Vascular TEA sensitive K ⁺ , Ca ²⁺
Isotriumalin ^[236]	<i>Derris urucu</i> (Kilip and A.C.Sm.) J.F.Macbr.	Thoracic aorta	Wistar rats	0.01–100 µM	PE	Activate endothelial-derived NO
Phytoestrogen α-zearalano ^[237]	–	Thoracic aorta	Female Wistar rats	0.0001–10 µM	PE	NO-cGMP
Quercetin-3'-sulfate ^[110]	–	Thoracic aorta	Sprague–Dawley rats	1–32 µM	PE	NO-cGMP

(Continued)

Table 8
(Continued)

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
R-(+)-3'-hydroxy-2,4,5-trimethoxydalbergiquinol isolated ^[238]	<i>Dalbergia torokinensis</i> Prain	Thoracic aorta	Sprague–Dawley rats	1–100 µM	PE	Ca ²⁺
Shikonin/alkannin ^[239]	<i>Macrotomia euchromon</i> (Royle ex Benth.) Paulsen	Descending thoracic aorta	Wistar rats	0.001–10 µM	PE	NO
Taurine ^[240]	–	Thoracic aorta	Wistar rats	0–80 mM	PE	K ⁺
Tetramethylpyrazine ^[129]	–	Thoracic aorta	Sprague–Dawley rats	1–10,000 µM	PE	The SIRT1-dependent PGC-1α pathway, NO
Tetramethylpyrazine ^[12]	–	Porcine coronary	Sprague–Dawley rats	0.1–1,000 µM	U4	Akt-eNOS-NO
2-Nitrate-1,3-dioctanoxopropan ^[241]	–	Thoracic aorta	C57BL/6, Wistar rats	0.1–1,000 µM	PE	NO-cGMP-PKG, K _{ir}
3-Demethyl-2-geranyl-4-prenylbelidifoline ^[242]	<i>Garcinia hanbunyi</i> Hook. f.	Thoracic aorta	Male spontaneous hypertensive rats	0.1 nm–10 µM	PE	NO, K ⁺ channels
4-Hydroxy-3-(isopenten-2-yl)-acetophenoxime ^[243]	<i>Senecio nutans</i> Sch. Bip.	Thoracic aorta	Male Sprague–Dawley rats	0.001–100 µM	PE	Ca ²⁺
WX-02 ^[244]	–	Thoracic aorta	Rabbits	30–1,000 µM	KCl, NE	Ca ²⁺
Angelicide ^[12]	–	Porcine coronary	Sprague–Dawley rats	0.1–1,000 µM	U4	–
Butylphthalide ^[12]	–	Porcine coronary	Sprague–Dawley rats	0.1–1,000 µM	U4	–
Chenopodium ^[245]	<i>Chenopodium album</i> L.	Thoracic aorta	SD rat	1–300 mg/kg		NO
Corynoxene ^[194]	Uncariae Ramulus et Uncus	Thoracic aorta	Wistar rat	0.1–100 µM	NE	–
Dihydrotanshinone ^[246]	<i>Salvia miltiorrhiza</i> Bunge	Thoracic aorta	SD rat	0–100 µM	5-HT	NO-cGMP
Ent-18-hydroxy-trachyloban-3-one ^[174]	<i>Croton zambesicus</i> Müll. Arg.	Thoracic aorta	Wistar rat	1–3 µM	KCl	eNOS
Ent-trachyloban-14,15-dione ^[174]	<i>Croton zambesicus</i> Müll. Arg.	Thoracic aorta	Wistar rat	1–3 µM	KCl	Ca ²⁺
Esquamosan ^[247]	<i>Amora squamosa</i> L.	Thoracic aorta	Rat	0.1 nM–100 µM	KCl, PE	Ca ²⁺
Gastrodin ^[248]	<i>Gastrodia elata</i> Bl	Thoracic aorta	Wistar rat	5–250 µM	PE	Ca ²⁺
Geissoschizine methyl ether ^[194]	Uncariae Ramulus et Uncus	Thoracic aorta	Wistar rat	0.1–100 µM	NE	–
Gentipicroside ^[176]	<i>Gentiana straminea</i> Maxim.	Thoracic aorta	SD rat	5–320 µM	PE	PI3K-Akt-Rho Ca ²⁺
Korean plum ^[249]	<i>Prunus mume</i> (Siebold) Siebold and Zucc.	Thoracic aorta	SD rat	2–30 µg/mL	PE	K ⁺

(Continued)

Table 8
(Continued)

Compounds	Natural medicine	Vascular type	Species investigated	Dosage	Vasoconstrictor	Mechanisms
2-Hydroxy-4-methoxyvalerophenone ^[250]	<i>Paeonia suffruticosa</i> Andrews	Mesenteric artery	Wistar rat	0.001–1,000 µM	KCl, PE	K ⁺
RA ^[166]	<i>Phlomis bracteosa</i> Royle ex Benth.	Thoracic aorta	SD rat	3.0–10 µg/mL	PE	NO/cGMP
RB ^[166]	<i>Phlomis bracteosa</i> Royle ex Benth.	Thoracic aorta	SD rat	3.0–10 µg/mL	PE	NO/cGMP
Rumex acetosa ^[251]	<i>Rumex acetosa</i> L.	Thoracic aorta	SD rat	10–50 mg/kg	High K ⁺	Ca ²⁺
Tambulin ^[252]	<i>Zanthoxylum armatum</i> DC.	Coronary artery	Pig	1–10 µM	U4	cAMP, cGMP

cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; eNOS, Endothelial nitric oxide synthase; iNOS, Inducible nitric oxide synthase; K_{ATP}, ATP-sensitive K⁺; NE, Norepinephrine; NO, Nitric oxide; PE, Phenylephrine; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-α; PKG, Protein kinase G; PKG, Protein kinase G; SHR, Spontaneously hypertensive rats; SD, Sprague-Dawley; SIRT1, Sirtuin 1; SKCa, Small-conductance Ca²⁺-activated K⁺ channels; TEA, Tetraethylammonium. "—" indicates that the cited literature does not mention this content.

These observations highlight a persistent translational gap between detailed mechanistic investigations and rigorously designed, pathway-driven clinical validation. Future studies integrating standardized pharmacological evaluation, validated endothelial biomarkers, and mechanism-specific outcome measures are essential to establish clear therapeutic positioning and clinical significance for natural product-derived vasodilators.

Most experimental studies typically employ traditional drug-screening approaches, focusing on a single compound and performing multiple assays to elucidate its mechanism of action. This methodology is often time-consuming and inefficient. The evidence presented in this review suggests that many naturally occurring bioactive compounds exert their vasodilatory effects through multiple mechanisms of action. Consequently, more comprehensive screening approaches are required to fully elucidate these potential mechanisms. By applying computational tools—such as molecular docking, molecular dynamics, and machine learning-driven screening models—large libraries of natural compounds can be efficiently screened for vasodilatory activity. Artificial intelligence algorithms trained on experimental data can identify relationships between protein targets involved in vasodilation and various influencing factors, thereby constructing a virtual drug-screening ecosystem. This approach facilitates the efficient screening of natural products, reducing the temporal and material resources required for wet experiments.

In summary, the diverse pharmacological properties of natural products and the emergence of computational tools have not only provided tools to elucidate other possible vasodilatory mechanisms of natural products but also techniques to develop innovative vasodilation therapies in the management of CVDs.

Conclusions and prospects

Natural products provide distinct advantages in cardiovascular therapy due to their multi-target and multi-pathway pharmacological profiles. Flavonoids, saponins, phenylpropanoids, terpenoids, phenols, phenolic acids, and alkaloids constitute the primary active constituents with well-documented vasodilatory effects. Their mechanisms of action involve various bioactive substances in ECs and the modulation of Ca²⁺ concentrations in VSMCs. These pathways include stimulating the production of vasodilatory factors (NO and PGI₂), activating K⁺ channels (K_v, BK_{Ca}, K_{ATP}, and K_{IR}), and inhibiting VOC, ROC, and SOC Ca²⁺ channels. Additionally, increasing the activity of myosin dephosphorylation enzymes (such as MLCP), inhibiting the RAAS, protecting eNOS activity, and mitigating oxidative stress are critical vasodilatory mechanisms.

Numerous natural products demonstrate potent vasodilatory activity and favorable safety profiles, providing promising therapeutic options for patients with CVD. Notably, several compounds have progressed into Phase I–IV clinical trials, supporting their translational potential. However, limitations related to bioavailability, long-term safety, and mechanism-specific clinical endpoints must be addressed. This review systematically

Table 9
Clinical research progress of natural compounds for vasodilation

Compound	NCT number	Clinical phase	Pharmacological activities	Administration
Daidzein	NCT00118846	Phase II	Atherosclerosis	Oral
Genistein	NCT06501768	Phase II/III	Heart failure	Oral
Puerarin	NCT03676296	Phase II	Cardiovascular disease risk factors	Oral
Rutin	NCT06579482	Phase IV	Chronic venous insufficiency	Oral
Silymarin	NCT06114719	Phase III	Atrial fibrillation new onset	Oral
Tetramethylpyrazine	NCT05942352	Phase IV	Alcohol addiction, Arteriosclerosis	Intravenous, Oral
Berberine	NCT04790942	Phase IV	Hypertension, endothelial dysfunction, blood pressure	Oral
Ginsenoside Rd	NCT00815763	Phase II	Ischemic stroke	Oral
Borneol	NCT03495206	Phase I	Stroke, acute intracranial hemorrhages	Oral
Gastrodin	NCT04035824	Phase IV	Hypertension	Oral
Anthocyanins	NCT05995002	Phase I/II	Coronary artery stenosis	Oral
Proanthocyanidins	NCT01688154	Phase I/II	Cardiovascular function	Oral
Procyanidins	NCT06422741	Phase I	Cardiovascular protection	Oral
Resveratrol	NCT03762096	Phase I/II	Coronary artery disease	Oral
Epigallocatechin Gallate	NCT01923597	Phase II	Hypertension	Oral
Butylphthalide	NCT03413202	Phase IV	Acute ischemic stroke	Oral
Carnosine	NCT02917928	Phase II	Cardiovascular risk factors	Oral

evaluates the pharmacology and vasodilatory efficacy of more than 200 medicinal plants and their bioactive constituents on the cardiovascular system while providing an in-depth analysis of their mechanisms of action. These insights offer innovative research methods and precise treatment strategies for the development and clinical application of natural products for patients with CVD.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This study was supported by the National Key R&D Program of China (2022YFC3501800, 2024YFC3505104), National Natural Science Foundation of China (No. 82474310), and Key Laboratory of Chinese Medicinal Resource and Chinese Herbal Compound of the Ministry of Education Funding (KF2024001).

Author contributions

Aomei Sun contributed to data curation, formal analysis, writing-original draft, writing-review and editing. Opoku Bonsu Francis contributed to writing-original draft, writing-review and editing, data curation. Shutong Yan and Jing Wang contributed to investigation, writing-original draft. Haoshuang Zhao investigated and wrote the article. Ling Leng, Ruiqiao Li, and Hongtao Liu contributed to writing-review and editing. Xiaoxuan Tian and Dake Qi contributed to supervision, writing-review & editing. Qilong Wang contributed to funding acquisition, supervision, writing-review & editing.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

Data availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Declaration of Generative AI in Scientific Writing

The conception and writing of this article were completed by all authors. ChatGPT was used to polish the sentence coherence and revise punctuation. All references in this section were manually searched and inserted. After using the above tools, the authors have reviewed and revised the content as needed and take full responsibility for the content of this publication.

References

[1] Christodoulou A, Nikolaou PE, Symeonidi L, et al. Cardioprotective potential of oleuropein, hydroxytyrosol, oleocanthal and their combination: unravelling complementary effects on acute myocardial infarction and metabolic syndrome. *Redox Biol* 2024;76:103311.

[2] Ran Q, Li A, Tan Y, et al. Action and therapeutic targets of myosin light chain kinase, an important cardiovascular signaling mechanism. *Pharmacol Res* 2024;206:107276.

[3] Yan Z, Zhong L, Zhu W, et al. Chinese herbal medicine for the treatment of cardiovascular diseases—targeting cardiac ion channels. *Pharmacol Res* 2023;192:106765.

[4] Kleeberg A, Luft T, Golkowski D, et al. Endothelial dysfunction in acute ischemic stroke: a review. *J Neurol* 2025;272(2):143.

[5] Okazaki RA, Rizvi SH, Lyons R, et al. Vascular dysfunction in diabetes and pharmacotherapeutic opportunities: a focus

- on endothelial cell health. *Am J Physiol Heart Circ Physiol* 2025;329(3):H705–H718.
- [6] Lukoschewitz JD, Miger KC, Olesen ASO, et al. Vasodilators for acute heart failure—a systematic review with meta-analysis. *NEJM Evid* 2024;3(6):EVIDOa2300335.
 - [7] Zhong C, Deng K, Lang X, et al. Therapeutic potential of natural flavonoids in atherosclerosis through endothelium-protective mechanisms: an update. *Pharmacol Ther* 2025;271:108864.
 - [8] Huang Y, Ye Q, Tian Y, et al. Choerospindias axillaris: a review of its clinical application, phytochemistry, and an investigation into its potential cardiovascular therapy. *Acupunct Herb Med* 2025;5(2):246–269.
 - [9] Li Y, Xiang Y, Liang J, et al. The mechanism and treatment strategies of GSDMD-mediated pyroptosis in myocardial infarction. *Acupunct Herb Med* 2024;4(3):295–305.
 - [10] Luo B, Wang W, Li Y, et al. Tetramethylpyrazine attenuates chronic intermittent hypoxia-exacerbated diabetic atherosclerosis: a mechanistic study of the IRE1 α -XBP1 signaling pathway. *Acupunct Herb Med* 2025;5(2):160–172.
 - [11] Sabando C, Rodríguez-Díaz M, Ide W, et al. Improvement of endothelial function by Gunnera tinctoria extract with antioxidant properties. *Biol Res* 2020;53(1):55.
 - [12] Li S, Zhan J, Wang Y, et al. Suxiao Jixun Pill attenuates acute myocardial ischemia via regulation of coronary artery tone. *Front Pharmacol* 2023;14:1104243.
 - [13] Arrigo E, Comità S, Pagliaro P, et al. Clinical applications for gasotransmitters in the cardiovascular system: are we there yet? *Int J Mol Sci* 2023;24(15):12480.
 - [14] Vu GH, Kim CS. Redox regulation of endogenous gasotransmitters in vascular health and disease. *Int J Mol Sci* 2025;26(18):9037.
 - [15] Behringer EJ. Impact of aging on vascular ion channels: perspectives and knowledge gaps across major organ systems. *Am J Physiol Heart Circ Physiol* 2023;325(5):H1012–H1038.
 - [16] Ning X, Zhu X, Wang Y, et al. Recent advances in carbon monoxide-releasing nanomaterials. *Bioact Mater* 2024;37:30–50.
 - [17] Siracusa R, Voltarelli VA, Salinaro AT, et al. NO, CO and H₂S: a trinacrium of bioactive gases in the brain. *Biochem Pharmacol* 2022;202:115122.
 - [18] Cesarini V, Guida E, Campolo F, et al. Type 5 phosphodiesterase (PDE5) and the vascular tree: from embryogenesis to aging and disease. *Mech Ageing Dev* 2020;190:111311.
 - [19] Liu XY, Qian LL, Wang RX. Hydrogen sulfide-induced vasodilation: the involvement of vascular potassium channels. *Front Pharmacol* 2022;13:911704.
 - [20] Munteanu C, Popescu C, Vlădulescu-Trandafir AI, et al. Signaling paradigms of H₂S-induced vasodilation: a comprehensive review. *Antioxidants (Basel)* 2024;13(10):1158.
 - [21] Bootman MD, Bultynck G. Fundamentals of cellular calcium signaling: a primer. *Cold Spring Harbor Perspect Biol* 2020;12(1):a038802.
 - [22] Teng X, Li H, Xue H, et al. GABA_A receptor, KATP channel and L-type Ca²⁺ channel is associated with facilitation effect of H₂S on the baroreceptor reflex in spontaneous hypertensive rats. *Pharmacol Rep* 2019;71(5):968–975.
 - [23] Wang JJ, Jin S, Zhang H, et al. Molecular recognition and activation of the prostacyclin receptor by anti-pulmonary arterial hypertension drugs. *Sci Adv* 2024;10(6):eadk5184.
 - [24] Liu L, Guo M, Lv X, et al. Role of transient receptor potential vanilloid 4 in vascular function. *Front Mol Biosci* 2021;8:677661.
 - [25] Rajabian A, Rajabian F, Babaei F, et al. Interaction of medicinal plants and their active constituents with potassium ion channels: a systematic review. *Front Pharmacol* 2022;13:831963.
 - [26] Jiang S, Han S, Wang DW. The involvement of soluble epoxide hydrolase in the development of cardiovascular diseases through epoxyeicosatrienoic acids. *Front Pharmacol* 2024;15:1358256.
 - [27] Johnson KA, Jeffery E, Bray JF, et al. Exercise training rescues impaired H₂O₂-mediated vasodilation in porcine collateral-dependent coronary arterioles through enhanced K⁺ channel activation. *Am J Physiol Heart Circ Physiol* 2023;324(5):H637–H653.
 - [28] Zhang Y, Wernly B, Cao X, et al. Adenosine and adenosine receptor-mediated action in coronary microcirculation. *Basic Res Cardiol* 2021;116(1):22.
 - [29] Qian Y, Zheng Y, Leng L, et al. Adenosine and adenosine receptors: a “double-edged sword” in cardiovascular system. *Front Pharmacol* 2025;16:1538680.
 - [30] Solanki N, Dodiya R, Vejpara D, et al. Adenosine receptor subtype modulators: Insight into molecular mechanisms and their therapeutic application. *Am J Transl Res* 2025;17(4):2376–2395.
 - [31] Chapman FA, Maguire JJ, Newby DE, et al. Targeting the apelin system for the treatment of cardiovascular diseases. *Cardiovasc Res* 2023;119(17):2683–2696.
 - [32] Gao Z, Zhong X, Tan YX, et al. Apelin-13 alleviates diabetic nephropathy by enhancing nitric oxide production and suppressing kidney tissue fibrosis. *Int J Mol Med* 2021;48(3):175.
 - [33] Robillard S, Trần K, Lachance MS, et al. Apelin prevents diabetes-induced poor collateral vessel formation and blood flow reperfusion in ischemic limb. *Front Cardiovasc Med* 2023;10:1191891.
 - [34] Lu J, Piper SJ, Zhao P, et al. Targeting VIP and PACAP receptor signaling: new insights into designing drugs for the PACAP subfamily of receptors. *Int J Mol Sci* 2022;23(15):8069.
 - [35] Argunhan F, Thapa D, Aubdool AA, et al. Calcitonin gene-related peptide protects against cardiovascular dysfunction independently of nitric oxide *in vivo*. *Hypertension* 2021;77(4):1178–1190.
 - [36] Argunhan F, Brain SD. The vascular-dependent and -independent actions of calcitonin gene-related peptide in cardiovascular disease. *Front Physiol* 2022;13:833645.
 - [37] Russo AF, Hay DL. CGRP physiology, pharmacology, and therapeutic targets: migraine and beyond. *Physiol Rev* 2023;103(2):1565–1644.
 - [38] de Vries T, Labrujere S, Rivera-Mancilla E, et al. Intracellular pathways of calcitonin gene-related peptide-induced relaxation of human coronary arteries: a key role for G $\beta\gamma$ subunit instead of cAMP. *Br J Pharmacol* 2024;181(15):2478–2491.
 - [39] Clement A, Christensen SL, Jansen-Olesen I, et al. The ATP sensitive potassium channel (KATP) is a novel target for migraine drug development. *Front Mol Neurosci* 2023;16:1182515.
 - [40] Coskun H, Elbahi FA, Al-Karaghli MAM, et al. The effect of K ATP channel blocker glibenclamide on CGRP-induced headache and hemodynamic in healthy volunteers. *Front Physiol* 2021;12:652136.
 - [41] Wang HY, Wang FZ, Chang R, et al. Adrenomedullin improves hypertension and vascular remodeling partly through the receptor-mediated AMPK pathway in rats with obesity-related hypertension. *Int J Mol Sci* 2023;24(4):3943.
 - [42] Bálint L, Nelson-Maney NP, Tian Y, et al. Clinical potential of adrenomedullin signaling in the cardiovascular system. *Circ Res* 2023;132(9):1185–1202.
 - [43] Ross GR, Yallampalli C. Endothelium-independent relaxation by adrenomedullin in pregnant rat mesenteric artery: role of cAMP-dependent protein kinase A and calcium-activated potassium channels. *J Pharmacol Exp Ther* 2006;317(3):1269–1275.
 - [44] Spoto S, Basili S, Cangemi R, et al. A focus on the pathophysiology of adrenomedullin expression: endothelitis and organ damage in severe viral and bacterial infections. *Cells* 2024;13(11):892.
 - [45] Dai C, Khalil RA. Calcium signaling dynamics in vascular cells and their dysregulation in vascular disease. *Biomolecules* 2025;15(6):892.
 - [46] Lu T, Zhang Y, Su Y, et al. Role of store-operated Ca²⁺ entry in cardiovascular disease. *Cell Commun Signal* 2022;20(1):33.
 - [47] Pereira da Silva EA, Martín-Aragón Baudel M, Navedo ME, et al. Ion channel molecular complexes in vascular smooth muscle. *Front Physiol* 2022;13:999369.
 - [48] Mironova GY, Haghbin N, Welsh DG. Functional tuning of vascular L-type Ca²⁺ channels. *Front Physiol* 2022;13:1058744.
 - [49] Woll KA, Van Petegem F. Calcium-release channels: structure and function of IP₃ receptors and ryanodine receptors. *Physiol Rev* 2022;102(1):209–268.
 - [50] Sun Z, Li Z, Rodgers M, et al. Myosin light chain phosphorylation exhibits a gradient across the wall of cerebellar arteries under sustained ex vivo vascular tone. *Sci Rep* 2023;13(1):909.
 - [51] Chen YC, Shih CL, Wu CL, et al. Exploring the impact of BKCa channel function in cellular membranes on cardiac electrical activity. *Int J Mol Sci* 2024;25(3):1537.
 - [52] Sung MW, Yang Z, Driggers CM, et al. Vascular KATP channel structural dynamics reveal regulatory mechanism by Mg-nucleotides. *Proc Natl Acad Sci USA* 2021;118(44):e2109441118.
 - [53] Li C, Yang Y. Advancements in the study of inward rectifying potassium channels on vascular cells. *Channels (Austin)* 2023;17(1):2237303.
 - [54] Maranduca MA, Tanase DM, Cozma CT, et al. The impact of angiotensin-converting enzyme-2/angiotensin 1–7 axis in establishing severe COVID-19 consequences. *Pharmaceutics* 2022;14(9):1906.
 - [55] Miller AJ, Arnold AC. The renin-angiotensin system and cardiovascular autonomic control in aging. *Peptides* 2022;150:170733.
 - [56] Johnstone E KM, Ayoub MA, Hertzman RJ, et al. Novel pharmacology following heteromerization of the angiotensin II type 2 receptor and the bradykinin type 2 receptor. *Front Endocrinol* 2022;13:848816.
 - [57] Steckelings UM, Widdop RE, Sturrock ED, et al. The angiotensin AT₂ receptor: from a binding site to a novel therapeutic target. *Pharmacol Rev* 2022;74(4):1051–1135.

- [58] Brunetti V, Berra-Romani R, Conca F, et al. Lysosomal TRPML1 triggers global Ca^{2+} signals and nitric oxide release in human cerebrovascular endothelial cells. *Front Physiol* 2024;15:1426783.
- [59] Lin Q, Zhao L, Jing R, et al. Inositol 1,4,5-trisphosphate receptors in endothelial cells play an essential role in vasodilation and blood pressure regulation. *J Am Heart Assoc* 2019;8(4):e011704.
- [60] Janaszak-Jasiecka A, Ploska A, Wierońska JM, et al. Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. *Cell Mol Biol Lett* 2023;28(1):21.
- [61] Penna C, Pagliaro P. Endothelial dysfunction: redox imbalance, NLRP3 inflammasome, and inflammatory responses in cardiovascular diseases. *Antioxidants (Basel)* 2025;14(3):256.
- [62] Zhang W, Sun Y, Yang Y, et al. Impaired intracellular calcium homeostasis enhances protein O-GlcNAcylation and promotes vascular calcification and stiffness in diabetes. *Redox Biol* 2023;63:102720.
- [63] Huang F, Zhang F, Huang L, et al. Inositol 1,4,5-trisphosphate receptors regulate vascular smooth muscle cell proliferation and neointima formation in mice. *J Am Heart Assoc* 2024;13(15):e034203.
- [64] Pourová J, Dias P, Pour M, et al. The machinery of healthy vasodilation: an overview. *Pflugers Arch* 2025;477(9):1135–1162.
- [65] Wang H, Li J, Wang Z, et al. Perivascular brown adipocytes-derived kynurenic acid relaxes blood vessel via endothelium PI3K-Akt-eNOS pathway. *Biomed Pharmacother* 2022;150:113040.
- [66] Li J, Wang S, Jin E, et al. Norisoboldine induces endothelium-dependent vasorelaxation and attenuates hypertension by modulating Ca^{2+} -eNOS signaling, oxidative stress, and inflammation. *Antioxidants (Basel)* 2026;15(1):131.
- [67] Angulo-Urarte A, Casado P, Castillo SD, et al. Endothelial cell rearrangements during vascular patterning require PI3-kinase-mediated inhibition of actomyosin contractility. *Nat Commun* 2018;9(1):4826.
- [68] Guan G, Cannon RD, Coates DE, et al. Effect of the rho-kinase/ROCK signaling pathway on cytoskeleton components. *Genes* 2023;14(2):272.
- [69] Lorigo M, Oliveira N, Cairrao E. PDE-mediated cyclic nucleotide compartmentation in vascular smooth muscle cells: from basic to a clinical perspective. *J Cardiovasc Dev Dis* 2021;9(1):4.
- [70] Niloy SI, Shen Y, Guo L, et al. Loss of IP3R-BKCa coupling is involved in vascular remodeling in spontaneously hypertensive rats. *Int J Mol Sci* 2023;24(13):10903.
- [71] Suzuki Y, Giles WR, Zamponi GW, et al. Ca^{2+} signaling in vascular smooth muscle and endothelial cells in blood vessel remodeling: a review. *Inflamm Regen* 2024;44(1):50.
- [72] Chan EC, Pannangpetch P, Woodman OL. Relaxation to flavones and flavonols in rat isolated thoracic aorta: mechanism of action and structure-activity relationships. *J Cardiovasc Pharmacol* 2000;35(2):326–333.
- [73] Woodman OL, Chan EC. Vascular and anti-oxidant actions of flavonols and flavones. *Clin Exp Pharmacol Physiol* 2004;31(11):786–790.
- [74] Tan CS, Yam MF. Mechanism of vasorelaxation induced by 3'-hydroxy-5,6,7,4'-tetramethoxyflavone in the rats aortic ring assay. *Naunyn Schmiedeberg Arch Pharmacol* 2018;391(6):561–569.
- [75] Bertin R, Chen Z, Martínez-Vázquez M, et al. Vasodilation and radical-scavenging activity of imperatorin and selected coumarinic and flavonoid compounds from genus *Casimiroa*. *Phytomedicine* 2014;21(5):586–594.
- [76] Dai R, Wang T, Si X, et al. Vasodilatory effects and underlying mechanisms of the ethyl acetate extracts from *Gastrodia elata*. *Can J Physiol Pharmacol* 2017;95(5):564–571.
- [77] Cheng YW, Li CH, Lee CC, et al. Alpha-naphthoflavone induces vasorelaxation through the induction of extracellular calcium influx and NO formation in endothelium. *Naunyn Schmiedeberg Arch Pharmacol* 2003;368(5):377–385.
- [78] Li Y, Dang Q, Li Z, et al. Restoration of mitochondrial function is essential in the endothelium-dependent vasodilation induced by acacetin in hypertensive rats. *Int J Mol Sci* 2022;23(19):11350.
- [79] Wang ZT, Lau CW, Chan FL, et al. Vasorelaxant effects of cardamonin and alpinetin from *Alpinia henryi* K. Schum. *J Cardiovasc Pharmacol* 2001;37(5):596–606.
- [80] Kang DG, Yin MH, Oh H, et al. Vasorelaxation by ameto-flavone isolated from *Selaginella tamariscina*. *Planta Med* 2004;70(8):718–722.
- [81] Zhang YH, Park YS, Kim TJ, et al. Endothelium-dependent vasorelaxant and antiproliferative effects of apigenin. *Gen Pharmacol* 2000;35(6):341–347.
- [82] Ma X, Li YF, Gao Q, et al. Inhibition of superoxide anion-mediated impairment of endothelium by treatment with luteolin and apigenin in rat mesenteric artery. *Life Sci* 2008;83(3–4):110–117.
- [83] Calderone V, Chericoni S, Martinelli C, et al. Vasorelaxing effects of flavonoids: investigation on the possible involvement of potassium channels. *Naunyn Schmiedeberg Arch Pharmacol* 2004;370(4):290–298.
- [84] Ma X, He D, Ru X, et al. Apigenin, a plant-derived flavone, activates transient receptor potential vanilloid 4 cation channel. *Br J Pharmacol* 2012;166(1):349–358.
- [85] Jin BH, Qian LB, Chen S, et al. Apigenin protects endothelium-dependent relaxation of rat aorta against oxidative stress. *Eur J Pharmacol* 2009;616(1–3):200–205.
- [86] Guerrero MF, Puebla P, Carrón R, et al. Quercetin 3,7-dimethyl ether: a vasorelaxant flavonoid isolated from *Croton schiedeana* Schlecht. *J Pharm Pharmacol* 2002;54(10):1373–1378.
- [87] Huang Y, Tsang SY, Yao X, et al. Baicalin-induced vascular response in rat mesenteric artery: role of endothelial nitric oxide. *Clin Exp Pharmacol Physiol* 2002;29(8):721–724.
- [88] Kumar T, Sharma M, Rana A, et al. Biochanin-A elicits relaxation in coronary artery of goat through different mechanisms. *Res Vet Sci* 2020;131:206–214.
- [89] Wu XL, Wang YY, Cheng J, et al. Calcium channel blocking activity of calycosin, a major active component of *Astragalus Radix*, on rat aorta. *Acta Pharmacol Sin* 2006;27(8):1007–1012.
- [90] Duarte J, Jiménez R, Villar IC, et al. Vasorelaxant effects of the bioflavonoid chrysin in isolated rat aorta. *Planta Med* 2001;67(6):567–569.
- [91] Tew WY, Tan CS, Yan CS, et al. Evaluation of vasodilatory effect and antihypertensive effect of chrysin through in vitro and subchronic in vivo study. *Biomed Pharmacother* 2023;157:114020.
- [92] Villar IC, Vera R, Galisteo M, et al. Endothelial nitric oxide production stimulated by the bioflavonoid chrysin in rat isolated aorta. *Planta Med* 2005;71(9):829–834.
- [93] Deng Y, Ng ESK, Yeung JHK, et al. Mechanisms of the cerebral vasodilator actions of isoflavonoids of *Gegen* on rat isolated basilar artery. *J Ethnopharmacol* 2012;139(1):294–304.
- [94] Avila-Villarreal G, Hernández-Abreu O, Hidalgo-Figueroa S, et al. Antihypertensive and vasorelaxant effects of dihydrospinochalcone-A isolated from *Lonchocarpus xuul* Lundell by NO production: computational and ex vivo approaches. *Phytomedicine* 2013;20(14):1241–1246.
- [95] Trigueiro F, Cortes SE, Almeida RN, et al. Endothelium-independent vasorelaxant effect of diocleins, a new flavonoid isolated from *Dioclea grandiflora*, in the rat aorta. *J Pharm Pharmacol* 2000;52(11):1431–1434.
- [96] Ahmad T, Shah AJ, Khan T, et al. Mechanism underlying the vasodilation induced by diosmetin in porcine coronary artery. *Eur J Pharmacol* 2020;884:173400.
- [97] Yam MF, Tan CS, Ahmad M, et al. Mechanism of vasorelaxation induced by eupatorin in the rats aortic ring. *Eur J Pharmacol* 2016;789:27–36.
- [98] Qin X, Hou X, Zhang M, et al. Relaxation of rat aorta by farrelor correlates with potency to reduce intracellular calcium of VSMCs. *Int J Mol Sci* 2014;15(4):6641–6656.
- [99] Lemos VS, Côrtes SE, dos Santos MH, et al. Structure and vasorelaxant activity of floranol, a flavonoid isolated from the roots of *Dioclea grandiflora*. *Chem Biodivers* 2006;3(6):635–645.
- [100] Zhao Y, Chen BN, Wang SB, et al. Vasorelaxant effect of formononetin in the rat thoracic aorta and its mechanisms. *J Asian Nat Prod Res* 2012;14(1):46–54.
- [101] Xiang Q, Huang Y, Xu J. Effects of phytoestrogen genistein on isolated thoracic aorta function of rats. *Chin J Geriatr Heart Brain Vessel Dis* 2008;10(8):617–619.
- [102] Xie YW, Ming DS, Xu HX, et al. Vasorelaxing effects of *Caesalpinia sappan* involvement of endogenous nitric oxide. *Life Sci* 2000;67(15):1913–1918.
- [103] Yu DJ, Jun JH, Kim TJ, et al. The relaxing effect of *Poncirus fructus* and its flavonoid content on porcine coronary artery. *Lab Anim Res* 2015;31(1):33–39.
- [104] Orallo F, Alvarez E, Basaran H, et al. Comparative study of the vasorelaxant activity, superoxide-scavenging ability and cyclic nucleotide phosphodiesterase-inhibitory effects of hesperetin and hesperidin. *Naunyn Schmiedeberg Arch Pharmacol* 2004;370(6):452–463.
- [105] Zhou Y, Wang L, Liu Y, et al. Homoplantaginins attenuates high glucose-induced vascular endothelial dysfunction via inhibiting store-operated calcium entry channel and endoplasmic reticulum stress. *J Pharm Pharmacol* 2023;75(12):1530–1543.

- [106] Ding L, Chen Z, Guo Y. Vasodilatation and mechanism of hyperin on rat cerebral basilar artery. *Acta Univ Med Anhui* 2016;51(11):1625–1629.
- [107] Wang Q, Chen Z. Study on the relaxing effect and mechanism of hyperoside on isolated rat abdominal aorta. *Chin Tradit Herb Drugs* 2010;41(5):766–770.
- [108] Xu HB, Huang ZQ. Vasorelaxant effects of icariin on isolated canine coronary artery. *J Cardiovasc Pharmacol* 2007;49(4):207–213.
- [109] Demirel S, Sahinturk S, Isbil N, et al. Physiological role of K⁺ channels in irisin-induced vasodilation in rat thoracic aorta. *Peptides* 2022;147:170685.
- [110] Lodi F, Jimenez R, Moreno L, et al. Glucuronidated and sulfated metabolites of the flavonoid quercetin prevent endothelial dysfunction but lack direct vasorelaxant effects in rat aorta. *Atherosclerosis* 2009;204(1):34–39.
- [111] Xu YC, Yeung DKY, Man RYK, et al. Kaempferol enhances endothelium-independent and dependent relaxation in the porcine coronary artery. *Mol Cell Biochem* 2006;287(1–2):61–67.
- [112] Leeya Y, Mulvany MJ, Queiroz EF, et al. Hypotensive activity of an n-butanol extract and their purified compounds from leaves of *Phyllanthus acidus* (L.) Skeels in rats. *Eur J Pharmacol* 2010;649(1–3):301–313.
- [113] Jiang H, Xia Q, Wang X, et al. Luteolin induces vasorelaxation in rat thoracic aorta *via* calcium and potassium channels. *Die Pharmazie* 2005;60(6):444–447.
- [114] Sun YH, Zhao J, Jin HT, et al. Vasorelaxant effects of the extracts and some flavonoids from the buds of *Coreopsis tinctoria*. *Pharm Biol* 2013;51(9):1158–1164.
- [115] Si H, Wyeth RP, Liu D. The flavonoid luteolin induces nitric oxide production and arterial relaxation. *Eur J Nutr* 2014;53(1):269–275.
- [116] Qian LB, Wang HP, Chen Y, et al. Luteolin reduces high glucose-mediated impairment of endothelium-dependent relaxation in rat aorta by reducing oxidative stress. *Pharmacol Res* 2010;61(4):281–287.
- [117] Orallo F, Camiña M, Alvarez E, et al. Implication of cyclic nucleotide phosphodiesterase inhibition in the vasorelaxant activity of the citrus-fruits flavonoid (+/-)-naringenin. *Planta Med* 2005;71(2):99–107.
- [118] Wong ESW, Li RWS, Li J, et al. Relaxation effect of narirutin on rat mesenteric arteries *via* nitric oxide release and activation of voltage-gated potassium channels. *Eur J Pharmacol* 2021;905:174190.
- [119] Yang W, Li S, Liao L, et al. Nobiletin relaxes isolated mesenteric arteries by activating the endothelial Ca²⁺-eNOS pathway in rats. *J Vasc Res* 2016;53(5–6):330–339.
- [120] Fu XC, Wang MW, Li SP, et al. Vasodilatation produced by orientin and its mechanism study. *Biol Pharm Bull* 2005;28(1):37–41.
- [121] Zhu XM, Fang LH, Li YJ, et al. Endothelium-dependent and -independent relaxation induced by pinocembrin in rat aortic rings. *Vascul Pharmacol* 2007;46(3):160–165.
- [122] Novakovic A, Marinko M, Jankovic G, et al. Endothelium-dependent vasorelaxant effect of procyanidin B2 on human internal mammary artery. *Eur J Pharmacol* 2017;807:75–81.
- [123] Ibarra M, Moreno L, Vera R, et al. Effects of the flavonoid quercetin and its methylated metabolite isorhamnetin in isolated arteries from spontaneously hypertensive rats. *Planta Med* 2003;69(11):995–1000.
- [124] Fusi F, Saponara S, Pessina F, et al. Effects of quercetin and rutin on vascular preparations: a comparison between mechanical and electrophysiological phenomena. *Eur J Nutr* 2003;42(1):10–17.
- [125] Zhou XM, Yao H, Xia ML, et al. Comparison of vasodilatation effect between quercetin and rutin in the isolated rat thoracic aorta. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2006;35(1):29–33.
- [126] Xia ML, Zhou XM, Yao H, et al. Rutin-induced endothelium-dependent vasorelaxation in rat aortic rings and the underlying mechanism. *Conf Proc IEEE Eng Med Biol Soc* 2005;2005:5595–5597.
- [127] Pan Z, Feng T, Shan L, et al. Scutellarin-induced endothelium-independent relaxation in rat aorta. *Phytother Res* 2008;22(11):1428–1433.
- [128] Chen YJ, Chen C, Li MY, et al. Scutellarin reduces cerebral ischemia reperfusion injury involving in vascular endothelium protection and PKG signal. *Nat Prod Bioprospect* 2021;11(6):659–670.
- [129] Xu Q, Xia P, Li X, et al. Tetramethylpyrazine ameliorates high glucose-induced endothelial dysfunction by increasing mitochondrial biogenesis. *PLoS One* 2014;9(2):e88243.
- [130] Zhang L, Ling S, Chen G, et al. Vasodilatory and anti-inflammatory mechanisms of extracts of *chrysanthemum indicum*. *Shanghai J Tradit Chin Med* 2009;43(5):60–63.
- [131] Mendes A, Desgranges C, Chèze C, et al. Vasorelaxant effects of grape polyphenols in rat isolated aorta. Possible involvement of a purinergic pathway. *Fundam Clin Pharmacol* 2003;17(6):673–681.
- [132] Unemoto T, Honda H, Kogo H. Differences in the mechanisms for relaxation of aorta induced by 17beta-estradiol or progesterone between normotensive and hypertensive rats. *Eur J Pharmacol* 2003;472(1–2):119–126.
- [133] Gan L, Wang ZH, Zhang H, et al. Endothelium-independent vasorelaxant effect of 20(S)-protopanaxadiol on isolated rat thoracic aorta. *Acta Pharmacol Sin* 2016;37(12):1555–1562.
- [134] Kim JH, Lee JH, Jeong SM, et al. Stereospecific effects of ginsenoside Rg3 epimers on swine coronary artery contractions. *Biol Pharm Bull* 2006;29(2):365–370.
- [135] Lin XP, Cui HJ, Yang AL, et al. Astragaloside IV improves vasodilatation function by regulating the PI3K/Akt/eNOS signaling pathway in rat aorta endothelial cells. *J Vasc Res* 2018;55(3):169–176.
- [136] Zhang WD, Zhang C, Wang XH, et al. Astragaloside IV dilates aortic vessels from normal and spontaneously hypertensive rats through endothelium-dependent and endothelium-independent ways. *Planta Med* 2006;72(7):621–626.
- [137] Kamkaew N, Paracha TU, Ingkaninan K, et al. Vasodilatory effects and mechanisms of action of *Bacopa monnieri* active compounds on rat mesenteric arteries. *Molecules (Basel)* 2019;24(12):2243.
- [138] Liu J, Zhu K, Ma D. Effects of dioscin on the aortic vascular rings isolated from rats. *J Tianjin Med Univ* 2012;18(1):24–26.
- [139] Wang Y, Ren Y, Xing L, et al. Endothelium-dependent vasodilation effects of *Panax notoginseng* and its main components are mediated by nitric oxide and cyclooxygenase pathways. *Exp Ther Med* 2016;12(6):3998–4006.
- [140] Ren Y, Liu T, Qi B, et al. Effect and mechanism of ginsenoside Rg2 on isolated rat thoracic aorta smooth muscle. *J Yichun Univ* 2022;44(3):20–25 + 82.
- [141] Kim ND, Kang SY, Kim MJ, et al. The ginsenoside Rg3 evokes endothelium-independent relaxation in rat aortic rings: role of K⁺ channels. *Eur J Pharmacol* 1999;367(1):51–57.
- [142] Kang YJ, Sohn JT, Chang KC. Relaxation of canine corporal smooth muscle relaxation by ginsenoside saponin Rg3 is independent from eNOS activation. *Life Sci* 2005;77(1):74–84.
- [143] Li Z, Chen X, Niwa Y, et al. Involvement of Ca²⁺-activated K⁺ channels in ginsenosides-induced aortic relaxation in rats. *J Cardiovasc Pharmacol* 2001;37(1):41–47.
- [144] Ul Haq I, Khan T, Ahmad T, et al. Insight into the cardiovascular mechanisms of blood pressure lowering effect of ginsenoside: a steroid saponin. *Clin Exp Hypertens* 2021;43(8):723–729.
- [145] Wong KL, Chan P, Yang HY, et al. Isosteviol acts on potassium channels to relax isolated aortic strips of Wistar rat. *Life Sci* 2004;74(19):2379–2387.
- [146] Shen K, Leung SWS, Ji L, et al. Notoginsenoside Ft1 activates both glucocorticoid and estrogen receptors to induce endothelium-dependent, nitric oxide-mediated relaxations in rat mesenteric arteries. *Biochem Pharmacol* 2014;88(1):66–74.
- [147] Zhao Y, Zhang X, Li J, et al. Jujuboside B reduces vascular tension by increasing Ca²⁺ influx and activating endothelial nitric oxide synthase. *PLoS One* 2016;11(2):e0149386.
- [148] Dias KL, Correia Nde A, Pereira KK, et al. Mechanisms involved in the vasodilator effect induced by diosgenin in rat superior mesenteric artery. *Eur J Pharmacol* 2007;574(2–3):172–178.
- [149] Kim ND, Kang SY, Park JH, et al. Ginsenoside Rg3 mediates endothelium-dependent relaxation in response to ginsenosides in rat aorta: role of K⁺ channels. *Eur J Pharmacol* 1999;367(1):41–49.
- [150] Carvalho MTM, Rezende KCS, Evora PRB, et al. The lignan (-)-cubebin inhibits vascular contraction and induces relaxation *via* nitric oxide activation in isolated rat aorta. *Phytother Res* 2013;27(12):1784–1789.
- [151] Raffai G, Kim B, Park S, et al. Cinnamaldehyde and cinnamaldehyde-containing micelles induce relaxation of isolated porcine coronary arteries: role of nitric oxide and calcium. *Int J Nanomedicine* 2014;9:2557–2566.
- [152] Xue YL, Shi HX, Murad F, et al. Vasodilatory effects of cinnamaldehyde and its mechanism of action in the rat aorta. *Vasc Health Risk Manag* 2011;7:273–280.
- [153] Alvarez-Collazo J, Alonso-Carballo L, López-Medina AI, et al. Cinnamaldehyde inhibits L-type calcium channels in mouse

- ventricular cardiomyocytes and vascular smooth muscle cells. *Pflugers Arch* 2014;466(11):2089–2099.
- [154] Yanaga A, Goto H, Nakagawa T, et al. Cinnamaldehyde induces endothelium-dependent and -independent vasorelaxant action on isolated rat aorta. *Biol Pharm Bull* 2006;29(12):2415–2418.
- [155] Raimundo JM, Trindade APF, Vellozo LSM, et al. The lignan eudesmin extracted from Piper truncatum induced vascular relaxation via activation of endothelial histamine H1 receptors. *Eur J Pharmacol* 2009;606(1–3):150–154.
- [156] Seok YM, Choi YW, Kim GD, et al. Effects of gomisin A on vascular contraction in rat aortic rings. *Naunyn Schmiedeberg Arch Pharmacol* 2011;383(1):45–56.
- [157] Park JY, Lee SJ, Yun MR, et al. Gomisin A from Schisandra chinensis induces endothelium-dependent and direct relaxation in rat thoracic aorta. *Planta Med* 2007;73(15):1537–1542.
- [158] Inchoo M, Chirdchupunseree H, Pramyothin P, et al. Endothelium-independent effects of phyllanthin and hypophyllanthin on vascular tension. *Fitoterapia* 2011;82(8):1231–1236.
- [159] Zhang H, Tian G, Yang T, et al. Vasodilative mechanism of magnolin in isolated rat thoracic aorta and its toxicity in rat renal cells NRK. *Chin J Exp Tradit Med Formul* 2013;19(23):209–212.
- [160] Piccinelli AL, Arana S, Caceres A, et al. New lignans from the roots of Valeriana prionophylla with antioxidative and vasorelaxant activities. *J Nat Prod* 2004;67(7):1135–1140.
- [161] Demirci B, Dost T, Gokalp F, et al. Silymarin improves vascular function of aged ovariectomized rats. *Phytother Res* 2014;28(6):868–872.
- [162] Xu Z, Wang X, Dai Y, et al. (+/-)-Praeruptorin A enantiomers exert distinct relaxant effects on isolated rat aorta rings dependent on endothelium and nitric oxide synthesis. *Chem Biol Interact* 2010;186(2):239–246.
- [163] Li X, Lee YJ, Kim YC, et al. Bakuchicin induces vascular relaxation via endothelium-dependent NO-cGMP signaling. *Phytother Res* 2011;25(10):1574–1578.
- [164] Lavaud A, Soletti R, Hay AE, et al. Paradoxical effects of polyphenolic compounds from Clusiaceae on angiogenesis. *Biochem Pharmacol* 2012;83(4):514–523.
- [165] Zhang S, Zhang J, Liu N, et al. In-vitro vasodilatory effects and mechanism of marmesin on thoracic aorta rings of rats. *Tradit Chin Drug Res Clin Pharmacol* 2016;27(5):637–643.
- [166] Khan AU, Ullah R, Khan A, et al. Vasodilator effect of Phlomis bracteosa constituents is mediated through dual endothelium-dependent and endothelium-independent pathways. *Clin Exp Hypertens* 2012;34(2):132–139.
- [167] Campos DR, Celotto AC, Albuquerque AAS, et al. The diterpene sclareol vascular effect in normotensive and hypertensive rats. *Arq Bras Cardiol* 2017;109(2):0.
- [168] Pinto NV, Assreuy AMS, Coelho-de-Souza AN, et al. Endothelium-dependent vasorelaxant effects of the essential oil from aerial parts of *Alpinia zerumbet* and its main constituent 1,8-cineole in rats. *Phytomedicine* 2009;16(12):1151–1155.
- [169] Tirapelli CR, Ambrosio SR, da Costa FB, et al. Evidence for the mechanisms underlying the effects of pimaradienoic acid isolated from the roots of *Viguiera arenaria* on rat aorta. *Pharmacology* 2004;70(1):31–38.
- [170] Fang J, Li R, Zhang Y, et al. Aristolone in *Nardostachys jatamansi* DC. induces mesenteric vasodilation and ameliorates hypertension via activation of the KATP channel and PDK1-Akt-eNOS pathway. *Phytomedicine* 2022;104:154257.
- [171] Fu JY, Xia ML, Lu JF, et al. Betulinic acid ameliorates impairment of endothelium-dependent relaxation induced by oxidative stress in rat aorta. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2010;39(5):523–529.
- [172] Fu JY, Qian LB, Zhu LG, et al. Betulinic acid ameliorates endothelium-dependent relaxation in L-NAME-induced hypertensive rats by reducing oxidative stress. *Eur J Pharm Sci* 2011;44(3):385–391.
- [173] Pereira SL, Marques AM, Sudo RT, et al. Vasodilator activity of the essential oil from aerial parts of *Pectis brevipedunculata* and its main constituent citral in rat aorta. *Molecules (Basel)* 2013;18(3):3072–3085.
- [174] Martinsen A, Baccelli C, Navarro I, et al. Vascular activity of a natural diterpene isolated from *Croton zambesicus* and of a structurally similar synthetic trachylobane. *Vascul Pharmacol* 2010;52(1–2):63–69.
- [175] Rodríguez-Rodríguez R, Herrera MD, Perona JS, et al. Potential vasorelaxant effects of oleanolic acid and erythrodilol, two triterpenoids contained in “orujo” olive oil, on rat aorta. *Br J Nutr* 2004;92(4):635–642.
- [176] Xing S, Nong F, Qin J, et al. Gentiopicroside produces endothelium-independent vasodilation by deactivating the PI3K/Akt/Rho-kinase pathway in isolated rat thoracic aorta. *Biomed Res Int* 2021;2021:5565748.
- [177] El-Bassossy HM, Elberry AA, Ghareib SA. Geraniol improves the impaired vascular reactivity in diabetes and metabolic syndrome through calcium channel blocking effect. *J Diabetes Complications* 2016;30(6):1008–1016.
- [178] Tirapelli CR, Ambrosio SR, Coutinho ST, et al. Pharmacological comparison of the vasorelaxant action displayed by kaurenoic acid and pimaradienoic acid. *J Pharm Pharmacol* 2005;57(8):997–1004.
- [179] Tirapelli CR, Ambrosio SR, da Costa FB, et al. Analysis of the mechanisms underlying the vasorelaxant action of kaurenoic acid in the isolated rat aorta. *Eur J Pharmacol* 2004;492(2–3):233–241.
- [180] Yoo MY, Oh KS, Lee JW, et al. Vasorelaxant effect of stilbenes from rhizome extract of rhubarb (*Rheum undulatum*) on the contractility of rat aorta. *Phytother Res* 2007;21(2):186–189.
- [181] Luna-Vázquez FJ, Ibarra-Alvarado C, Rojas-Molina A, et al. Role of nitric oxide and hydrogen sulfide in the vasodilator effect of ursolic acid and uvaol from black cherry *Prunus serotina* fruits. *Molecules (Basel)* 2016;21(1):78.
- [182] Fusi F, Durante M, Sgaragli G, et al. In vitro vasoactivity of zerumbone from *Zingiber zerumbet*. *Planta Med* 2015;81(4):298–304.
- [183] Santos SE, Ribeiro FPRA, Menezes PMN, et al. New insights on relaxant effects of (–)-borneol monoterpene in rat aortic rings. *Fundam Clin Pharmacol* 2019;33(2):148–158.
- [184] Wicha P, Onsa-Ard A, Chaichompoo W, et al. Vasorelaxant and antihypertensive effects of neferine in rats: an in vitro and in vivo study. *Planta Med* 2020;86(7):496–504.
- [185] Matsumoto T, Kobayashi T, Ishida K, et al. Vasodilator effect of Cassiarin A, a novel antiplasmodial alkaloid from *Cassia siamea*, in rat isolated mesenteric artery. *Biol Pharm Bull* 2010;33(5):844–848.
- [186] Ko WH, Yao XQ, Lau CW, et al. Vasorelaxant and antiproliferative effects of berberine. *Eur J Pharmacol* 2000;399(2–3):187–196.
- [187] Panthiya L, Pantan R, Tocharus J, et al. Endothelium-dependent and endothelium-independent vasorelaxant effects of tiliacoronine 12'-O-acetate and mechanisms on isolated rat aorta. *Biomed Pharmacother* 2019;109:2090–2099.
- [188] Cifuentes F, Palacios J, Paredes A, et al. 8-Oxo-9-dihydromakomakine isolated from *Aristolochia chilensis* induces vasodilation in rat aorta: role of the extracellular calcium influx. *Molecules (Basel)* 2018;23(11):3050.
- [189] Lee PY, Chen W, Liu IM, et al. Vasodilatation induced by sinomenine lowers blood pressure in spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol* 2007;34(10):979–984.
- [190] Ma HY, Song YC, Mao YY, et al. Endophytic fungal metabolite fumigaclavine C causes relaxation of isolated rat aortic rings. *Planta Med* 2006;72(5):387–392.
- [191] Mitamura M, Horie S, Sakaguchi M, et al. Mesaconitine-induced relaxation in rat aorta: involvement of Ca²⁺ influx and nitric-oxide synthase in the endothelium. *Eur J Pharmacol* 2002;436(3):217–225.
- [192] Li T, Xu K, Che D, et al. Endothelium-independent vasodilator effect of isocorynoxine in vitro isolated from the hook of *Uncaria rhynchophylla* (Miquel). *Naunyn Schmiedeberg Arch Pharmacol* 2018;391(11):1285–1293.
- [193] Shen J, Gao J, Gao Z, et al. Comparison of the vasorelaxant effects of cyclovirobuxine and its derivatives in rat aorta rings. *Chin J New Drugs* 2012;21(3):240–245.
- [194] Yuzurihara M, Ikarashi Y, Goto K, et al. Geissoschizine methyl ether, an indole alkaloid extracted from *Uncariae Ramulus et Uncus*, is a potent vasorelaxant of isolated rat aorta. *Eur J Pharmacol* 2002;444(3):183–189.
- [195] Li Y, Tang N, Bian K. Vasodilatory effect of oxymatrine and its mechanisms. *Shanghai J Tradit Chin* 2009;43(4):62–66.
- [196] Dongmo AB, Nkeng-Efouet PA, Devkota KP, et al. Tetraacetyljugasterone a new constituent of *Vitex cincinnoskii* with vasorelaxant activity. *Phytomedicine* 2014;21(6):787–792.
- [197] Senejoux F, Girard-Thernier C, Berthelot A, et al. New insights into the mechanisms of the vasorelaxant effects of apocynin in rat thoracic aorta. *Fundam Clin Pharmacol* 2013;27(3):262–270.
- [198] Matsui T, Korematsu S, Byun EB, et al. Apple procyanidins induced vascular relaxation in isolated rat aorta through NO/cGMP pathway in combination with hyperpolarization by multiple K⁺ channel activations. *Biosci Biotechnol Biochem* 2009;73(10):2246–2251.

- [199] Zhang H, Liu H, Chen Y, et al. The curcumin-induced vasorelaxation in rat superior mesenteric arteries. *Ann Vasc Surg* 2018;48:233–240.
- [200] Jain M, Singh A, Singh V, et al. Gingerol inhibits serum-induced vascular smooth muscle cell proliferation and injury-induced neointimal hyperplasia by suppressing p38 MAPK activation. *J Cardiovasc Pharmacol Ther* 2016;21(2):187–200.
- [201] Peixoto-Neves D, Silva-Alves KS, Gomes MDM, et al. Vasorelaxant effects of the monoterpene phenol isomers, carvacrol and thymol, on rat isolated aorta. *Fundam Clin Pharmacol* 2010;24(3):341–350.
- [202] Testai L, Chericoni S, Martelli A, et al. Voltage-operated potassium (Kv) channels contribute to endothelium-dependent vasorelaxation of carvacrol on rat aorta. *J Pharm Pharmacol* 2016;68(9):1177–1183.
- [203] Kim JA, Formoso G, Li Y, et al. Epigallocatechin gallate, a green tea polyphenol, mediates NO-dependent vasodilation using signaling pathways in vascular endothelium requiring reactive oxygen species and Fyn. *J Biol Chem* 2007;282(18):13736–13745.
- [204] Wang GJ, Lin YL, Chen CH, et al. Cellular calcium regulatory machinery of vasorelaxation elicited by petasin. *Clin Exp Pharmacol Physiol* 2010;37(3):309–315.
- [205] Moohammadaree A, Changtam C, Wicha P, et al. Mechanisms of vasorelaxation induced by hexahydrocurcumin isolated rat thoracic aorta. *Phytother Res* 2015;29(11):1806–1813.
- [206] Chen ZY, Yao XQ, Chan FL, et al. (-)epicatechin induces and modulates endothelium-dependent relaxation in isolated rat mesenteric artery rings. *Acta Pharmacol Sin* 2002;23(12):1188–1192.
- [207] Novakovic A, Marinko M, Vranic A, et al. Mechanisms underlying the vasorelaxation of human internal mammary artery induced by (-)epicatechin. *Eur J Pharmacol* 2015;762:306–312.
- [208] Matsuura M, Kimura Y, Nakata K, et al. Artery relaxation by chalcones isolated from the roots of *Angelica keiskei*. *Planta Med* 2001;67(3):230–235.
- [209] Tom ENL, Girard-Thernier C, Demougeot C. The Janus face of chlorogenic acid on vascular reactivity: a study on rat isolated vessels. *Phytomedicine* 2016;23(10):1037–1042.
- [210] He WJ, Fang TH, Ma X, et al. Echinacoside elicits endothelium-dependent relaxation in rat aortic rings via an NO-cGMP pathway. *Planta Med* 2009;75(13):1400–1404.
- [211] Ramón Sánchez de Rojas V, Somoza B, Ortega T, et al. Vasodilatory effect in rat aorta of eriodictyol obtained from *Satureja obovata*. *Planta Med* 1999;65(3):234–238.
- [212] Guo Z, Yang X, Wu M, et al. Gastrodin attenuates angiotensin II-induced vascular contraction and MLCK/p-MLC2 pathway activation. *Pharm Biol* 2023;61(1):858–867.
- [213] Zhang J, Zhao L, Yu X. Vasodilation effect of paeonol on renal artery and coronary artery in healthy and hyperlipidemia rats. *Chin J New Drugs* 2013;22(20):2414–2417.
- [214] Wang Y, Peng X, Zhang C. Study on the mechanism of the vasodilation effect of proanthocyanidins on resistance vessels in rats. *Chin J Clin Pharmacol Ther* 2010;15(2):170–174.
- [215] Matsui T, Kudo A, Tokuda S, et al. Identification of a new natural vasorelaxant compound, (+)-osbeckic acid, from rutin-free tartary buckwheat extract. *J Agric Food Chem* 2010;58(20):10876–10879.
- [216] Zhang H, Zhang H, Liu Y, et al. The vasodilatory effect of salidroside on the salidroside aortic ring isolated from rats. *Pharmacol Clin Chin Materia Medica* 2015;31(1):37–40.
- [217] Raffai G, Khang G, Vanhoutte PM. Vanillin and vanillin analogs relax porcine coronary and basilar arteries by inhibiting L-type Ca²⁺ channels. *J Pharmacol Exp Ther* 2015;352(1):14–22.
- [218] de Oliveira LM, de Oliveira TS, da Costa RM, et al. The vasorelaxant effect of gallic acid involves endothelium-dependent and -independent mechanisms. *Vascul Pharmacol* 2016;81:69–74.
- [219] Li YJ, Duan CL, Liu JX. Salvianolic acid A promotes the acceleration of neovascularization in the ischemic rat myocardium and the functions of endothelial progenitor cells. *J Ethnopharmacol* 2014;151(1):218–227.
- [220] Yu M, Kim HJ, Heo H, et al. Comparison of the antihypertensive activity of phenolic acids. *Molecules* 2022;27(19):6185.
- [221] Safaeian L, Asghari-Varzaneh M, Alavi SS, et al. Cardiovascular protective effects of cinnamic acid as a natural phenolic acid: a review. *Arch Physiol Biochem* 2025;131(1):52–62.
- [222] Al Shukor N, Van Camp J, Gonzales GB, et al. Angiotensin-converting enzyme inhibitory effects by plant phenolic compounds: a study of structure activity relationships. *J Agric Food Chem* 2013;61(48):11832–11839.
- [223] Ekowati J, Tejo BA, Maulana S, et al. Potential utilization of phenolic acid compounds as anti-inflammatory agents through TNF- α convertase inhibition mechanisms: a network pharmacology, docking, and molecular dynamics approach. *ACS Omega* 2023;8(49):46851–46868.
- [224] Arruda-Barbosa L, Rodrigues KM, Souza-Neto FD, et al. Vasorelaxant effects of 1-nitro-2-phenylethene in rat isolated aortic rings. *Vascul Pharmacol* 2014;63(2):55–62.
- [225] Wang SP, Zang WJ, Kong SS, et al. Vasorelaxant effect of isopropyl 3-(3, 4-dihydroxyphenyl)-2-hydroxypropanoate, a novel metabolite from *Salvia miltiorrhiza*, on isolated rat mesenteric artery. *Eur J Pharmacol* 2008;579(1–3):283–288.
- [226] Paredes A, Palacios J, Quispe C, et al. Hydroalcoholic extract and pure compounds from *Senecio nutans* Sch. Bip (Compositae) induce vasodilation in rat aorta through endothelium-dependent and independent mechanisms. *J Ethnopharmacol* 2016;192:99–107.
- [227] Grbović L, Radenković M. Analysis of adenosine vascular effect in isolated rat aorta: possible role of Na⁺/K⁺-ATPase. *Pharmacol Toxicol* 2003;92(6):265–271.
- [228] Gauthier KM, Spitzbarth N, Edwards EM, et al. Apamin-sensitive K⁺ currents mediate arachidonic acid-induced relaxations of rabbit aorta. *Hypertension* 2004;43(2):413–419.
- [229] Ririe DG, Roberts PR, Shouse MN, et al. Vasodilatory actions of the dietary peptide carnosine. *Nutrition* 2000;16(3):168–172.
- [230] Rubiolo JA, Lence E, González-Bello C, et al. Crambesin C1 acts as a possible substrate of iNOS and eNOS increasing nitric oxide production and inducing in vivo hypotensive effect. *Front Pharmacol* 2021;12:694639.
- [231] Meng Z, Zhang H. The vasodilator effect and its mechanism of sulfur dioxide-derivatives on isolated aortic rings of rats. *Inhal Toxicol* 2007;19(11):979–986.
- [232] Engler MB, Engler MM. Docosahexaenoic acid-induced vasorelaxation in hypertensive rats: mechanisms of action. *Biol Res Nurs* 2000;2(2):85–95.
- [233] Wicha P, Tocharus J, Nakaew A, et al. Ethyl rosmarinat relaxes rat aorta by an endothelium-independent pathway. *Eur J Pharmacol* 2015;766:9–15.
- [234] Terroni B, de Moraes LHO, Pavan AR, et al. Vascular effects of the fetal hemoglobin inducer agent 3-(1,3-dioxoisindolin-2-yl) benzyl nitrate. *Pharmaceuticals (Basel)* 2022;15(11):1311.
- [235] Paredes-Gamero EJ, Medeiros VP, Farias EHC, et al. Heparin induces rat aorta relaxation via integrin-dependent activation of muscarinic M3 receptors. *Hypertension* 2010;56(4):713–721.
- [236] Mendes LJ, Capettini LS, Lôbo LT, et al. Endothelial nitric oxide-dependent vasorelaxant effect of isotirumalin, a dihydroflavonol from *Derris urucu*, on the rat aorta. *Biol Pharm Bull* 2011;34(9):1499–1500.
- [237] Jiang D, Xu C, Zhu Y, et al. Study on mechanism of endothelium-dependent vasodilating effect of phytoestrogen α -zealanol. *Chin J Geriatric Heart Brain Vessel Dis* 2008;10(9):699–702.
- [238] Cuong NM, Son NT, Nhan NT, et al. Vasorelaxing activity of R-(-)-3'-hydroxy-2,4,5-trimethoxydalbergiquinol from *Dalbergia tonkinensis*: involvement of smooth muscle CaV1.2 channels. *Planta Med* 2020;86(4):284–293.
- [239] Hu CM, Cheng YW, Cheng HW, et al. Impairment of vascular function of rat thoracic aorta in an endothelium-dependent manner by shikonin/alkannin and derivatives isolated from roots of *Macrotomia euchroma*. *Planta Med* 2004;70(1):23–28.
- [240] Niu LG, Zhang MS, Liu Y, et al. Vasorelaxant effect of taurine is diminished by tetraethylammonium in rat isolated arteries. *Eur J Pharmacol* 2008;580(1–2):169–174.
- [241] Bernardino-Paula R, Carvalho-Galvão A, Cavalcanti ALM, et al. The new organic nitrate 2-nitrate-1,3-dioctanoxypuran (NDOP) induces nitric oxide production and vasorelaxation via activation of inward-rectifier potassium channels (KIR). *Nitric Oxide* 2020;104–105:61–69.
- [242] Mariano LNB, da Silva RCV, Niero R, et al. Vasodilation and blood pressure-lowering effect of 3-demethyl-2-geranyl-4-prenylbellidifoline, a xanthone obtained from *garcinia achachairu*, in hypertensive rats. *Plants (Basel)* 2024;13(4):528.
- [243] Palacios J, Paredes A, Catalán MA, et al. Novel oxime synthesized from a natural product of *senecio nutans* Sch. Bip. (Asteraceae) enhances vascular relaxation in rats by an endothelium-independent mechanism. *Molecules* 2022;27(10):3333.
- [244] Liu H, Fu S, Hu C, et al. Relaxing effect of a flavonoid WX-02 on isolated vascular rings of rabbits. *J Shenyang Pharm Univ* 2013;30(9):709–712.
- [245] Javed A, Khan S, Salma U, et al. Extract of *Chenopodium album* lowers blood pressure in rats through endothelium-dependent and -independent vasorelaxation. *Ann Pharm Fr* 2024;82(1):84–95.

- [246] Lam FFY, Yeung JHK, Chan KM, et al. Dihydrotanshinone, a lipophilic component of *Salvia miltiorrhiza* (danshen), relaxes rat coronary artery by inhibition of calcium channels. *J Ethnopharmacol* 2008;119(2):318–321.
- [247] Di Giulio C, Gonzalez Guzman JM, Dutra Gomes JV, et al. A new Lignan from *Annona squamosa* L. (Annonaceae) demonstrates vasorelaxant effects in vitro. *Molecules* 2023;28(11):4256.
- [248] Xie YL, Zhou M, Ma HH, et al. Vasorelaxation effect of gastrodin on isolated thoracic aorta rings of rats. *Chin J Integr Med* 2015;21(12):944–948.
- [249] Jo C, Kim B, Lee S, et al. Vasorelaxant effect of *prunus mume* (Siebold) Siebold & Zucc. Branch through the endothelium-dependent pathway. *Molecules* 2019;24(18):3340.
- [250] Li L, Su XL, Bai TT, et al. New paeonol derivative C302 reduces hypertension in spontaneously hypertensive rats through endothelium-dependent and endothelium-independent vasodilation. *Eur J Pharmacol* 2022;927:175057.
- [251] Qamar HMUD, Qayyum R, Salma U, et al. Vascular mechanisms underlying the hypotensive effect of *Rumex acetosa*. *Pharm Biol* 2018;56(1):225–234.
- [252] Mushtaq MN, Ghimire S, Alamgeer, et al. Tambulin is a major active compound of a methanolic extract of fruits of *Zanthoxylum armatum* DC causing endothelium-independent relaxations in porcine coronary artery rings *via* the cyclic AMP and cyclic GMP relaxing pathways. *Phytomedicine* 2019;53:163–170.
- [253] Domingo-Fernández D, Gadiya Y, Preto AJ, et al. Natural products have increased rates of clinical trial success throughout the drug development process. *J Nat Prod* 2024;87(7):1844–1851.