Review Articles

Acupuncture and Herbal Medicine

# Natural vasodilators: mechanisms and therapeutic potential in cardiovascular diseases

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**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

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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 $Ca^{2+}$ 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 $Ca^{2+}$ 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 $Ca^{2+}$ efflux, which reduces cytosolic $Ca^{2+}$ 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 $Ca^{2+}$ 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 ($H_2S$) exerts a vasodilatory effect partly by inhibiting phosphodiesterase (PDE) enzymes, particularly PDE5, thereby increasing cGMP levels in VSMCs and promoting relaxation[18–19]. $H_2S$ also elevates cGMP and activates PKG while directly modulating $K^+$ channels. Specifically, $H_2S$ 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 $Ca^{2+}$-activated $K^+$ ($BK_{Ca}$) channels. The resulting $K^+$ efflux and membrane hyperpolarization inhibit voltage-dependent calcium channel activity, attenuate $Ca^{2+}$ influx, and promote smooth muscle relaxation[20]. Additionally, $H_2S$ inhibits L-type $Ca^{2+}$ channels, further reducing $Ca^{2+}$ influx[21–22].

#### *Prostacyclin*

Prostacyclin ($PGI_2$) is synthesized in ECs from arachidonic acid (AA) through the enzymatic cascade of



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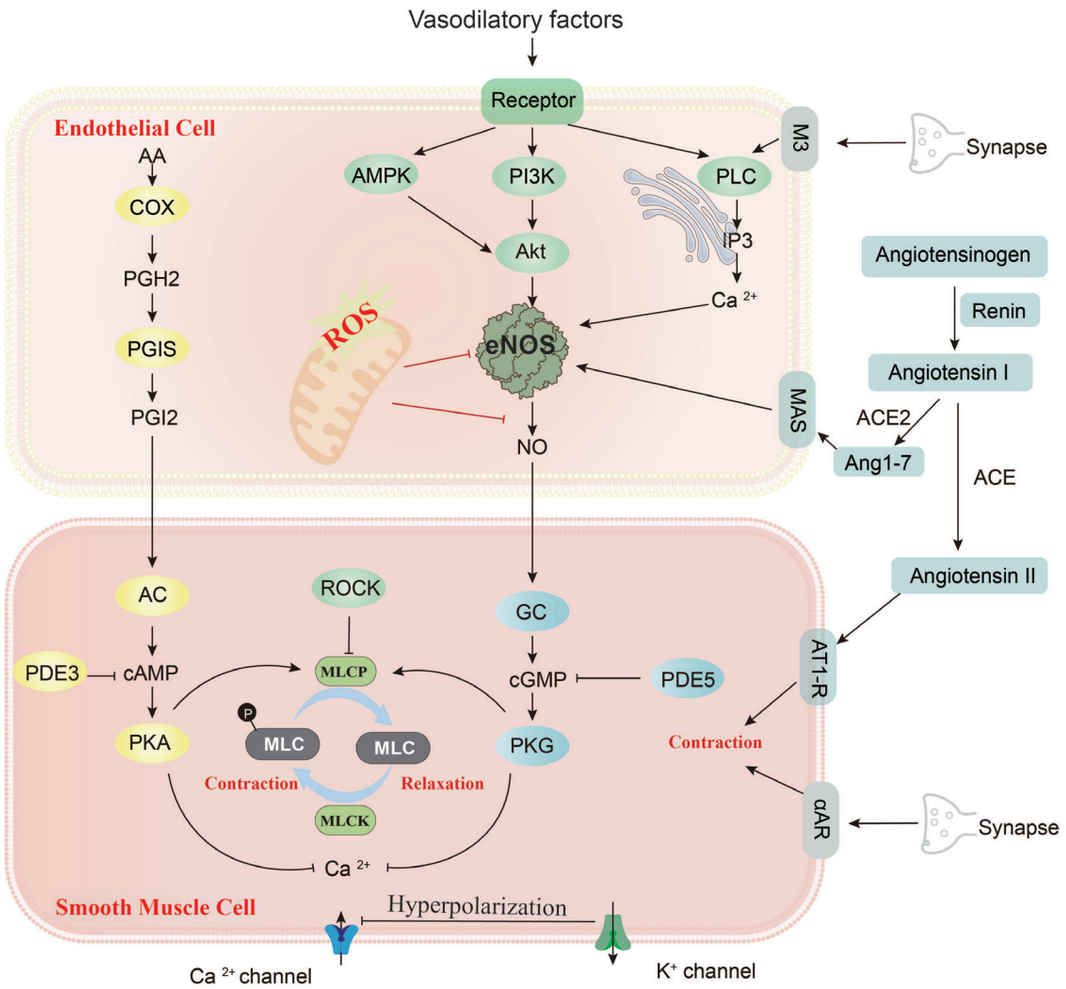



**Figure 1.** Overview of key physiological systems and cellular mechanisms regulating vascular tone and vasodilation. Vascular tone is regulated through integrated interactions across several systems: (1) Endothelial cells synthesize diverse vasoactive factors, including NO, $PGI_2$, and EDHF, which 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 ($Ca^{2+}$, $K^+$) activity. (3) The RAAS influences vascular tone through Ang-II, which promotes vasoconstriction and serves as a target for achieving vasodilation *via* 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; $PGH_2$, Prostaglandin $H_2$; PGIS, Prostacyclin synthase; $PGI_2$, Prostacyclin; PI3K, Phosphatidylinositide 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, $PGI_2$ 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 $Ca^{2+}$ 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 $Ca^{2+}$ 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 ($H_2O_2$) modulate multiple ion channels to regulate vascular tone. In small human coronary arteries, $H_2O_2$-induced vasodilation is primarily promoted by PKG dimerization and $BK_{Ca}$ channel activation[27]. Furthermore, $H_2O_2$ enhances the 4-aminopyridine (4-AP)–sensitive voltage-gated $K^+$ current, leading to VSMC hyperpolarization and vasodilation[27].



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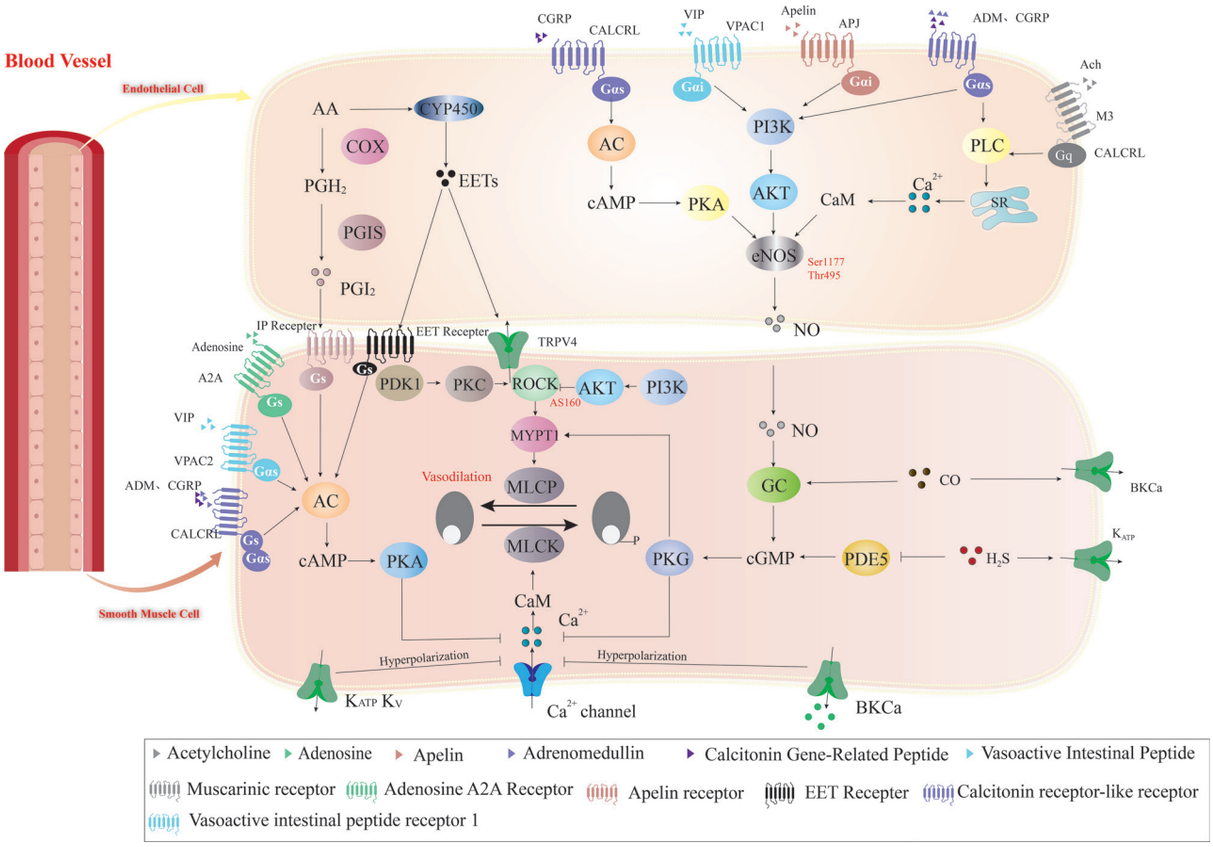



**Figure 2.** Major vasodilatory factors and mechanisms regulating vascular tone. This diagram illustrates the principal molecular mechanisms by which diverse vasodilatory factors—such as acetylcholine, adenosine, apelin, adrenomedullin, CGRP, and VIP—induce vascular relaxation. In endothelial cells, these ligands bind to their respective receptors (eg, muscarinic M3 receptor, adenosine $A_2A$ receptor, apelin receptor, and calcitonin receptor-like receptor), activating intracellular signaling cascades that stimulate the synthesis of vasodilators, including NO, $PGI_2$, 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; $PGI_2$, Prostacyclin; PI3K, Phosphatidylinositide 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 $A_2B$ receptor ($A_2BR$) on ECs, promoting eNOS activity, increasing the production and release of NO, and promoting vasodilation[28]. Additionally, adenosine activates the adenosine $A_2A$ receptor ($A_2AR$), 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 Gαi, which subsequently triggers phosphatidylinositide 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



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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-$IP_3$-$Ca^{2+}$ 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 ($IP_3$) 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 $\alpha_1$-adrenergic receptors on VSMCs, leading to $Ca^{2+}$ influx and contraction. In addition, $\alpha_1$-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



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sustain MLC phosphorylation. Conversely, stimulation of $\beta_2$-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-$IP_3$-$Ca^{2+}$ signaling cascade[58–59]. Elevated cytosolic $Ca^{2+}$ 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 ($O_2^-$), which reduces NO bioavailability. Oxygen radicals react with $H^+$ to form $H_2O_2$ and with NO to form peroxynitrite ($ONOO^-$)[60]. The resulting products, $O_2$-, $H_2O_2$, 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 $Ca^{2+}$ 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-$IP_3$-$Ca^{2+}$ pathway*

Upon receptor activation by agonists such as ACh or bradykinin, PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate ($PIP_2$) to generate diacylglycerol (DAG) and $IP_3$. $IP_3$ binds to receptors on the endoplasmic reticulum, triggering $Ca^{2+}$ release into the cytosol. The PLC-$IP_3$-$Ca^{2+}$ signaling pathway exerts dual and context-dependent effects in vascular tissues[63]. In ECs, the rise in cytosolic $Ca^{2+}$ binds to CaM, which activates eNOS, thereby promoting vasorelaxation. Conversely, in VSMCs, elevated intracellular $Ca^{2+}$ 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 $PIP_2$ to $PIP_3$, 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 $Ca^{2+}$ back into the sarcoplasmic reticulum and reduces the concentration of $Ca^{2+}$. 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 $Ca^{2+}$. 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. $Ca^{2+}$-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



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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-$Ca^{2+}$-eNOS and PI3K-AKT-eNOS cascades to enhance NO production, inhibit protein kinase C (PKC), and regulate potassium and calcium channels to maintain intracellular $Ca^{2+}$ 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 $Ca^{2+}$ 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, $PGI_2$, EDHF, etc.), leading to smooth muscle relaxation and vasodilation[131].

### *Saponins*

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

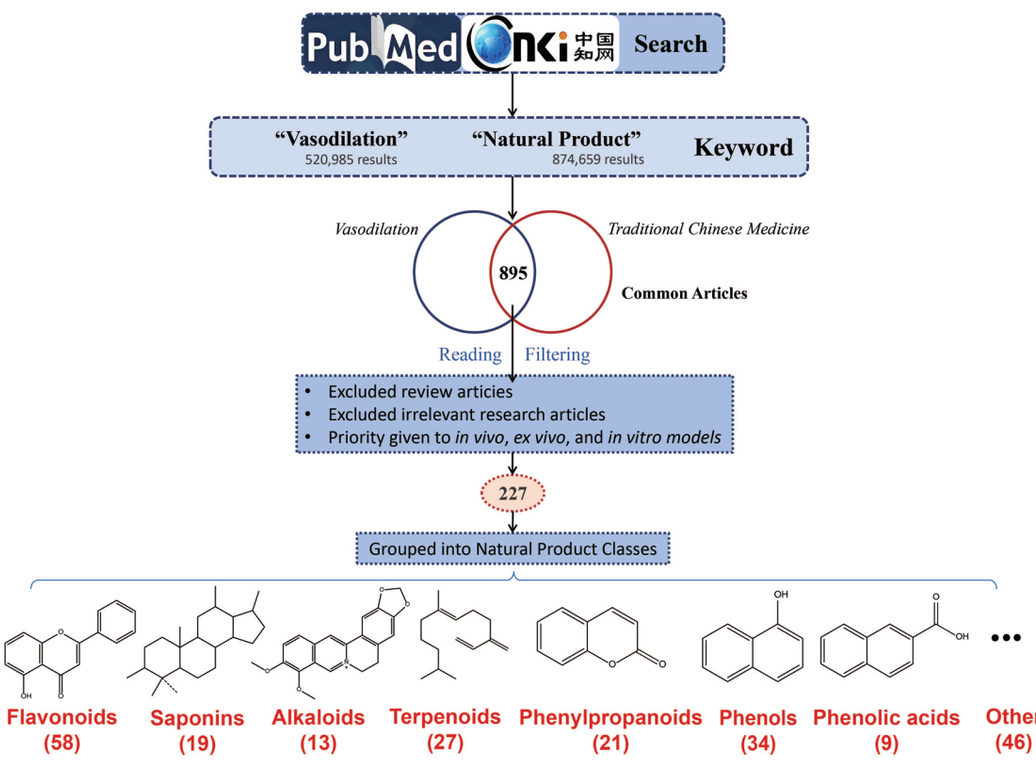



**Figure 3.** Flowchart of literature search strategy and classification of natural products with vasodilatory activity. Literature was searched in PubMed and CNKI using "Vasodilation" and "Natural Product" as keywords. After excluding reviews and irrelevant studies (prioritizing *in vivo*, *ex vivo*, 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.



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**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] | *Orthosiphon aristatus* (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] | *Casimiroa edulis* La Llave and Lex., *Casimiroa pubescens* Ramírez | Caudal ring | Wistar rat | 0.1–100 μM | PE | $M_3$ muscarinic receptor activation, NO-cGMP signaling |
| 4-Hydroxybenzaldehyde[76] | *Gastrodia elata* 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 VOCC, 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] | *Alpinia* Roxb.; *Ficus katsumadai* Hayata; *Amomum subulatum* Roxb.; *Scutellaria rivularis* 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] | *Selaginella tamariscina* (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] | *Apium graveolens* 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] | *Chrysanthemum morifolium* 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] | *Chrysanthemum* × *morifolium* (Ramat.) Hemsl. | Thoracic aorta | SD rat | 0.5–72 μM | PE | eNOS-NO-sGC-cGMP signaling, antioxidant activity, attenuation of NO reduction |
| Ayanin[86] | *Croton schiedeanus* Schltdl. | Thoracic ring | Wistar rat | 1–1,000 μM | PE, KCL | NO-sGC-cGMP signaling |
| Baicalin[87] | *Scutellaria baicalensis* 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 $Ca_v1.2$ channel modulation |

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**Table 1**
**(Continued)**

| Compounds | Natural medicine | Vascular type | Species investigated | Dosage | Vasoconstrictor | Mechanisms |
|---|---|---|---|---|---|---|
| Calycosin[89] | *Astragalus membranaceus* (Fisch.) Bunge | Thoracic aorta | SD rat | 1–100 μM | PE, KCL | VOC and ROC inhibition |
| Cardamonin[79] | – | 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[83] | – | 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 $IP_3R$) 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] | *Pueraria lobata* (Willd.) Ohwi | Basilar artery | SD rat | 20–200 μM | U46619 | $K^+$, $BK_{Ca}$ |
| Daidzin[93] | *Pueraria lobata* (Willd.) Ohwi | Basilar artery | SD rat | 1–1,680 μM | U46619 | $K^+$, $BK_{Ca}$ |
| Dihydrospinochalcone-A[94] | *Lonchocarpus xuul* Lundell | Thoracic ring | Spontaneously hypertensive rats | 1–300 μM | NE | eNOS-NO-sGC-PKG, $K^+$ |
| Dioclein (5,2',5'-trihydroxy-6-7-dimethoxyflavanone)[95] | *Dioclea grandiflora* 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, VOCs |
| Diosmetin[96] | *Citrus limon* L.; *Olea europaea* L. | Coronary artery | Pig | 0.001–10 μM | u46620, KCL | Kv, PKC, $Ca^{2+}$ |
| Eupatorin[97] | *Orthosiphon stamineus* 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] | *Rhododendron dauricum* 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] | *Dioclea grandiflora* Mart. ex Benth. | Thoracic aorta | SD rat | 1–300 μM | PE | Scavenging oxygen-free radicals |
| Formononetin[100] | *Trifolium pratense* 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] | *Caesalpinia sappan* L. | Thoracic aorta | SD rat | 0–100 μM | PE | NO, cGMP |

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**Table 1**
**(Continued)**

| Compounds | Natural medicine | Vascular type | Species investigated | Dosage | Vasoconstrictor | Mechanisms |
|---|---|---|---|---|---|---|
| Hesperetin[83] | – | Thoracic aorta | Wistar rat | 3–100 μM | KCl | KCa, $K_{ATP}$ |
| Hesperetin[103] | *Poncirus trifoliata* (L.) Raf. | Coronary artery | pig | 0.1 SIRT1-dependent PGC-1α 100 μM | U46619 | NO-cGMP |
| Hesperetin[104] | – | Thoracic aorta | Wistar rat | 10–300 μM | NE, KCL | PDE1 and PDE4, cAMP and cGMP |
| Homoplantaginin[105] | *Salvia plebeia* R.Br. | Thoracic aorta | SD rat | 0.1–10 μM | KCL, PE | NO and p-eNOS, SOCE-$Ca^{2+}$, ERS |
| Hyperin[106] | – | Basilar artery | SD rat | 10–1,000 μM | U46619, KCL | Endothelial relaxation factor, PKC, $BK_{Ca}$, KCa |
| Hyperoside[107] | – | Thoracic aorta | SD rat | 0.3–100 μM | U46619, KCL | NO, $PGI_2$, EDHF |
| Icariin[108] | *Epimedii* | Thoracic aorta | Beagle | 3.75–30 μM | KCl, PGF2a | eNOS, NO-CGMP, PDE |
| Irisin[109] | – | Thoracic aorta | Wistar rat | 0.001–1 μM | PE, KCL | Kv, $K_{ATP}$, SKCa, $BK_{Ca}$, IKCa, Kir, NO |
| Isocordoin[94] | *Lonchocarpus xuul* Lundell | Thoracic aorta | Wistar, SHR | 1–300 μM | NA | – |
| Isorhamnetin[110] | – | The mesenteric artery, iliac artery, aorta | SHR | 1–31.62 μM | PE | Removal of superoxide, NO, direct relaxation of smooth muscle |
| Isorhamnetin-3-glucuronide[110] | – | Thoracic aorta | SD rat | 1–30 μM | 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] | *Carthamus tinctorius* L. | Coronary artery | Pig | 1 nM-100 μM | U46619, KCL | Inhibition of lipoxygenase, PKC, PDEs, MLCK |
| Kaempferol[112] | Phyllanthus acidus (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 μM | High $K^+$ | Superoxide radical, $Ca^{2+}$ |
| Luteolin[113] | – | Thoracic aorta | Rat | 4.5–36 μM | PE, KCL | $Ca^{2+}$, $K^+$ |
| Luteolin[83] | – | Thoracic aorta | Wistar rat | 3–100 μM | KCl | KCa, $K_{ATP}$ |
| Luteolin[114] | *Coreopsis tinctoria* Nutt. | Thoracic aorta | Wistar rat | 5.6–560 μM | PE, KCL | $Ca^{2+}$ |
| Luteolin[115] | – | Thoracic aorta | SD rat | 10–100 μM | PE, KCL | eNOS-NO |
| Luteolin[116] | *Chrysanthemum* × *morifolium* (Ramat.) Hemsl. | Thoracic aorta | SD rat | 0.1–100 μM | PE | Reducing oxidative stress, NO |
| Luteolin[82] | *Chrysanthemum* × *morifolium* (Ramat.) Hemsl. | Thoracic aorta | SD rat | 1–50 μM | PE, KCL | Superoxide anion, IKCa, SKCa, EDHF |
| Naringenin[117] | – | Thoracic aorta | Wistar rat | 1–300 μM | PE, KCL | PDE1, PDE4, PDE5-cGMP, cAMP, $Ca^{2+}$ |

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**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, Kv |
| Nobiletin[119] | *Citrus × depressa* Hayata | Thoracic aorta | SD rat | 0.001–10 μM | PE | $Ca^{2+}$-eNOS-NO |
| Orientin[120] | *Phyllostachys nigra* (Lodd. ex Lindl.) Munro | Thoracic aorta | New Zealand rabbit | 0.1–30 mM | PE, NE, KCL | NO-sGC-cGMP, VDCC, ROCC |
| Pinocembrin[121] | *Cistanche tubulosa* Hook.fil. | Thoracic aorta | SD rat | 30–300 μM | PE, KCL | NO-cGMP, $K^+$, $Ca^{2+}$ |
| Poncirin[103] | *Poncirus trifoliata* (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, $BK_{Ca}$, $K_{ATP}$, Kv, IKCa, IP3 receptors |
| Puerarin[93] | *Pueraria lobata* (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] | *Croton schiedeanus* 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] | *Coreopsis tinctoria* 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] | *Croton schiedeanus* 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 |
| Rhoifolin[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] | *Erigeron breviscapus* (Vaniot) Hand.-Mazz. | Thoracic aorta | Wistar rat | 3–100 μM | NE | Inhibition of $Ca^{2+}$ influx, VDCC modulation |
| Scutellarin[128] | *Erigeron breviscapus* (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-1α pathway, mitochondrial biogenesis, NO signaling |

AKT, Protein kinase B; BKCa, 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; PGI2, Prostacyclin; PKC, Protein kinase C; PKG, Protein kinase G; ROCC, 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.





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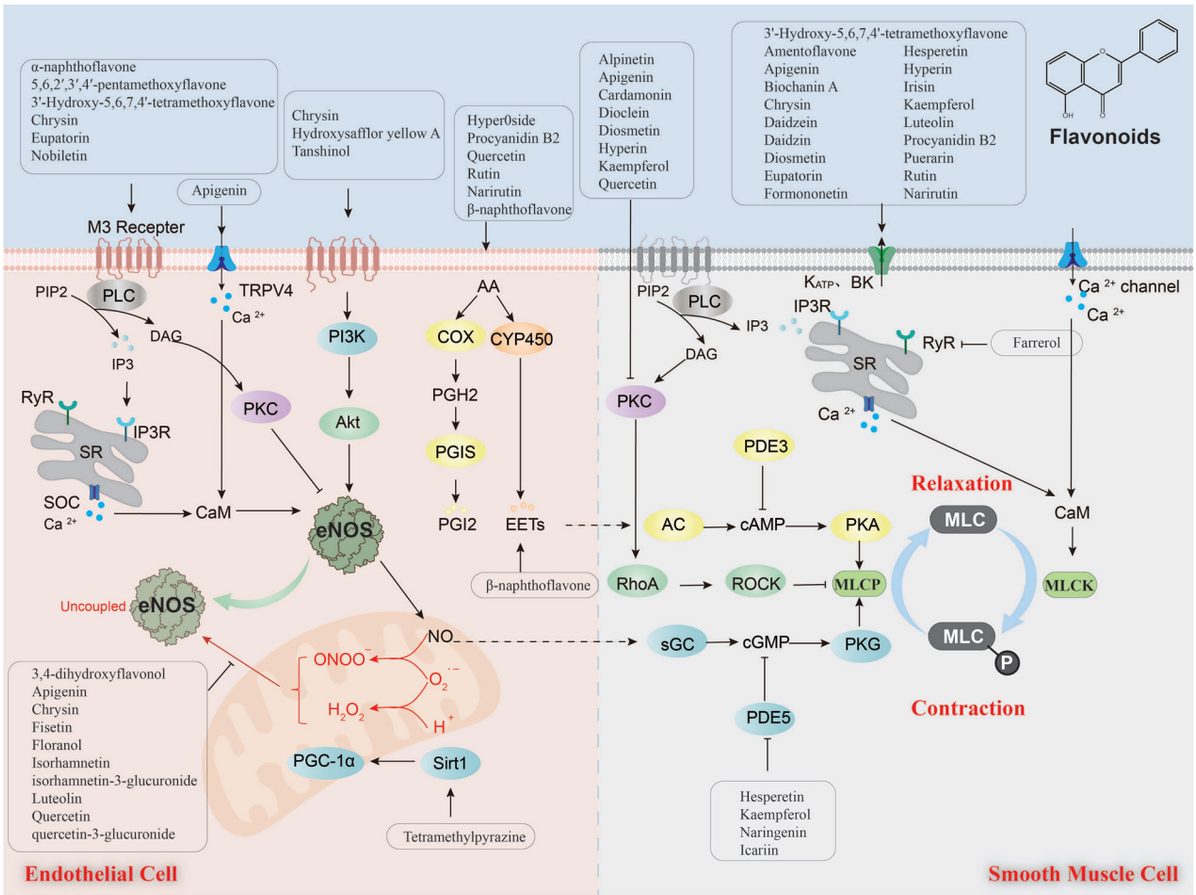



**Figure 4.** Mechanisms of vasodilation induced by flavonoids. In endothelial cells, flavonoids activate eNOS-NO, COX-$PGI_2$, and CYP450-EETs pathways, modulate $Ca^{2+}$ signaling, and attenuate oxidative stress to enhance NO bioavailability. In smooth muscle cells, flavonoids inhibit $Ca^{2+}$ influx, 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; $PGI_2$, Prostacyclin; PI3K, Phosphatidylinositide 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 $PGI_2$-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 $Ca^{2+}$ channels, and (ii) an endothelium-dependent pathway in which the release of NO and $PGI_2$ 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 $Ca^{2+}$ channels and the activation of $K^+$ channels, which induce membrane hyperpolarization and reduce intracellular $Ca^{2+}$ 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 $Ca^{2+}$ 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 $Ca^{2+}$ 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].



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**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 μM | PE | $Ca^{2+}$ |
| 20 (S)-Protopanaxadiol[133] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Thoracic aorta | Wistar rats | 21.5–108.5 μM | KCl and PE | VDCC, ROCC, $K^+$ |
| 20 (R)-Ginsenoside Rg3[134] | *Panax notoginseng* (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] | *Panax notoginseng* (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] | *Astragalus membranaceus* (Fisch.) Bunge | Thoracic aorta | SD rats | 1–10,000 μM | KCL | PI3K-Akt-eNOS |
| Astragaloside IV[136] | *Astragalus membranaceus* (Fisch.) Bunge | Thoracic aorta | Wistar rats | 1.3–130 μM | PE | NO-cGMP pathway and by extracellular calcium blockade |
| Bacopaside I[137] | *Bacopa monnieri* (L.) Wettst. | Mesenteric artery | Wistar rats | 0.1–100 μM | PE | Blockade of $Ca^{2+}$ influx and its release from SR |
| Bacoside A[137] | *Bacopa monnieri* (L.) Wettst. | Mesenteric artery | Wistar rats | 0.1–100 μM | 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] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Thoracic aorta | Wistar rats | 0.01–10 μM | PE | NO-sGC |
| Ginsenoside Re[139] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Thoracic aorta | Wistar rats | 0.01–10 μM | PE | NO-sGC |
| Ginsenoside Rg1[139] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Thoracic aorta | Wistar rats | 0.01–10 μM | PE | NO-sGC |
| Ginsenoside Rg2[140] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Thoracic aorta | Wistar rats | 10–10,000 μM | Norepinephrine | NO-cGMP |
| Ginsenoside Rg3[141] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Thoracic aorta | SD rats | 1–100 μM | KCl | $Ca^{2+}$, $K^+$ |
| Ginsenoside Rg3[142] | *Panax ginseng* C. A. Mey. | Corpus cavernosum | Canine | 1–1,000 μg/mL | PE | Inhibit PDEs |
| Ginsenosides[143] | *Panax ginseng* C.A.Mey. | Thoracic aorta | rats | 50 μg/mL | PE | $Ca^{2+}$, $K^+$ |
| Gitogenin[144] | *Tribulus longipetalus* Viv. | Thoracic aorta | Wistar rats | | PE | – |
| Isosteviol[145] | *Stevia rebaudiana* (Bertoni) Bertoni | Thoracic aorta | Wistar rats | 0.01–10 μM | KCl | Related to the opening of SKCa and $K_{ATP}$ channels |
| Notoginsenoside Ft1[146] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Mesenteric artery | SD rats | 0.01–10 μM | KCl and PE | NO, GR, Erb |
| Notoginsenoside R1[139] | *Panax notoginseng* (Burkill) F.H.Chen ex C.H.Chow | Thoracic aorta | Wistar rats | 0.01–10 μM | PE | NO-sGC |
| Jujuboside B[147] | *Ziziphus jujuba* Mill. var. | Thoracic aorta | SD rats | 10 μM | PE | Activated eNOS and phosphorylated eNOS, TRPC |
| Diosgenin[148] | – | Mesenteric artery | Wistar rats | 2–2,000 μM | PE | Activate $BK_{Ca}$ channels |

BKCa, Large-conductance $Ca^{2+}$-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, Phosphatidylinositide 3-kinases; ROCC, Receptor-operated calcium channel; SD, Sprague-Dawley; sGC, Soluble guanylyl cyclase; SHR, Spontaneously hypertensive rats; SKCa, Small-conductance $Ca^{2+}$-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 (ERβ) 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



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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. (+/–) Praeruptorin 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

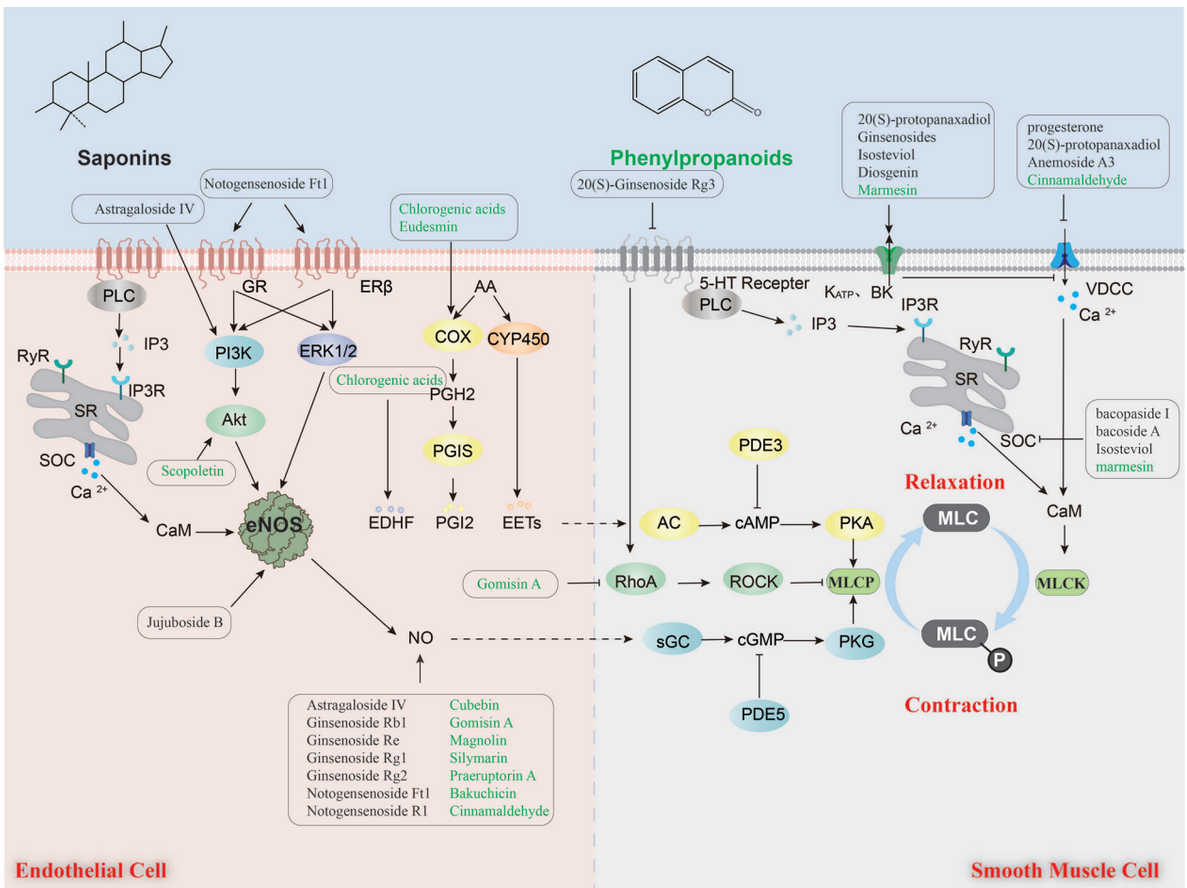



**Figure 5.** Mechanisms of vasodilation induced by saponins (black font) and phenylpropanoids (green font) in ECs and VSMCs. In endothelial cells, saponins and phenylpropanoids activate eNOS-NO, COX-$PGI_2$, and CYP450-EETs pathways to produce vasodilatory mediators. In smooth muscle cells, compounds 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; $PGI_2$, Prostacyclin; PI3K, Phosphatidylinositide 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.



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**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] | *Piper cubeba* L.fil. | Thoracic aorta | Wistar rats | | PE | NO-cGMP |
| Cinnamaldehyde[151] | *Cinnamomum zeylanicum* Blume, *Cinnamomum cassia* (L.) J.Presl | Coronary artery rings | Porcine | 0.1–0.32 μM | U4, KCl | $Ca^{2+}$ |
| Cinnamaldehyde[152] | *Cinnamomum cassia* (L.) J.Presl | Aorta rings | SD rats | 0.1–100 μg/mL | PE | $Ca^{2+}$ |
| Cinnamaldehyde[153] | *Cinnamomum cassia* (L.) J.Presl | Aortic rings | Wistar rats | 0.1–3,000 μM | KCl | $Ca^{2+}$ |
| Cinnamaldehyde[154] | *Cinnamomum cassia* (L.) J.Presl | Thoracic aorta | Wistar rats | 1–1,000 μM | KCl, NE | NO, $Ca^{2+}$ |
| Eudesmin[155] | *Piper cubeba* L.fil. | Thoracic aorta | SD rats | 30–35 μg/mL | PE | NO, $PGI_2$, histamine receptor |
| Gomisin A[156] | *Schisandra chinensis* (Turcz.) Baill. | Thoracic aorta | SD rats | 0.1–1 mM | NaF, U46619 | Inhibition of RhoA-Rho-kinase pathway |
| Gomisin A[157] | *Schisandra chinensis* (Turcz.) Baill. | Thoracic aorta | SD rats | 1-300 μM | PE | Activating NO pathway, and partially dephosphorylation of MLC |
| Hypophyllanthin[158] | *Phyllanthus niruri* L. | Thoracic aorta | Wistar rats | 100 μM | PE | Blockade of $Ca^{2+}$ entry into VMSCs |
| Magnolin[159] | *Magnoliaceae* Juss. | Thoracic aorta | SD rats | 0.1–1,000 μM | PE | eNOS-NO |
| Phyllanthin[158] | *Phyllanthus niruri* L. | Thoracic aorta | Wistar rats | 100 μM | PE | Blockade of $Ca^{2+}$ entry into VMSCs |
| Prinsepiol-4-O-beta-D-glucopyranoside[160] | *Valeriana prionophylla* Standl. | Thoracic aorta | Wistar rats | 1–100 μM | PE | – |
| Silymarin[161] | *Silybum marianum* (L.) Gaertn. | Thoracic aorta | Wistar rats | 50 mg/L | PE | NO-$Ca^{2+}$ |
| (-)-Praeruptorin A[162] | *Peucedanum praeruptorum* Dunn | Thoracic aorta | SD rats | 1–30 μM, 3–100 μM | KCL, PE | Blocking $Ca^{2+}$ channels |
| (+)-Praeruptorin A[162] | *Peucedanum praeruptorum* Dunn | Thoracic aorta | SD rats | 1–100 μM | KCL and PE | Blocking $Ca^{2+}$ channels, NO-cGMP |
| 8-Geranyloxypsoralen | *Casimiroa edulis* Llave et Lex | Caudal arterial | Wistar rats | 0.1–100 μM | PE | – |
| Bakuchicin[163] | *Psoralea corylifolia* L. | Thoracic aorta | SD rats | 0.1–100 μM | PE | NO-cGMP, $Ca^{2+}$ |
| Herniarin[75] | Casimiroa edulis Llave et Lex | Caudal arterial | Wistar rats | 0.3–300 μM | PE | – |
| Imperatorin[75] | *Casimiroa edulis* Llave et Lex | Caudal arterial | Wistar rats | 0.3–300 μM | PE | $O^{2-}$ in the regulation of arterial tone |
| Mammea A/AA cycloF[164] | *Clusiaceae* | Thoracic aorta | MS rats | 0.32–32 μM | U46619 | NO-cGMP |
| Marmesin[165] | *Angelica citriodora* 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] | *Scopolia japonica* 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; $PGI_2$, 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.



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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, tiliacorinine 12'-O-acetate induces vasodilation by promoting $Ca^{2+}$ release *via* ryanodine receptors and $IP_3R$[187]. 8-Oxo-9-dihydromakomakine, isolated from *Aristotelia 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 isocorynoxeine—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, isocorynoxeine 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



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**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] | *Phlomis bracteosa* L. | Thoracic aorta | SD rat | 1–1,000 μg/mL | KCL, PE | $Ca^{2+}$, NO |
| Sclareol[167] | *Salvia sclarea* L. | Thoracic aorta | Normotensive/ hypertensive rats | $10^{-4}$–100 μM | PE | NO-cGMP |
| 1,8-Cineole[168] | *Alpinia zerumbet* (Pers.) B.L.Burtt 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] | *Viguiera arenaria* Baker | Thoracic aorta | Wistar rat | 10–100 μM | KCL, PE | $Ca^{2+}$, NO |
| Aristolone[170] | *Nardostachys jatamansi* (D.Don) DC. | Thoracic aorta and mesenteric arterial rings | Hypertensive rats | 0– 200 μM | U46619 | $K_{ATP}$, PDK1-Akt-eNOS |
| Betulinic acid[171] | *Ziziphus jujuba* Mill. var. | Thoracic aorta | SD rat | 0.01–100 μM | PE | eNOS, NO |
| Betulinic acid[172] | *Ziziphus jujuba* 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] | *Pectis brevipedunculata* (Gardner) Sch.Bip. | Thoracic aorta | Wistar Kyoto | 10–10,000 μM | PE | $Ca^{2+}$ |
| Ent-18-hydroxy-trachyloban-3-one[174] | *Croton zambesicus* Müll. Arg. | Thoracic aorta | Wistar rat | 1–3 μM | KCL, noradrenaline | $Ca^{2+}$, NO-cGMP |
| Erythrodiol[175] | – | Thoracic aorta | Wistar rat | 0.1–100 μM | KCL, PE | $Ca^{2+}$, NO |
| Gentiopicroside[176] | *Gentiana straminea* Maxim., *Gentiana macrophylla* 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] | *Viguiera robusta* Gardner | Thoracic aorta | Wistar rat | 50, 100 μM | KCL, PE | $Ca^{2+}$, NO-cGMP |
| Kaurenoic acid[179] | *Viguiera robusta* 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] | *Nardostachys jatamansi* (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] | *Phlomis bracteosa* L. | Thoracic aorta | SD rat | 1.0–1,000 μg/mL | KCl, PE | $Ca^{2+}$, NO |
| Piceatannol[180] | *Rheum undulatum* L. | Thoracic aorta | SD rat | 1–30 μM | PE | NO-cGMP |
| Pimaradienoic acid[178] | *Viguiera arenaria* Baker | Thoracic aorta | Wistar rat | 50, 100 μM | KCl, PE | $Ca^{2+}$, NO |
| Ursolic acid[181] | *Prunus serotina* Ehrh. | Thoracic aorta | Wistar rat | 1.0–1,000 μg/mL | PE | NO-cGMP, $H_2S$-$K_{ATP}$ |
| Uvaol[181] | *Prunus serotina* Ehrh. | Thoracic aorta | Wistar rat | 1.0–1,000 μg/mL | PE | NO-cGMP, $H_2S$-$K_{ATP}$ |
| Zerumbone[182] | *Zingiber zerumbet* (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 | – |
| Sedanolide[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, Phosphatidylinositide 3-kinases; SD, Sprague-Dawley; sGC, Soluble guanylyl cyclase. "–" indicates that the cited literature does not mention this content.



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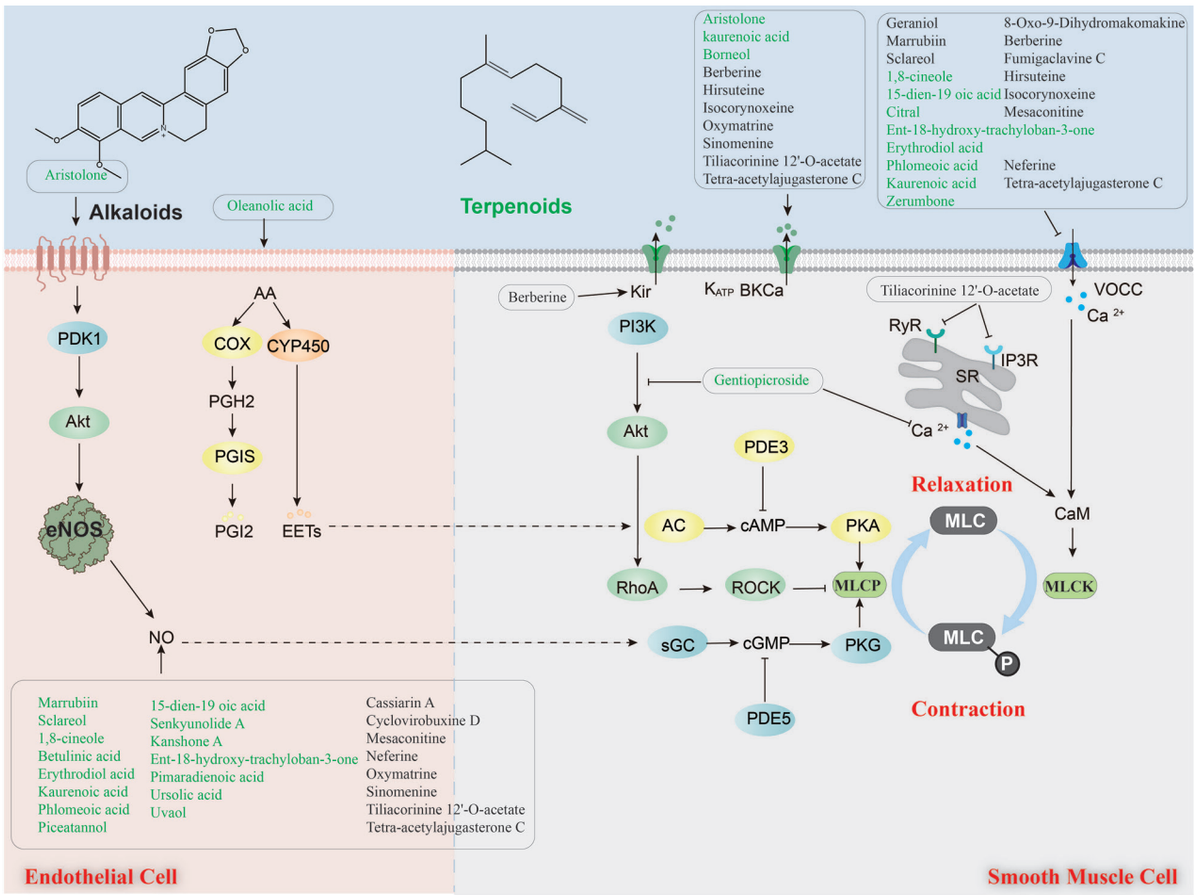



**Figure 6.** Mechanisms of vasodilation induced by alkaloids (black font) and terpenoids (green font) in ECs and VSMCs. In endothelial cells, alkaloids activate the PDK1-Akt-eNOS-NO pathway, while terpenoids regulate the COX-$PGI_2$ and CYP450-EETs pathways to produce vasodilatory mediators. In smooth muscle cells, these compounds inhibit $Ca^{2+}$ 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; $PGI_2$, Prostacyclin; PI3K, Phosphatidylinositide 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 $Ca^{2+}$ 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



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**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] | *Aristotelia chilensis* (Molina) Stuntz | Thoracic aorta | SD rats | 0.001–100 μM | PE | $Ca^{2+}$ |
| Berberine[186] | *Coptis chinensis* Franch. | Mesenteric arteries | SD rats | 1–30 μM | PE | $K^+$, $Ca^{2+}$ |
| Cassiarin A[185] | *Cassia siamea* Lam. | Mesenteric arteries | Wistar rats | 10 nM–100 mM | PE | NO-cGMP |
| Cyclovirobuxine D[193] | *Buxus sinica var. parvifolia* M.Cheng | Thoracic aorta | Wistar rats | 10–600 μM | KCl | NO-cGMP |
| Fumigaclavine C[190] | *Aspergillus fumigatus* Fresen. | Thoracic aorta | SD rats | 1–100 μM | PE, KCl | $Ca^{2+}$ |
| Hirsuteine[194] | Uncariae Ramulus et Uncus | Thoracic aorta | Wistar rats | 0.1–100 μM | NE | – |
| Isocorynoxeine[192] | *Uncaria rhynchophylla* (Miq.) Miq. | Mesenteric arteries | SD rats | 0.01–100 μM | PE, KCl | $Ca^{2+}$, Kv |
| Mesaconitine[191] | *Aconitum napellus* L. | Thoracic aorta | Wistar rats | 10–300 μM | PE | $Ca^{2+}$, NO |
| Neferine[184] | *Nelumbo nucifera* Gaertn. | Thoracic aorta | Wistar rats | $10^{-6}$–100 μM | PE, KCl | eNOS-NO-sGC, $Ca^{2+}$ |
| Oxymatrine[195] | *Sophora flavescens* Aiton | Thoracic aorta | SD rats | 0.9–34.2 mM | PE, KCl | NO-cGMP, $BK_{Ca}$, Kir |
| Sinomenine[189] | *Sinomenium acutum* (Thunb.) Rehder and E.H.Wilson | Thoracic aorta | Wistar rats, SHR | 0.1–10 mM | PE, KCl | $K_{ATP}$ |
| Tiliacorinine 12'-O-acetate[187] | *Tiliacora triandra* (Colebr.) Diels | Thoracic aorta | Wistar rats, SHR | $10^{-9}$–316 μM | PE | eNOS-NO-sGC, $Ca^{2+}$, Kv |
| Tetra-acetylajugasterone C[196] | *Vitex cienkowskii* Kotschy and Peyr. | Thoracic aorta | Rats | 0.01–100 μM | PE, KCl | NO-cGMP-cGKI, $K^+$, $Ca^{2+}$ |

$BK_{Ca}$, Large-conductance $Ca^{2+}$-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 $Ca^{2+}$ 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 $Ca^{2+}$ channels and inhibiting $Ca^{2+}$ 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



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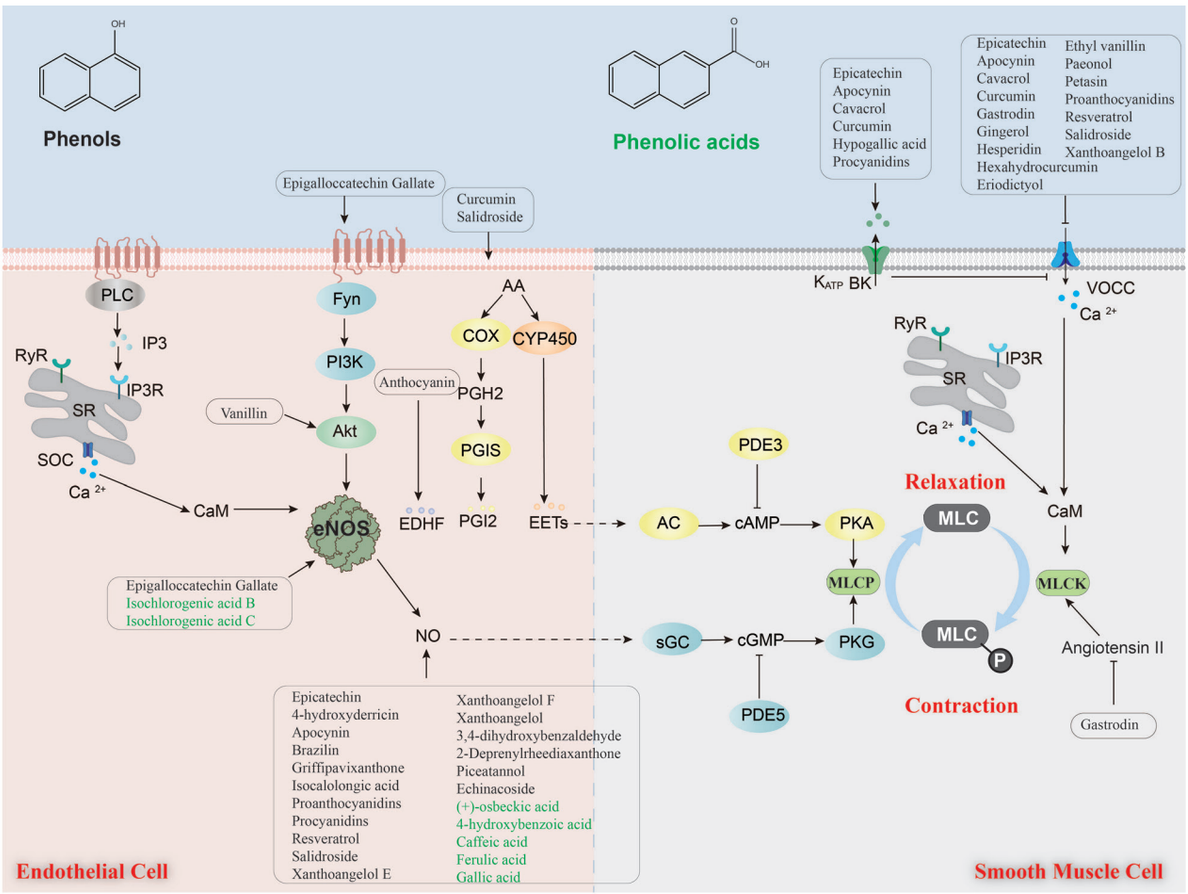



**Figure 7.** Mechanisms of vasodilation induced by phenolic (black font) compounds and phenolic acids (green font) in ECs and VSMCs. In endothelial cells, phenolic and phenolic acids activate the Fyn-PI3K-Akt-eNOS-NO pathway, regulate COX-$PGI_2$ and CYP450-EETs signaling, and modulate $Ca^{2+}$ dynamics to produce vasodilatory mediators. In smooth muscle cells, they inhibit $Ca^{2+}$ 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; $PGI_2$, Prostacyclin; PI3K, Phosphatidylinositide 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.

ischemia[219]. Tanshinone IIa, also isolated from *Salvia miltiorrhiza* Bunge, regulates vascular tone and vasodilation. The former is achieved *via* decreasing cyclic strain andtumor 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-1β (IL-1β), 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-κB) 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].



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**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] | *Clusiaceae* | Thoracic aorta | Male Swiss mice | 0.32–32 μM | U4 | NO-cGMP |
| (-) Epicatechin[206] | *Jasminum sambac* (L.) Aiton | Mesenteric arteries | SD rats | 10–300 μM | PE, U46619 | NO |
| (-) Epicatechin[207] | – | Internal mammary artery | Humans | 0.1–500 μM | PE | Kv, $BK_{Ca}$, $K_{ATP}$, $Ca^{2+}$ |
| 4-Hydroxyderricin[208] | *Angelica keiskei* (Miq.) Koidz. | Thoracic aorta | Wistar rat | 10–100 μg/mL | PE | NO |
| Anthocyanins/Flavylium[131] | – | Thoracic aorta | Wistar rats | 0.0001–100 μg/L | NE | ATP-P2Y1-P2Y2-NO, NO-GC-cGMP, PGI2, EDHF |
| Apocynin[197] | *Picrorhiza kurroa* Royle ex Benth. | Thoracic aorta | Wistar rats/SHR | 0.03–10 mM | PE | NO, $Ca^{2+}$, $K_{ATP}$ |
| Brazilin[102] | *Caesalpinia sappan* L. | Thoracic aorta | SD rats | 1–100 μM | PE | NO, cGMP |
| Carvacrol[201] | *Thymus vulgaris* L., *Origanum compactum* Benth., *Acalypha phleoides* Cav., *Species Lippia sidoides* Cham. | Thoracic aorta | Wistar rats | 1–1,000 μM | PE, KCl | $Ca^{2+}$ |
| Carvacrol[202] | – | Thoracic aorta | Wistar rats | 0.1–100 μM | KCl | $K^+$ |
| Chlorogenic acid[209] | *Eucommia* Oliv. | Thoracic aorta | Wistar rats | 0.0001–100 μM | PE | Increasing NOS, COX, and EDHF signaling pathways |
| Curcumin[199] | *Curcuma longa* L. | Mesenteric arteries | SD rats | 0.01–100 μM | PE, KCl | $PGI_2$, $K^+$, $Ca^{2+}$ |
| Echinacoside[210] | *Cistanche tubulosa* (Schenk) Wight | Thoracic aorta | SD rats | 30–300 μM | KCl, PE | NO-cGMP |
| Epigallocatechin Gallate[203] | – | Mesenteric vascular beds | Wistar rat | 1–100 μM | Norepinephrine | eNOS, phosphatidylinositol 3-kinase, Fyn kinase |
| Eriodictyol[211] | *Satureja obovata* Lag. | Thoracic aorta | Wistar rats | 10–100 μM | KCl, NE | $Ca^{2+}$ |
| Gastrodin[212] | *Gastrodia elata* Bl. | Abdominal aorta | c57bl/6 mice | 0.25–1.5 mg/mL | NE | $Ca^{2+}$, MLCK/p-MLC2 |
| Gingerol[200] | *Zingiber officinale* Roscoe | Carotid arteries, Thoracic aorta | SD rats | 50–400 mM | PE | p38 MAPK, $Ca^{2+}$ |
| Griffipavixanthone[164] | *Clusiaceae* | Thoracic aorta | Swiss mice | 0.32–32 μM | U4 | NO-cGMP |
| Hexahydrocurcumin[205] | *Curcuma longa* L. | Thoracic aorta | Wistar rats | 1 nM–1 mM | PE, KCl | $Ca^{2+}$, VOCC |
| Hypogallic acid[112] | *Phyllanthus acidus* (L.) Skeels | Thoracic aorta | Wistar rats | 1–10 mg/kg | PE | $K_{ATP}$ |
| Isocalolongic acid[164] | *Calophyllum caledonicum* Vieill. | Thoracic aorta | Male Swiss mice (6–8 weeks) | 0.25–25 mM | U46619 | NO |
| Paeonol[213] | *Paeonia × suffruticosa* Andrews., *Cynanchum paniculatum* (Bunge) Kitag. | Renal artery, coronary artery | Hyperlipidemic model rats | 0.251–10 mM | KCl | $Ca^{2+}$ |
| Petasin[204] | *Petasites formosanus* Kitam. | Thoracic aorta | SD rat, Wistar rat, SHR | 0.01–100 μM | KCl | VOCC |
| Proanthocyanidins[214] | – | Mesenteric arterial bed, mesenteric artery | Wistar rats | 1–100 μg/mL | PE | NO-cGMP, $Ca^{2+}$ |

(Continued)



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**Table6**
**(Continued)**

| Compounds | Natural medicine | Vascular type | Species investigated | Dosage | Vasoconstrictor | Mechanisms |
|---|---|---|---|---|---|---|
| Procyanidins[198] | *Malus pumila* Mill. | Thoracic aorta | SD rats | 0.3–100 mg/mL | PE, KCl | NO-cGMP, $K^+$ |
| Protocatechuic acid[215] | *Fagopyrum tataricum* (L.) Gaertn. | Thoracic aorta | SD rats | 0.5–2.5 mg/mL | PE | – |
| Resveratrol[180] | *Rheum rhabarbarum* L. | Thoracic aorta | SD rats | 1–30 μM | PE | – |
| Salidroside[216] | *Rhodiola rosea* L. | Thoracic aorta | SD rat | $10^{-5}$–10 μM | PE | COX-$PGI_2$, VDCC, ROCC |
| Thymol[201] | *Thymus vulgaris* L., *Origanum compactum* Benth., *Acalypha phleoides* Cav., *Species Lippia sidoides* Cham. | Thoracic aorta | Wistar rats, SHR | 1–1,000 μM | PE, KCl | – |
| Panthoangelol B[208] | *Angelica keiskei* (Miq.) Koidz. | Thoracic aorta | Wistar rats | 10–100 μg/mL | PE | $Ca^{2+}$ |
| Xanthoangelol E[208] | *Angelica keiskei* (Miq.) Koidz. | Thoracic aorta | Wistar rats | 10–100 μg/mL | PE | EDRF-NO |
| Xanthoangelol F[208] | *Angelica keiskei* (Miq.) Koidz. | Thoracic aorta | Wistar rats | 10–100 μg/mL | PE | EDRF-NO |
| Xanthoangelol[208] | *Angelica keiskei* (Miq.) Koidz. | Thoracic aorta | Wistar rats | 10–100 μg/mL | PE | EDRF-NO |
| 3,4-Dihydroxybenzaldehyde[76] | *Gastrodia elata* Bl. | Thoracic aorta | SD rats | 0.1–10 μM | PE | NO-cGMP |
| Piceatannol[180] | *Rheum rhabarbarum* L. | Thoracic aorta | SD rats | 1–30 μM | PE | NO |
| Vanillin[217] | – | Porcine coronary and basilar arteries | Pigs | 1–10,000 μM | U4, KCl | L-Type $Ca^{2+}$ Channels |
| Vanillin[12] | – | Porcine coronary | SD rats | 0.1–1,000 μM | U4 | Akt-eNOS-NO |
| Vanillyl alcohol[217] | – | Porcine coronary and basilar arteries | Pigs | 1–10,000 μM | U4, KCl | L-Type $Ca^{2+}$ channels |

$BK_{CA}$, Large-conductance $Ca^{2+}$-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; $PGI_2$, 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 $Ca^{2+}$ 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.



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**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] | *Rheum rhabarbarum* L. | Thoracic aorta | SD rats | 1–30 μM | PE | – |
| (+)-Osbeckic acid[215] | *Fagopyrum tataricum* (L.) Gaertn. | Thoracic aorta | SD rats | 0.5–2.5 mg/mL | PE | NO-cGMP |
| 4-Hydroxybenzoic acid[112] | *Phyllanthus acidus* (L.) Skeels | Thoracic aorta | Wistar rats | 1–10 mg/kg | PE | sGC pathway |
| Caffeic acid[112] | *Phyllanthus acidus* (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 ($Ca^{2+}$ and $K^{+}$) modulation, and free radical scavenging. Increased cytosolic $Ca^{2+}$ 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 $Ca^{2+}$ directly activates downstream signaling, ultimately modulating $Ca^{2+}$ levels. Consequently, natural products such as tanshinone IIA and ligustilide, which modulate eNOS expression and inhibit $Ca^{2+}$ 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.



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**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-phenylethene[224] | – | Thoracic aorta | Wistar rats | 0.1–100 μg/mL | PE, KCl | $Ca^{2+}$ |
| 3-(3, 4-Dihydroxyphenyl)-2-hydroxypropanoate[225] | *Salvia miltiorrhiza* Bunge | Intestinal artery | SD rats | 0.0001–30 μM | NE | $Ca^{2+}$ |
| 4,4'-Dihydroxydiphenyl methane[76] | *Gastrodia elata* Bl | Thoracic aorta | SD rats | 0.3–3 mM | PE | $Ca^{2+}$ |
| 4-Hydroxy-3-(3-methyl-2-butenyl) acetophenone[226] | *Senecio nutans* Sch.Bip. | Thoracic aorta | SD rats | 10 μM | PE | $Ca^{2+}$ |
| 5-Acetyl-6-hydroxy-2-isopropenyl-2,3-dihydrobenzofurane[226] | *Senecio nutans* Sch.Bip. | Thoracic aorta | SD rats | 10 μM | PE | $Ca^{2+}$ |
| 5-Hydroxymethyl-2-furoic acid[215] | *Fagopyrum tataricum* (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] | *Phyllanthus acidus* (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] | *Crambe* L. | Aortic rings | Wistar rats | 0.1–10 μM | PE | eNOS, iNOS |
| Piceatannol[180] | *Rheum rhabarbarum* L. | Thoracic aorta | SD rats | 0–30 μM | PE | NO |
| Resveratrol[180] | *Rheum rhabarbarum* L. | Thoracic aorta | SD rats | 0–30 μM | | 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 rosmarinate[233] | *Hyptis suaveolens* (L.) Poit. | Thoracic aorta | Wistar rats | 0.1–3 mM | PE | $Ca^{2+}$ |
| 3-(1,3-Dioxoisoindolin-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] | *Salvia miltiorrhiza* Bunge | Mesenteric artery | Male SD rats | 0.001–10 μM | NE | Vascular TEA sensitive $K^+$, $Ca^{2+}$ |
| Isotirumalin[236] | *Derris urucu* (Killip and A.C.Sm.) J.F.Macbr. | Thoracic aorta | Wistar rats | 0.01–100 μM | PE | Activate endothelial-derived NO |
| Phytoestrogen α-zearalanol[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)





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**Table 8**

**(Continued)**

| Compounds | Natural medicine | Vascular type | Species investigated | Dosage | Vasoconstrictor | Mechanisms |
|---|---|---|---|---|---|---|
| R-(-)-3'-hydroxy-2,4,5-trimethoxydalbergiquinol isolated[238] | *Dalbergia tonkinensis* Prain | Thoracic aorta | Sprague–Dawley rats | 1–100 μM | PE | $Ca^{2+}$ |
| Shikonin/alkannin[239] | *Macrotomia euchromon* (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-dioctanoxypropan[241] | – | Thoracic aorta | C57BL/6, Wistar rats | 0.1–1,000 μM | PE | NO-cGMP-PKG, $K_{IR}$ |
| 3-Demethyl-2-geranyl-4-prenylbellidifoline[242] | *Garcinia hanburyi* 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] | *Senecio nutans* 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] | *Chenopodium album* L. | Thoracic aorta | SD rat | 1–300 mg/kg | | NO |
| Corynoxeine[194] | Uncariae Ramulus et Uncus | Thoracic aorta | Wistar rat | 0.1-100 μM | NE | – |
| Dihydrotanshinone[246] | *Salvia miltiorrhiza* Bunge | Thoracic aorta | SD rat | 0–100 μM | 5-HT | NO-cGMP |
| Ent-18-hydroxy-trachyloban-3-one[174] | *Croton zambesicus* Müll. Arg. | Thoracic aorta | Wistar rat | 1–3 μM | KCl | eNOS |
| Ent-trachyloban-14,15-dione[174] | *Croton zambesicus* Müll. Arg. | Thoracic aorta | Wistar rat | 1–3 μM | KCl | $Ca^{2+}$ |
| Esquamosan[247] | *Annona squamosa* L. | Thoracic aorta | Rat | 0.1 nM–100 μM | KCl, PE | $Ca^{2+}$ |
| Gastrodin[248] | *Gastrodia elata* 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 | – |
| Gentiopicroside[176] | *Gentiana straminea* Maxim. | Thoracic aorta | SD rat | 5–320 μM | PE | PI3K-Akt-Rho $Ca^{2+}$ |
| Korean plum[249] | *Prunus mume* (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] | *Paeonia suffruticosa* Andrews | Mesenteric artery | Wistar rat | 0.001–1,000 μM | KCl, PE | $K^+$ |
| RA[166] | *Phlomis bracteosa* Royle ex Benth. | Thoracic aorta | SD rat | 3.0–10 μg/mL | PE | NO/cGMP |
| RB[166] | *Phlomis bracteosa* Royle ex Benth. | Thoracic aorta | SD rat | 3.0–10 μg/mL | PE | NO/cGMP |
| Rumex acetosa L.[251] | *Rumex acetosa* L. | Thoracic aorta | SD rat | 10–50 mg/kg | High $K^+$ | $Ca^{2+}$ |
| Tambulin[252] | *Zanthoxylum armatum* 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-alpha; $PGI_2$, Prostacyclin; PI3K, Phosphatidylinositide 3-kinases; PKG, Protein kinase G; SHR, Spontaneously hypertensive rats; SD, Sprague-Dawley; SIRT1, Sirtuin 1; SKCa, Small-conductance $Ca^{2+}$-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 $Ca^{2+}$ concentrations in VSMCs. These pathways include stimulating the production of vasodilatory factors (NO and $PGI_2$), activating $K^+$ channels (Kv, $BK_{Ca}$, $K_{ATP}$, and $K_{IR}$), and inhibiting VOC, ROC, and SOC $Ca^{2+}$ 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



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**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.

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## 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.

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## 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.

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