

REVIEW ARTICLE

Significance of the PI3K/AKT pathway in coronary microvascular dysfunction and advances in natural compound therapeutic research

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Abstract

Introduction: Coronary microvascular dysfunction (CMD) contributes to myocardial ischemia and adverse cardiovascular outcomes, but effective treatments remain limited.**Objective:** This review aims to clarify the role of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway in CMD and assess the therapeutic potential of natural compounds that modulate it.**Methods:** Available mechanistic and preclinical evidence on PI3K/AKT-mediated regulation of endothelial dysfunction, oxidative stress, inflammation, apoptosis, angiogenic repair, and microvascular homeostasis in CMD was reviewed. Natural compounds were classified into flavonoids, saponins, phenolic compounds, alkaloids, and polysaccharides, and their reported effects on PI3K/AKT-related downstream signaling axes were summarized.**Results:** The PI3K/AKT pathway acts as a context-dependent signaling hub in CMD. Appropriate activation supports endothelial survival, vasodilation, antioxidant defense, anti-inflammatory responses, and inhibition of cardiomyocyte apoptosis through signaling axes including AKT/eNOS, AKT/NRF2, AKT/mTOR, and BCL-2/BAX/caspase. Preclinical studies indicate that several natural compounds can ameliorate cardiovascular injury by modulating these axes, thereby reducing oxidative stress and inflammation, limiting apoptosis and autophagy-related injury, and promoting angiogenesis and microvascular repair. However, most evidence derives from non-CMD-specific cellular and animal models and relies primarily on changes in pathway phosphorylation or pharmacological inhibitor experiments. Direct genetic validation, pharmacokinetic characterization, formulation standardization, and clinical evidence remain insufficient.**Conclusion:** Natural compounds represent promising multi-target modulators of PI3K/AKT-related signaling in CMD, but their efficacy and pathway dependence require rigorous validation. Future studies should employ CMD-relevant models, objective microvascular endpoints, genetic approaches, optimized delivery systems, and integrative platforms such as organoids, multi-omics, artificial intelligence, and network pharmacology to facilitate clinical translation.**Keywords:** Coronary microvascular dysfunction; PI3K/AKT pathway; Oxidative stress; Inflammatory response; Natural products; Therapeutic target[†]These authors contributed equally to this work.***Corresponding authors:**Zhao Ge
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1. Introduction

Coronary microvascular dysfunction (CMD) is a complex condition characterized by structural and/or functional abnormalities of the coronary microcirculation, resulting in impaired regulation of myocardial blood flow. It may cause myocardial ischemia with or without angina and can occur in the absence of obstructive epicardial coronary artery disease. Importantly, CMD has been identified as an independent predictor of adverse cardiovascular events, underscoring its significance beyond traditional coronary artery disease.¹ The disease primarily targets the coronary microcirculation—a delicate network of small vessels that plays a critical role in sustaining myocardial metabolism and meticulously regulating the equilibrium between blood flow and oxygen consumption, particularly during diastole and periods of vasoconstriction. When the coronary microcirculatory system endures prolonged structural and functional impairments—including microvascular obstruction, stenosis of the small arteries and capillary lumens, capillary rarefaction,² abnormalities in endothelium-dependent and endothelium-independent vasodilation, microvascular constriction irregularities, microvascular embolism, altered blood viscosity, and other pathological conditions³—microcirculatory disorders become increasingly prone to development. These disturbances subsequently trigger the clinical symptoms of CMD, such as chest tightness, chest pain, and myocardial dystrophy, as illustrated in [Figure 1](#).⁴

Microvascular angina is one of the clinical manifestations of myocardial ischemia caused by CMD. Its diagnostic criteria require the presence of ischemia-related symptoms, absence of obstructive coronary artery disease, objective evidence of myocardial ischemia, and documented impairment of coronary microvascular function. In recent years, the European Society of Cardiology Guidelines for Chronic Coronary Syndromes and the EAPCI/COVADIS consensus statements have incorporated angina with non-obstructive coronary arteries (ANOCA) and ischemia with non-obstructive coronary arteries (INOCA) as key clinical phenotypes into the diagnostic and therapeutic framework. Specifically, ANOCA is defined as the coexistence of angina or angina-equivalent symptoms with non-obstructive coronary arteries, whereas INOCA highlights the presence of objective myocardial ischemia in the setting of non-obstructive coronary arteries. Together with epicardial coronary vasospasm, endothelial dysfunction, diffuse non-obstructive atherosclerosis and myocardial bridging, CMD represents a major pathophysiological endotype of ANOCA/INOCA and serves as a critical mechanism underlying anginal symptoms and/or myocardial ischemia. Nevertheless, CMD is not exclusive

to patients with ANOCA/INOCA; it can also develop in a broad spectrum of clinical scenarios, including obstructive coronary artery disease, cardiomyopathy, heart failure, myocardial hypertrophy, and following percutaneous coronary intervention.

Phosphoinositide 3-kinase (PI3K), a lipid kinase, plays a central role in cardiovascular biology by regulating multiple cellular processes, including cell survival, energy metabolism, myocardial hypertrophy, electrophysiology, and contractility. These effects support PI3K as a potential therapeutic target for heart failure intervention.⁵ The PI3K/protein kinase B (AKT) signaling pathway is critically involved in inflammation and oxidative stress associated with CMD. Dysregulation of this pathway may contribute to the pathogenesis of CMD-associated cardiovascular injury. Activation of this pathway may have context-dependent effects: Physiological activation of this pathway may protect cardiomyocytes and endothelial cells from injury, whereas aberrant or sustained activation may promote cardiac remodeling and thereby aggravate microvascular dysfunction.⁶⁻⁸ This complexity suggests that the PI3K/AKT pathway functions as a dynamic integrator of CMD pathology, positioning it as a promising but challenging therapeutic target. The development of direct kinase modulators faces major challenges, including limited specificity and systemic adverse effects, which complicate their clinical application.

In this context, natural products derived from traditional medicinal plants offer a compelling alternative. Characterized by multi-target activities, low toxicity, and synergistic effects, they are particularly suited for modulating complex pathways such as PI3K/AKT, which governs interconnected biological processes in CMD.⁹ A growing body of preclinical evidence suggests that various natural products can ameliorate CMD by fine-tuning this pathway to attenuate oxidative stress, suppress inflammation, and inhibit apoptosis.¹⁰

This review explores the PI3K/AKT pathway in CMD, highlighting novel insights into the role of natural compounds in modulating this pathway to address CMD. In general, our findings offer a new therapeutic approach to the clinical management of CMD.

2. Overview of the PI3K/AKT pathway

The PI3K/AKT pathway stands as a pivotal intracellular signaling hub, orchestrating essential cellular processes such as metabolism and angiogenesis in direct response to extracellular cues. This pathway is distinctly marked by the phosphorylation of downstream substrates at serine or threonine residues, a process primarily driven by the master regulators PI3K and AKT.

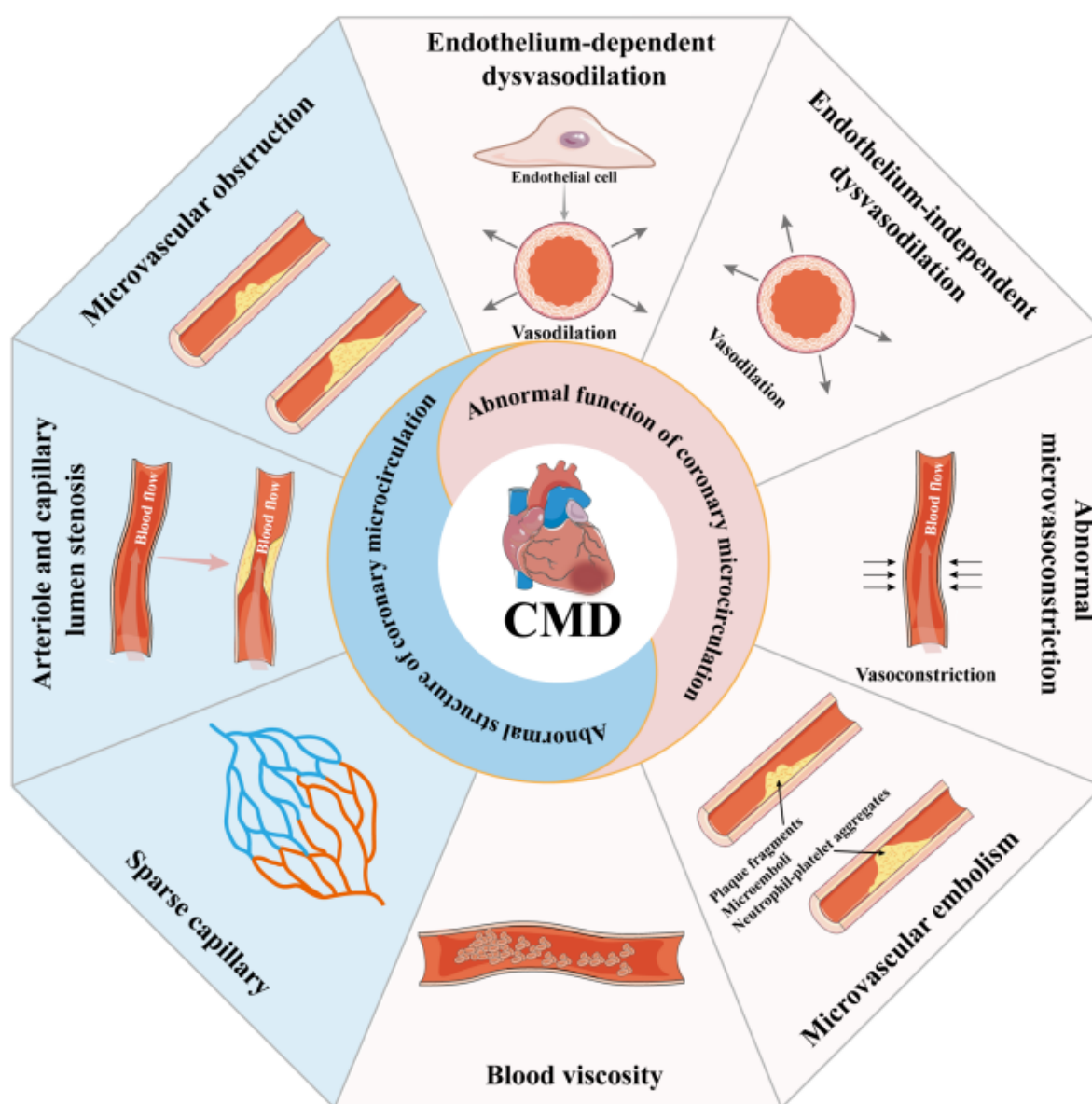


Figure 1. The pathophysiological mechanism of coronary microvascular dysfunction (CMD). It primarily involves the abnormal structure and function of the coronary microcirculation. The structural abnormalities primarily include microvascular obstruction, stenosis of arterioles and capillary lumens, and sparse capillaries. Functional abnormalities mainly include endothelium-dependent vasodilation, endothelium-independent vasodilation, microvascular constriction, microvascular embolism, and blood viscosity. Figure created by the authors with Adobe Illustrator 2023.

Studies have established the PI3K/AKT pathway as a key intracellular signaling cascade. Its activation is typically initiated by extracellular stimuli binding to cell surface receptors, leading to PI3K phosphorylation and subsequent AKT phosphorylation. Activated AKT then transmits signals to downstream effectors that regulate multiple cellular functions.¹¹

Phosphoinositide 3-kinase belongs to the

phosphatidylinositol kinase family and has both lipid kinase and protein kinase activities.¹² According to sequence similarity and substrate specificity, PI3K is divided into three classes: Class I, II, and III. Class I PI3K is particularly associated with malignant tissues and tumor-related signaling.¹³ Class I and II PI3Ks mainly participate in intracellular signal transduction, whereas Class III PI3K is more closely involved in membrane transport and vesicular trafficking.¹⁴

Class I PI3K is the best-characterized subtype and consists of regulatory subunits, including p85 α , p85 β , and p55 γ , as well as catalytic subunits, including p110 α , p110 β , p110 δ , and p110 γ .¹⁵ Class IA PI3Ks are activated primarily downstream of receptor tyrosine kinases, although certain isoforms can also be regulated by G protein-coupled receptors and RAS-family small GTPases. By contrast, Class IB PI3K is activated mainly downstream of G protein-coupled receptors. After activation, the p85 regulatory subunit interacts with tyrosine receptors, enabling the p110 catalytic subunit to convert phosphatidylinositol diphosphate into phosphatidylinositol triphosphate.¹⁶ PIP3 then acts as a second messenger to promote AKT phosphorylation and activation, thereby regulating cell survival, growth, and metabolism.¹⁷

Protein kinase B is a central downstream effector of PI3K signaling and participates in cell proliferation, transcription, metabolism, and survival. It has three major isoforms: AKT1, AKT2, and AKT3. AKT1 is widely expressed in multiple tissues; AKT2 is mainly distributed in insulin-sensitive tissues, such as skeletal muscle and liver; and AKT3 is predominantly expressed in the brain and testis.¹⁸ Through these isoforms, the PI3K/AKT pathway regulates cell growth, homeostasis, and intracellular signaling during the cell cycle.

Activation of PI3K generates phosphatidylinositol 3,4,5-trisphosphate (PIP3), which recruits AKT to the plasma membrane, where it is phosphorylated and activated.¹⁹ Once activated, AKT regulates downstream effectors such as mechanistic target of rapamycin complex 1 (mTOR1), glycogen synthase kinase 3 β , and forkhead box O transcription factors, thereby influencing cell growth, metabolism, and protein synthesis.²⁰ Through these downstream effectors, the PI3K/AKT pathway is closely associated with the development and progression of cardiac fibrosis (Figure 2).

3. The PI3K/AKT pathway in coronary microvascular dysfunction

Activation of the PI3K/AKT pathway does not exert a unidirectional biological effect. Instead, its ultimate impact depends on multiple regulatory factors within a specific cellular microenvironment, including the source of upstream stimuli, cell type, the status of negative regulators such as phosphatase and tensin homolog, the intensity and duration of AKT phosphorylation, and the selective activation of downstream effector branches. For instance, in tumor cells or airway smooth muscle cells, sustained activation of PI3K/AKT/mTOR driven by pro-proliferative or pro-remodeling signals, including growth factors, inflammatory mediators, activation of RAS-family

small GTPases, or alterations in *PIK3CA*, can promote cell proliferation, migration, survival, and tissue remodeling, thereby exacerbating tumor progression or asthma-related airway remodeling.²¹⁻²³ In contrast, in cardiovascular disease models, activation of this pathway is often considered protective, reducing cardiomyocyte apoptosis and mitigating myocardial injury during ischemic events.²⁴ Studies further indicate that microvascular dysfunction is closely associated with atherosclerotic changes in patients with cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia.²⁵ In healthy endothelial cells, low levels of phosphorylated PI3K and AKT are essential for sustaining vascular homeostasis and preventing aberrant cellular responses. However, when endothelial cells are damaged, this triggers the secretion of growth factors and the activation of neurokinin 1 receptors, which in turn initiates the PI3K/AKT signaling cascade. This activation enhances endothelial cell proliferation and migration while simultaneously suppressing apoptosis and inflammatory processes, thereby promoting vascular repair and remodeling.²⁶

Hyperglycemia, hyperosmotic stress, elevated levels of inflammatory mediators and cytokines, exposure to toxicants, and microbial infections collectively disrupt the delicate balance of endothelial cell function and the normal regulation of the PI3K/AKT pathway. These disruptions are intricately linked to the pathogenesis of numerous diseases, including ischemic cardiomyopathy, hypertrophic cardiomyopathy, diabetic cardiomyopathy, and atherosclerosis. The initiation and progression of these conditions are primarily driven by alterations in cardiomyocyte oxygen demand, vascular endothelial injury, chronic inflammation, and programmed cell death, all of which are modulated by the nuanced dysregulation of the PI3K/AKT signaling network.

3.1. Role of PI3K/AKT signaling in coronary microvascular dysfunction-related oxidative stress

Endothelial injury within coronary microvessels is an important initiating factor in coronary microcirculatory disorders. Stress-induced dysfunction of coronary microvascular endothelial cells is closely associated with CMD and represents an early pathological feature of this condition. An excessive accumulation of cellular reactive oxygen species (ROS) triggers oxidative stress, which is recognized as a key contributor to the pathogenesis of CMD. However, the precise mechanisms require further investigation.²⁷

During myocardial ischemia/reperfusion (I/R) injury, reperfusion after ischemia and hypoxia promotes the generation of ROS through multiple pathways, including

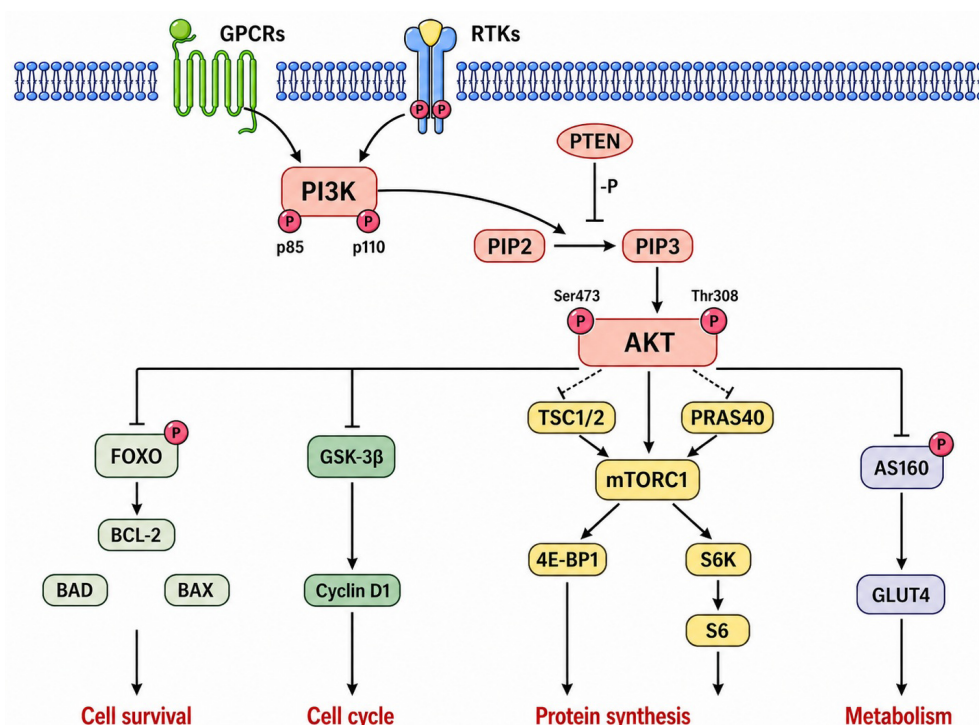


Figure 2. Overview of PI3K/AKT signaling. GPCRs and RTKs activate PI3K through receptor- and isoform-specific mechanisms. Activated PI3K converts PIP2 into PIP3. PIP3 serves as a membrane docking site for AKT, which is activated through phosphorylation at Ser473 and Thr308. Activated AKT regulates major biological processes, including cell survival, cell cycle regulation, protein synthesis, and glucose metabolism, by phosphorylating multiple downstream effectors. (i) Cell survival: AKT phosphorylates and inhibits FOXO transcription factors, thereby reducing the transcription of pro-apoptotic genes and promoting cell survival. (ii) Cell-cycle regulation: AKT phosphorylates and inhibits GSK-3 β , thereby increasing cyclin D1 stability and promoting cell-cycle progression. (iii) Protein synthesis: AKT phosphorylates the mTORC1-interacting protein PRAS40 and the mTORC1 regulatory factor TSC1/2, thereby relieving the inhibitory effects of TSC1/2 and promoting mTORC1 activation. Activated mTORC1 promotes protein synthesis through downstream effectors such as S6K and 4E-BP1. (iv) Metabolic regulation: AKT phosphorylates AS160, facilitating GLUT4 vesicle translocation to the plasma membrane and increasing glucose uptake. Figure created by the authors with Adobe Illustrator 2023.

Abbreviations: 4E-BP1: Eukaryotic initiation factor 4E-binding protein; AKT: Protein kinase B; AS160: AKT substrate of 160 kDa; BAD: BCL-2-associated agonist of cell death; BAX: BCL-2-associated X protein; BCL-2: B-cell lymphoma 2; FOXO: Forkhead box O; GLUT4: Glucose transporter 4; GPCRs: G protein-coupled receptors; GSK-3 β : Glycogen synthase kinase-3 β ; mTORC1: Mechanistic target of rapamycin complex 1; p85: PI3K regulatory subunit p85; p110: PI3K catalytic subunit p110; PI3Ks: Phosphoinositide 3-kinases; PIP2: Phosphatidylinositol 4,5-bisphosphate; PIP3: Phosphatidylinositol 3,4,5-trisphosphate; PRAS40: Proline-rich Akt substrate of 40 kDa; PTEN: Phosphatase and tensin homolog; RTKs: Receptor tyrosine kinases; S6: Ribosomal protein S6; S6K: Ribosomal S6 kinase; TSC1/2: Tuberous sclerosis complex 1/2.

the xanthine oxidase pathway, phagocytic cell activation, and the mitochondrial respiratory chain. This cascade results in a marked increase in ROS levels coupled with insufficient scavenging mechanisms, ultimately leading to significant damage to myocardial cells. Elevated ROS levels can impair myocardial endothelial cells by promoting the formation of lipid peroxides, inhibiting mitochondrial oxidative phosphorylation, and disrupting the integrity of microcirculation.²⁸

Phosphoinositide 3-kinase demonstrates notable sensitivity to redox modifications and can be activated by fluctuations in intracellular ROS concentrations.

Myocardial I/R injury elevates intracellular ROS levels and oxidative stress, which in turn triggers a compensatory activation of the PI3K/AKT signaling pathway. Furthermore, activation of this pathway may mitigate oxidative stress injury during myocardial I/R by upregulating Nuclear factor erythroid 2-related factor 2 (NRF2), a key transcription factor involved in antioxidant defense.²⁹

3.2. Role of PI3K/AKT signaling in inflammation associated with coronary microvascular dysfunction

Microvascular inflammation is increasingly recognized

as an important contributor to CMD. Accumulating evidence suggests an association between microvascular impairment and elevated systemic inflammatory levels. During the earliest phase of I/R injury, proinflammatory chemokines and cytokines are markedly increased, accompanied by a substantial release of ROS.³⁰ This initial response promotes a neutrophil-driven inflammatory cascade. Stimulated early in the process by these proinflammatory and chemokine factors, neutrophils begin to adhere to the endothelium and aggregate at the site of injury. These activated neutrophils then release an abundance of proteolytic enzymes that act upon cellular membranes and components of the extracellular matrix, thereby facilitating cellular degradation. Furthermore, these cells release additional inflammatory mediators, including proteolytic enzymes, lipocalin-2 (also known as neutrophil gelatinase-associated lipocalin), and ROS.³¹ Following adhesion mediated by macrophage-1 antigen, neutrophils release myeloperoxidase and various proteases through degranulation and generate superoxide through nicotinamide adenine dinucleotide phosphate oxidase. This superoxide can directly damage the endothelium or indirectly promote tissue injury by activating inflammatory mediators.³²

Ischemia/reperfusion injury increases high-mobility group box 1 levels, which in turn triggers the activation of Toll-like receptor 4 (TLR4) and the subsequent recruitment of myeloid differentiation primary response88. This activation stimulates downstream signaling pathways, culminating in increased expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and tumor necrosis factor- α (TNF- α). In contrast, PI3K can effectively suppress TLR4 signaling by blocking the recruitment of Toll/interleukin-1 receptor domain-containing adaptor protein to the cell membrane, thereby inhibiting NF- κ B activation and the production of its downstream proinflammatory cytokines. This inhibition ultimately alleviates myocardial I/R injury. Conversely, the inhibition of the PI3K/AKT pathway enhances NF- κ B transcription and the release of TNF- α and interleukin-6, thereby worsening I/R injury.³³ Methyl eugenol has been reported to activate the PI3K/AKT signaling pathway, decrease inflammatory factor expression, and reduce apoptosis.³⁴

3.3. Regulation of apoptosis in coronary microvascular dysfunction by PI3K/AKT signaling

Apoptosis is a form of programmed cell death associated with CMD and is regulated by multiple interconnected molecular events. These events include ROS generation, impaired cellular energy metabolism, intracellular calcium overload, activation of proinflammatory cytokines, and

the orchestrated expression of key regulatory genes such as the caspases and the B-cell lymphoma 2 (BCL-2) family. Together, these alterations contribute to disease progression and highlight the importance of apoptosis in pathological states. The mitochondrial pathway, also known as the intrinsic apoptotic pathway, is a major mechanism of apoptosis. Endogenous apoptotic signals activate BCL-2-associated X protein (BAX)/BCL2 antagonist/killer 1 (BAK), promoting mitochondrial outer membrane permeabilization.³⁵

When endogenous apoptotic signals are triggered, they activate pro-apoptotic proteins such as BAX and BAK. This breach in the mitochondrial outer membrane allows cytochrome c, a key pro-apoptotic factor, to be released from the intermembrane space into the cytoplasm.³⁶ Once released into the cytoplasm, cytochrome c binds to apoptotic protease activating factor 1 and pro-caspase-9, forming a multi-protein complex known as the apoptosome. This complex acts as a molecular scaffold that initiates the conversion of inactive pro-caspase-9 into active caspase-9.³⁷ Activation of caspase-9 then initiates a downstream caspase activation cascade, particularly including the executioner caspase, caspase-3. This sequential activation ultimately leads to apoptotic cell death.

In contrast, the PI3K/AKT signaling pathway is a well-established and potent anti-apoptotic mechanism that serves as a critical cellular survival pathway. When activated, the PI3K/AKT pathway robustly antagonizes apoptosis by phosphorylating and thereby inhibiting key pro-apoptotic mediators such as BAD and caspase-9.³⁸ This phosphorylation event effectively neutralizes their death-promoting activities. Studies have shown that activation of the PI3K/AKT pathway increases the levels of the anti-apoptotic protein Bcl-2, while simultaneously reducing the expression of the pro-apoptotic proteins BAX and caspase-3.³⁴ By tipping the balance in favor of cell survival, this pathway effectively prevents the onset of apoptosis. Therefore, modulation of the PI3K/AKT pathway may help alleviate CMD-related myocardial injury by activating the NRF2/HO-1 antioxidant axis, suppressing TLR4/NF- κ B-mediated inflammatory signaling, and shifting the Bcl-2/Bax/caspase-3 balance toward cell survival (Figure 3).

4. Natural products targeting the PI3K/AKT pathway in coronary microvascular dysfunction

Natural products have therapeutic potential because they act on multiple biological targets and pathways. Recent studies have highlighted the potential role of traditional Chinese medicine in the prevention and treatment of CMD.

Natural medicines contain diverse chemical constituents, such as flavonoids, saponins, phenols, alkaloids, and polysaccharides, each of which may serve as an active compound with significant therapeutic potential. Table 1 summarizes these active constituents, their experimental models, PI3K/AKT-related targets or signaling axes, and main experimental efficacy outcomes.

4.1. Flavonoids

Flavonoids and other natural products are renowned for their diverse and potent biological activities, encompassing antioxidant capabilities, the stimulation of angiogenesis, anti-allergic responses, hepatoprotective effects against hepatic injury, anti-tumor mechanisms, and the

safeguarding of endothelial cell integrity. These compounds intricately participate in fundamental biological processes—such as programmed cell death (apoptosis), cellular proliferation, and immune modulation—through the engagement of multiple signaling pathways.

Puerarin, a prominent isoflavone extracted from the roots of the lobed kudzu root (*Pueraria lobata*), has been scientifically validated to enhance cardiac angiogenesis in rat models of myocardial infarction, thereby significantly improving overall heart function.³⁹ In a related study, Li *et al.*⁴⁰ demonstrated that puerarin effectively inhibits hydrogen peroxide (H₂O₂)-induced endothelial-mesenchymal transition through the activation of the PI3K/AKT signaling pathway, which in turn reduces

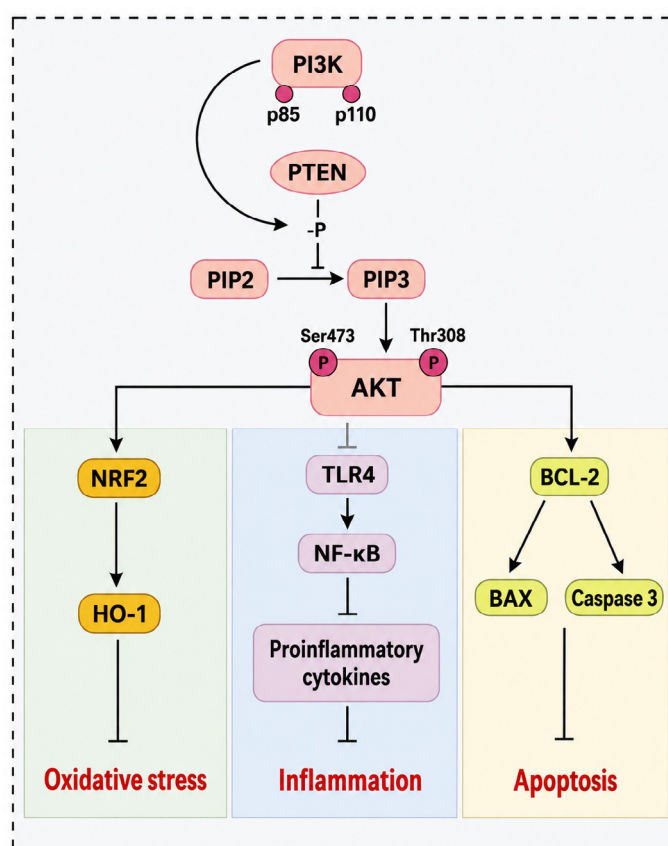


Figure 3. Overview of the PI3K/AKT pathway in CMD. Activated PI3K/AKT is involved in CMD treatment by implementing triple biological regulation through targeting different substrate proteins. (i) Oxidative stress response: PI3K/AKT-mediated NRF2 phosphorylation promotes its nuclear translocation, initiating transcription of antioxidant genes such as HO-1. (ii) Inflammatory signaling: PI3K/AKT activation inhibits downstream TLR4/NF-κB-mediated inflammatory cascades. (iii) Apoptosis regulation: PI3K/AKT activation enhances the expression of anti-apoptotic protein Bcl-2, while suppressing the activity of pro-apoptotic molecules BAX and caspase 3, thereby establishing an anti-cell death protective mechanism. Figure created by the authors with Adobe Illustrator 2023.

Abbreviations: AKT: Protein kinase B; BAX: Bcl-2-associated X protein; BCL-2: B-cell lymphoma 2; CMD: Coronary microvascular dysfunction; HO 1: Heme oxygenase-1; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NRF2: Nuclear factor erythroid 2-related factor 2; p85: PI3K regulatory subunit p85; p110: PI3K catalytic subunit p110; PI3K: Phosphoinositide 3-kinase; PIP2: Phosphatidylinositol 4,5-bisphosphate; PIP3: Phosphatidylinositol 3,4,5-trisphosphate; PTEN: Phosphatase and tensin homolog; TLR4: Toll-like receptor 4.

myocardial fibrosis and exerts robust cardioprotective effects.

Luteolin, another bioactive flavonoid, is well-known for its anti-inflammatory and antioxidant properties. In a rat model of cardiac injury induced by mercury chloride (HgCl_2), researchers observed pronounced histopathological changes in cardiac tissue, substantial oxidative stress, and a marked reduction in the expression levels of PI3K and AKT proteins within the myocardium.⁴¹ Remarkably, treatment with luteolin significantly upregulated the expression of PI3K and AKT in the hearts of these rats, thereby alleviating HgCl_2 -induced cardiac damage. Moreover, PI3K can be activated via phosphorylation, and its phosphorylated form subsequently phosphorylates AKT, which facilitates the nuclear translocation of NRF2. This process enhances the transcriptional activity of antioxidant proteins, effectively mitigating oxidative stress-induced cardiac injury.⁴² It is noteworthy that luteolin exerts dual regulatory effects on the PI3K/AKT pathway. For instance, Gao *et al.*⁴³ reported that luteolin can inhibit this pathway to reduce blood pressure in hypertensive rats, a phenomenon likely attributable to the pathway's multifaceted roles across different pathological contexts.

Scutellarin, a naturally occurring flavonoid and the principal bioactive constituent derived from *Erigeron breviscapus* (Vaniot) Hand.-Mazz, has been extensively validated for its cardioprotective properties through a multitude of scientific investigations. For instance, Sun *et al.*⁴⁴ demonstrated that scutellarin effectively diminishes the exposure of cardiac tissues to doxorubicin, thereby preventing the onset of acute cardiotoxicity induced by this chemotherapeutic agent, primarily through its potent antioxidant mechanisms. In an experimental model of atherosclerosis in rats, the administration of scutellarin significantly counteracted the dose-dependent suppression of PI3K and phosphorylated AKT (p-AKT) expression, thereby reversing the detrimental effects elicited by the PI3K inhibitor LY294002.⁴⁵ This observation carries profound implications for the advancement of cardiac protective strategies, highlighting scutellarin's potential as a therapeutic agent.

Quercetin, a widely studied flavonoid, is renowned for its multifaceted biological activities, including anti-inflammatory, anti-apoptotic, and antioxidant properties.⁴⁶ It exhibits robust cardioprotective effects, and epidemiological evidence suggests that increasing dietary intake of quercetin may substantially lower the risk of developing heart disease.⁴⁷ Notably, quercetin has been reported to attenuate lipopolysaccharide (LPS)-induced pyroptosis and ferroptosis in cardiomyocytes, thereby

alleviating the severity of sepsis-induced cardiomyopathy (SIC).⁴⁸ SIC is intricately linked to the PI3K/AKT signaling pathway, and inhibition of this pathway exacerbates the progression of cardiac dysfunction.⁴⁹ Treatment of LPS-exposed cardiomyocytes with quercetin promotes the activation of the PI3K/AKT pathway, consequently mitigating cellular damage and offering promising therapeutic benefits for the management of SIC.⁵⁰

Hydroxylsafflor yellow A (HSYA), a pivotal natural compound isolated from *Carthamus tinctorius* L., has been traditionally employed for the treatment of cardiovascular diseases due to its notable anticoagulant, antioxidant, and angiogenic characteristics.⁵¹ HSYA enhances ischemic myocardial hemodynamics, mitigates myocardial tissue damage, and facilitates angiogenesis by elevating nucleolin levels and modulating the expression of key angiogenic factors such as vascular endothelial growth factor A and matrix metalloproteinase-9.⁵² Furthermore, HSYA demonstrates cardioprotective effects by reducing oxidative stress through the downregulation of lactate dehydrogenase and caspase-3 levels, while simultaneously enhancing mitochondrial energy metabolism in a hypoxia and reoxygenation (H/R) cell model.⁵³ These findings underscore the therapeutic potential of HSYA in combating cardiovascular pathologies. However, the protective effects of HSYA were significantly attenuated when treated with the PI3K inhibitor LY294002, indicating that the cardioprotective action of HSYA partially depends on the PI3K/AKT pathway.⁵³

4.2. Saponins

Ginsenosides, the key bioactive compounds derived from *Panax ginseng*, serve as the primary constituents responsible for its therapeutic properties. These natural saponins have been shown to exhibit a diverse array of biological activities, including the modulation of critical cellular processes such as apoptosis, inflammation, and oxidative stress. A substantial body of research has explored numerous types of ginsenosides, each with distinct mechanisms of action. For instance, experimental studies have revealed that ginsenoside Rb1 effectively mitigates myocardial I/R injury by suppressing excessive myocardial autophagy through the activation of the PI3K/AKT/mTOR signaling pathway.⁵⁴ Furthermore, ginsenoside Rg1 has been demonstrated not only to promote angiogenesis via the same PI3K/AKT/mTOR pathway but also to exert potent anti-inflammatory and antioxidant effects.⁵⁵ Similarly, ginsenoside Rd has been shown to activate the PI3K/AKT pathway by enhancing the phosphorylation levels of both PI3K and AKT, thereby significantly alleviating apoptosis and inflammation in cardiomyocytes under both *in vitro* and *in vivo* conditions.

Notably, the administration of LY294002, a specific PI3K inhibitor, substantially blocked the protective effects of ginsenoside Rd against apoptosis and inflammation.⁵⁶ This compelling evidence suggests that the therapeutic efficacy of ginsenoside Rd in combating myocardial injury is primarily dependent on the activation of the PI3K/AKT pathway, which in turn inhibits inflammatory responses and cardiomyocyte apoptosis, underscoring its potential as a targeted treatment for cardiac conditions.

Astragalus membranaceus is a traditional Chinese medicinal herb that is widely used and has been shown to have beneficial cardioprotective effects. Astragaloside IV, a major constituent of *Astragalus membranaceus*, has demonstrated therapeutic effects in multiple cardiac injury models. For instance, Qi *et al.*⁵⁷ found that astragaloside IV alleviated H₂O₂-induced cardiomyocyte apoptosis and ROS production, inhibited mitochondrial autophagy, and upregulated PI3K and p-AKT expression. Astragaloside IV modulated the expression of PI3K and AKT, effectively reducing oxidative stress and inflammatory responses in the H/R-injured H9C2 cells.⁵⁸ Treatment of I/R rats with astragaloside IV (2.5, 5, and 10 mg/kg) elevated the p-AKT/AKT ratio in rat myocardial tissue and reduced infarct size in the high-dose group.⁵⁹ Astragaloside is another important active component of *Astragalus membranaceus*. Astragaloside intravenous injection could dilate blood vessels by regulating endothelial nitric oxide synthase release through the PI3K/AKT pathway.⁶⁰

4.3. Phenolic acids

Phenolic acids represent a class of aromatic secondary metabolites that are abundantly distributed across the natural world, with a particularly rich presence in a diverse array of medicinal plants, including but not limited to honeysuckle, dandelion, angelica, and chuanxiong. These compounds are structurally defined by the presence of phenolic hydroxyl and carboxylic acid functional groups, and they are predominantly found conjugated with sugars, lipids, and organic acids. As a result, phenolic acids exhibit a broad spectrum of pharmacological activities, notably including anti-tumor and anti-inflammatory properties, which underscore their therapeutic potential. Among these, specific phenolic acids such as ferulic acid and curcumin have been extensively documented to exert potent cardioprotective effects, suggesting their utility in cardiovascular health. The underlying mechanisms of these therapeutic benefits may involve the modulation of the PI3K/AKT signaling pathway, positioning this pathway as a promising and strategic target for the treatment of various cardiac conditions, including CMD.

Ferulic acid, which exists in both bound and free forms,

stands as the primary organic acid active component in *Ligusticum chuanxiong*.⁶¹ In a seminal study, Sahu *et al.*⁶² elucidated the protective mechanism of ferulic acid against doxorubicin-induced cardiotoxicity, revealing that treatment with 50 μ M ferulic acid effectively restored the PI3K/AKT pathway in rat primary cardiomyocytes exposed to doxorubicin, bringing it back to near-normal levels. This finding highlights ferulic acid's potential as a cardioprotective agent. Similarly, chlorogenic acid, an ester formed from trans-cinnamic acid and quinic acid, is widely distributed in plants such as those of the *Eucommiaceae* family.⁶³ Research has demonstrated that chlorogenic acid can downregulate galectin-3, thereby alleviating cardiac hypertrophy and fibrosis.⁶⁴ Furthermore, molecular docking studies have provided evidence that chlorogenic acid can stably bind to AKT, suggesting its role as a modulator of the PI3K/AKT pathway, which may confer protective effects against drug-induced cardiac injury.⁶⁵

Curcumin is a polyphenol isolated from the root of *Curcuma longa* L. It has been reported to have diverse pharmacological activities, including anticancer, antioxidant, and anti-inflammatory effects, and has garnered significant attention.⁶⁶ In recent years, several studies have reported the cardioprotective effects of curcumin. In the doxorubicin-induced mouse model of cardiac injury, curcumin treatment inhibited cardiomyocyte pyroptosis by modulating the PI3K/AKT/mTOR pathway.⁶⁷ In the diabetic cardiomyopathy rat model, curcumin alleviated cardiac dysfunction in diabetic rats by inhibiting apoptosis through modulation of the PI3K/AKT pathway.⁶⁶ Exposure of primary rat cardiomyocytes to 30 mmol/L hyperglycemia caused a dramatic increase in intracellular ROS levels and a decrease in p-AKT levels.⁶⁸ Treatment with 10 μ M curcumin reversed these effects, and the therapeutic action of curcumin could be blocked by the PI3K inhibitor LY294002.⁶⁸ Furthermore, the curcumin metabolite tetrahydrocurcumin has been demonstrated to promote phosphorylation of the PI3K/AKT/mTOR pathway, effectively inhibiting H/R-induced autophagy and cell death in H9C2 cells.⁶⁹

4.4. Others

Berberine, a naturally occurring isoquinoline alkaloid extracted from the roots of Chinese goldthread (*Coptis chinensis*), has long been recognized as a potent antibacterial agent, particularly effective in treating gastrointestinal infections, while also demonstrating remarkable therapeutic potential for cardiovascular diseases.⁷⁰ Notably, clinical studies have reported that berberine administration significantly reduces mortality rates among patients suffering from heart failure, highlighting its profound cardioprotective properties.⁷¹ In

a well-established rat model of diabetic cardiomyopathy, treatment with berberine at varying doses of 100, 200, and 400 mg/kg/day over a four-week period not only substantially restored cardiac contraction and relaxation functions but also markedly suppressed myocardial cell apoptosis, thereby preserving overall cardiac structure and function.⁷² Subsequent *in vitro* investigations further elucidated the underlying molecular mechanisms, revealing that pre-incubation with wortmannin, a specific inhibitor of the PI3K/AKT signaling pathway, effectively attenuated the anti-apoptotic effects of berberine, suggesting that berberine's protective actions are mediated, at least in part, through PI3K/AKT-dependent signaling cascades.⁷²

Astragalus polysaccharide is a key active component of *Astragalus membranaceus*. Astragalus polysaccharide has been demonstrated to restore autophagy to protect cardiomyocytes.⁷³ NRF2 is a downstream target of PI3K/AKT and is closely associated with ferroptosis.⁷⁴ A recent study by Bai *et al.*⁷⁵ indicated that Astragalus polysaccharide treatment significantly reversed the reduction in viability and mitochondrial membrane potential in AC16 and H9C2 cells induced by doxorubicin, while decreasing ROS production. Additionally, Astragalus polysaccharide activated the PI3K/AKT/NRF2 pathway to alleviate ferroptosis. Treatment with the PI3K inhibitor LY294002 and the NRF2 inhibitor ML385 abolished the protective effects of Astragalus polysaccharide, indicating that Astragalus polysaccharide mediated its cardioprotective effects through the PI3K/AKT/NRF2 signaling axis.⁷⁵

5. Discussion

As a robust and independent predictor of adverse cardiovascular events, the underlying pathological mechanisms of CMD are deeply rooted in both structural and functional abnormalities of the microcirculation system—encompassing endothelial cell dysfunction, vascular remodeling, and impaired vasodilatory capacity. Currently, no specific therapeutic agents have been approved to directly target and reverse these microvascular derangements. In recent years, the PI3K/AKT signaling pathway has emerged as a pivotal molecular axis, playing a critical role in the onset, progression, and perpetuation of CMD. Targeted modulation of the PI3K/AKT cascade has been experimentally demonstrated as a promising therapeutic approach for CMD; however, its clinical utility remains unvalidated, largely due to the complexity of translating preclinical findings into human trials. Although natural products that specifically modulate the PI3K/AKT pathway have exhibited tremendous therapeutic potential in preclinical studies—offering anti-inflammatory, anti-apoptotic, and pro-angiogenic benefits—translating these compounds into clinically effective drugs continues to

pose a formidable and multifaceted challenge. A clear and comprehensive understanding of these limitations is essential to advancing CMD therapies and bridging the gap between bench and bedside.

Currently, no animal model of CMD is universally recognized as uniquely specific or explicitly recommended by clinical guidelines. As CMD represents a pathophysiological phenotype arising from structural and/or functional abnormalities of the coronary microcirculation rather than a single-etiology disease, experimental models are generally selected according to the specific pathological process under investigation. Myocardial I/R models are commonly used to mimic acute microcirculatory injury, including endothelial damage, oxidative stress, inflammation, microvascular obstruction, and no-reflow. In contrast, models of metabolic syndrome, high-fat diet, diabetes, and hypertension are more suitable for studying CMD driven by chronic risk factors, involving insulin resistance, dyslipidemia, low-grade inflammation, endothelial dysfunction, abnormal vasomotor responses, microvascular remodeling, and impaired coronary flow reserve. Coronary microembolization or microthrombosis models, induced by microspheres, autologous thrombi, or chemical embolic agents, can reproduce focal microvascular obstruction, regional ischemia, inflammatory amplification, and impaired myocardial perfusion.⁷⁶ However, these models only capture partial aspects of CMD and cannot fully recapitulate the chronic, heterogeneous, and multi-endotype features of human CMD, particularly ANOCA/INOCA-related CMD. Therefore, model selection should be guided by the specific scientific question, and the pathological context and translational limitations of each model should be carefully considered when interpreting experimental findings.

Although natural compounds may exert cardioprotective effects partly through modulation of the PI3K/AKT signaling pathway, the current evidence remains insufficient to establish a direct PI3K/AKT-dependent mechanism. Most studies have relied on changes in pathway phosphorylation levels and pharmacological inhibitor experiments, whereas direct genetic validation targeting core PI3K/AKT molecules using small interfering RNA, CRISPR gene editing, or transgenic/knockout models is still lacking. Therefore, these compounds should be regarded as modulators involved in, or contributing to, PI3K/AKT-mediated cardioprotection rather than strictly PI3K/AKT-dependent agents. Moreover, low bioavailability, complex pharmacokinetics, and poor standardization remain major obstacles to their clinical translation in CMD.⁷⁷ Future research should prioritize formulation and delivery optimization, including

Table 1. Natural compounds targeting PI3K/AKT-related signaling pathways in cardiovascular injury models

Compound class	Natural compound	Experimental model	PI3K/AKT-related target(s) or signaling axis	Main experimental efficacy outcomes	References
Flavonoids	Puerarin	H ₂ O ₂ -induced HCAEC oxidative stress-EndMT model	Activated the PI3K/AKT signaling pathway	Reduced ROS; inhibited EndMT and cell migration	40
Flavonoids	Luteolin	HgCl ₂ -induced rat myocardial injury model; spontaneously hypertensive rats (SHRs)	Activated PI3K/AKT/NRF2 and inhibited NF-κB; context-dependent inhibition of PI3K/AKT	Exerted antioxidant and anti-apoptotic effects; alleviated myocardial injury; attenuated hypertension-related inflammatory responses	41-43
Flavonoids	Scutellarin	Vitamin D ₃ + high-fat diet-induced atherosclerosis rat model; Ang II-induced HAEc injury model	Activated PI3K/AKT; inhibited Hippo-FOXO3A; reversed LY294002-induced suppression of PI3K and p-AKT expression	Lowered blood lipids; exerted antioxidant/anti-inflammatory effects; inhibited endothelial injury and apoptosis	45
Flavonoids	Quercetin	LPS-induced cardiomyocyte injury model	Activated ALOX5/PI3K/AKT signaling; also regulated NOX2/ROS/NF-κB/TXNIP and related pathways	Alleviated LPS-induced myocardial injury; inhibited cardiomyocyte pyroptosis and ferroptosis; reduced inflammatory injury and cellular damage	50
Flavonoids	Hydroxysafflor yellow A	Hypoxia/reoxygenation cell model	Cardioprotection was partly dependent on PI3K/AKT signaling, and this effect was attenuated by LY294002	Improved hemodynamics in ischemic myocardium; alleviated myocardial tissue injury; promoted angiogenesis by regulating VEGF-A and MMP-9; decreased LDH and caspase-3 levels; improved mitochondrial energy metabolism	53
Saponins	Ginsenoside Rb1	Myocardial ischemia/reperfusion injury model	Activated the PI3K/AKT/mTOR signaling pathway	Inhibited excessive autophagy in cardiomyocytes; alleviated myocardial ischemia/reperfusion injury	54
Saponins	Ginsenoside Rg1	Hypoxia-induced cardiomyocyte injury model	Activated the PI3K/AKT/mTOR signaling pathway	Promoted angiogenesis; exerted anti-inflammatory and antioxidant effects; protected cardiomyocytes from hypoxic injury	55
Saponins	Ginsenoside Rd	Myocardial ischemia/reperfusion injury model; <i>in vitro</i> cardiomyocyte injury model	Enhanced PI3K and AKT phosphorylation levels, and the protective effect was blocked by LY294002	Alleviated myocardial ischemia/reperfusion injury; inhibited cardiomyocyte inflammatory responses and apoptosis under <i>in vivo</i> and <i>in vitro</i> conditions	56
Saponins	Astragaloside IV	H ₂ O ₂ -induced cardiomyocyte injury model; hypoxia/reoxygenation-induced H9C2 cardiomyocyte injury model; rat myocardial ischemia/reperfusion model	Upregulated PI3K, p-AKT, and PI3K/AKT/mTOR; regulated the PI3K/AKT/HO-1 and PI3K/AKT/GSK-3β signaling axes	Reduced cardiomyocyte apoptosis and ROS generation; protected mitochondria; alleviated oxidative stress and inflammatory responses; reduced myocardial infarct size	57-59

(cont'd...)

Table 1. (Continued)

Compound class	Natural compound	Experimental model	PI3K/AKT-related target(s) or signaling axis	Main experimental efficacy outcomes	References
Saponins	Total astragalosides	Isoproterenol-induced myocardial injury model in SD rats	Regulated PI3K/AKT/eNOS signaling, thereby modulating Ca ²⁺ homeostasis and energy metabolism	Promoted eNOS release and vasodilation; alleviated myocardial injury	60
Phenolic acids	Ferulic acid	Doxorubicin-induced cytotoxic injury model in primary rat cardiomyocytes	Restored impaired PI3K/AKT pathway activity; inhibited MAPK/NF-κB	Inhibited cardiomyocyte apoptosis; improved blood biochemical indices and myocardial tissue injury	62
Phenolic acids	Chlorogenic acid	Molecular docking study (non-experimental study)	Could stably bind to AKT, suggesting possible regulation of AKT/mTOR signaling	May inhibit ferroptosis and apoptosis through AKT/mTOR-related mechanisms	65
Phenolic acids	Curcumin	STZ + high-glucose/high-fat diet-induced DCM rat model; doxorubicin-induced mouse cardiac injury model; diabetic cardiomyopathy rat model; high-glucose-induced neonatal rat primary cardiomyocyte injury model	Activated PI3K/AKT and regulated the SIRT1/FOXO1 pathway; modulated PI3K/AKT/mTOR signaling; activated the PI3K/AKT/GSK-3β pathway, and this effect was blocked by LY294002	Improved cardiac function; reduced oxidative stress; inhibited cardiomyocyte apoptosis; inhibited doxorubicin-induced cardiomyocyte pyroptosis; improved cardiac dysfunction in diabetic rats	66-68
Phenolic acids	Tetrahydrocurcumin	Hypoxia/reoxygenation-induced H9C2 cardiomyocyte injury model	Promoted phosphorylation of the PI3K/AKT/mTOR pathway and increased HIF-1α expression	Inhibited hypoxia/reoxygenation-induced autophagy and cell death; exerted cardioprotective effects	69
Others	Berberine	Diabetic cardiomyopathy rat model; <i>in vitro</i> mechanistic validation model involving a PI3K/AKT inhibitor	Activated AMPK and PI3K/AKT signaling, and its anti-apoptotic effect was attenuated by wortmannin	Inhibited cardiomyocyte apoptosis; improved cardiac systolic and diastolic function	72
Others	Astragalus polysaccharide	Doxorubicin-induced cytotoxic injury model in AC16 and H9C2 cardiomyocytes	Activated PI3K/AKT/NRF2 signaling, and the protective effect was inhibited by LY294002 and ML385	Alleviated ferroptosis and protected cardiomyocytes	75

Abbreviations: AC16: Human cardiomyocyte cell line; AKT: Protein kinase B; ALOX5: Arachidonate 5-lipoxygenase; AMPK: AMP-activated protein kinase; Ang II: Angiotensin II; DCM: Diabetic cardiomyopathy; EndMT: Endothelial-to-mesenchymal transition; eNOS: Endothelial nitric oxide synthase; FOXO1: Forkhead box O1; FOXO3A: Forkhead box O3A; GSK-3β: Glycogen synthase kinase 3β; HAEC: Human aortic endothelial cell; HCAEC: Human coronary artery endothelial cell; HIF-1α: Hypoxia-inducible factor 1α; HO-1: Heme oxygenase 1; LDH: Lactate dehydrogenase; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; MMP-9: Matrix metalloproteinase 9; mTOR: Mechanistic target of rapamycin; NF-κB: Nuclear factor kappa B; NOX2: NADPH oxidase 2; NRF2: Nuclear factor erythroid 2-related factor 2; p-AKT: Phosphorylated protein kinase B; PI3K: Phosphoinositide 3-kinase; ROS: Reactive oxygen species; SD: Sprague-Dawley; SHRs: Spontaneously hypertensive rats; SIRT1: Sirtuin 1; STZ: Streptozotocin; TXNIP: Thioredoxin-interacting protein; VEGF-A: Vascular endothelial growth factor A.

nanocarriers, liposomes, micelles, solid lipid nanoparticles, cyclodextrin inclusion systems, prodrug design, and endothelial-targeted or injury-responsive delivery systems. Their efficacy and safety should be further validated using CMD-related objective endpoints, such as coronary flow reserve, index of microcirculatory resistance, acetylcholine provocation testing of coronary microvascular function, and myocardial perfusion assessed by positron emission tomography or stress cardiovascular magnetic resonance. Circulating PI3K/AKT-related molecules may be used as exploratory pharmacodynamic biomarkers, but no validated CMD-specific circulating PI3K/AKT marker is currently available.

Despite its limitations, drug development is overcoming bottlenecks through technological innovation. On the one hand, alternative models, such as organoids, better mimic human environments, reducing experimental errors in animal studies.⁷⁸ On the other hand, artificial intelligence accelerates target discovery and drug design, providing insights for screening and structural optimization of PI3K activators/inhibitors. Furthermore, multi-omics and network pharmacology technologies enable analysis of the component-target-pathway networks, advancing the elucidation of natural product therapeutic mechanisms. In summary, natural products targeting the PI3K/AKT pathway open new avenues for the prevention and treatment of CMD. Future in-depth research into the mechanisms of action and clinical applications of natural products holds promise for delivering safer and more effective therapeutic options for patients with CMD.

6. Conclusion

In conclusion, this review highlights the PI3K/AKT pathway as a context-dependent signaling hub in CMD and evaluates the therapeutic potential of natural compounds that modulate its downstream networks. Current preclinical evidence suggests that appropriate activation of the pathway may alleviate oxidative stress, inflammation, and autophagy-related injury; reduce apoptosis; and promote endothelial cell survival, angiogenesis, and microvascular repair. However, the available evidence is largely derived from non-CMD-specific models and remains insufficient to establish direct dependence on the pathway or clinical efficacy. Clinical translation will therefore require disease-relevant CMD models, genetic validation, pharmacokinetic characterization, formulation standardization, objective microvascular endpoints, and well-designed clinical trials.

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Conflict of interest

The authors declare they have no competing interests.

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Further disclosure

Grammarly was used exclusively for spelling and grammar correction to improve the readability of the manuscript. No AI tools were used to generate scientific content, analyze data, interpret results, or draw conclusions.

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