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Phytomedicine in Cardiovascular Disease: Molecular Mechanisms, Clinical Evidence, and Translational Challenges

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ABSTRACT: Cardiovascular diseases remain a major cause of morbidity and mortality worldwide and arise from interacting disturbances in vascular function, inflammation, redox regulation, lipid and energy metabolism, mitochondrial homeostasis, cardiac remodelling, and thrombosis. Plant-derived compounds have attracted considerable interest because many influence more than one of these processes. This review examines the cardiovascular relevance of major phytochemicals and botanical preparations, with emphasis on their molecular mechanisms, experimental evidence, clinical findings, and barriers to therapeutic translation. Particular attention is given to signalling pathways involving Nrf2, eNOS, AMPK, sirtuins, PI3K/Akt, NF-κB, NLRP3, and TGF-β/Smad, and to their relevance in endothelial dysfunction, hypertension, atherosclerosis and dyslipidaemia, myocardial ischaemia/reperfusion injury, heart failure, cardiac remodelling, and thrombosis. Although experimental studies provide substantial evidence of biological activity, the strength of clinical evidence is uneven. Many human studies rely on biomarkers or physiological endpoints, whereas evidence for patient-important cardiovascular outcomes remains limited. Translation is further complicated by poor or variable bioavailability, metabolism to active or inactive derivatives, differences in botanical composition and standardisation, uncertain tissue exposure, and potential herb-drug interactions. A clinically meaningful assessment, therefore, requires evidence that a reproducible intervention achieves sufficient systemic or tissue exposure, engages the proposed molecular target, produces a measurable pharmacodynamic response, and ultimately improves relevant cardiovascular outcomes. Greater attention to pharmacokinetics, preparation-specific standardisation, adequately powered clinical trials, clinically meaningful endpoints, and long-term safety will be necessary to determine which phytomedicines can progress from promising experimental agents to evidence-based cardiovascular interventions.

1. INTRODUCTION

Cardiovascular diseases (CVDs) remain a major cause of morbidity and mortality worldwide and include atherosclerosis, coronary artery disease, hypertension, myocardial infarction, heart failure, cardiomyopathies, cerebrovascular disease, and thromboembolic disorders. Despite major advances in pharmacological and interventional therapies, the cardiovascular burden continues to increase, driven by dyslipidaemia, hypertension, obesity, diabetes, physical inactivity, and chronic inflammation [1]. CVDs arise not from a single pathological pathway but from interconnected processes involving oxidative stress, endothelial dysfunction, inflammation, metabolic disturbances, mitochondrial impairment, vascular remodelling, and thrombosis [2]. This complex pathophysiology provides a rationale for investigating therapeutic strategies that can modulate multiple disease-related pathways.

Phytomedicine, encompassing medicinal plants, standardised botanical preparations, phytopharmaceuticals, and plant-derived bioactive compounds, has therefore attracted considerable interest in cardiovascular research. Major phytochemical classes, including polyphenols, flavonoids, alkaloids, terpenoids, saponins, phenolic acids, carotenoids, phytosterols, and organosulfur compounds, have been investigated for anti-inflammatory, antihypertensive, lipid-modifying, antithrombotic, and cardioprotective effects [3]. Their cardiovascular actions extend beyond simple free-radical scavenging and involve modulation of signalling pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor kappa B (NF-κB), AMP-activated protein kinase (AMPK), sirtuins, phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinases (MAPKs), transforming growth factor-β (TGF-β), the renin-angiotensin-aldosterone system, and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. Through these pathways, phytochemicals may influence oxidative balance, inflammation, nitric oxide bioavailability, lipid metabolism, mitochondrial function, vascular tone, and cardiac remodelling [3,4].

However, mechanistic breadth should not be equated with clinical efficacy. Much of the evidence supporting individual phytochemicals originates from cellular and animal studies, often using concentrations that may not be achievable in humans. Translation is further complicated by limited absorption, extensive metabolism, the formation of active metabolites, variability in botanical composition, and differences among purified compounds, standardised extracts, and whole-plant preparations [3,5]. Consequently, cardiovascular phytomedicine should be evaluated within a translational framework that links a well-characterised intervention to pharmacokinetically achievable exposure, molecular target engagement, biomarker modification, physiological response, and ultimately clinically meaningful outcomes.

Safety and reproducibility are equally important because patients with CVD commonly receive multiple medications, including statins, antihypertensive agents, antiplatelet drugs, anticoagulants, and glucose-lowering therapies. Botanical preparations may alter drug metabolism or transport, or produce additive pharmacodynamic effects on blood pressure, platelet function, coagulation, glucose regulation, or cardiac electrophysiology [5,6]. Moreover, growing evidence indicates that interactions between phytochemicals and the gut microbiome may modify phytochemical metabolism, systemic exposure, inflammation, and cardiovascular responses, potentially contributing to interindividual variability [7]. These considerations highlight the importance of botanical standardisation, pharmacokinetic assessment, safety evaluation, and herb-drug interaction studies in cardiovascular phytomedicine.

Against this background, this review adopts a mechanism-to-clinic framework rather than providing a conventional catalogue of medicinal plants. It first considers CVD as an interconnected pathophysiological network and examines the major molecular pathways targeted by phytochemicals. It then evaluates phytomedicine in endothelial dysfunction and hypertension, atherosclerosis and dyslipidaemia, myocardial ischaemia/reperfusion injury, heart failure and cardiac remodelling, and thrombosis and platelet dysfunction, with particular attention to differences among mechanistic, preclinical, and clinical evidence. The review subsequently examines the major translational barriers posed by pharmacokinetics, metabolism, botanical standardisation, safety, and herb-drug interactions, before considering emerging approaches including precision phytomedicine, advanced delivery systems, microbiome-informed strategies, and evidence-based clinical translation.

2. CARDIOVASCULAR DISEASE AS AN INTERCONNECTED PATHOPHYSIOLOGICAL NETWORK

Cardiovascular disease develops through a network of closely related pathological processes rather than through a single molecular defect. Atherosclerosis, hypertension, myocardial ischaemia/reperfusion injury, cardiac remodelling, heart failure, and thrombosis share several features, particularly oxidative stress, inflammation, endothelial dysfunction, metabolic disturbances, mitochondrial impairment, and changes in vascular or myocardial structure. These processes often reinforce one another and contribute to the initiation and progression of cardiovascular disease [1,2].

2.1 Oxidative Stress and Endothelial Dysfunction

Oxidative stress is closely involved in the development of cardiovascular disease. Excessive production of reactive oxygen species (ROS) reduces nitric oxide (NO) bioavailability, promotes lipoprotein oxidation, activates inflammatory signalling, and disrupts mitochondrial function. Impaired endothelial function, in turn, favours vasoconstriction, leukocyte adhesion, increased vascular permeability, and a prothrombotic state. These changes link common metabolic and vascular risk factors with the development of hypertension and atherosclerosis [2,4].

Oxidative stress and endothelial dysfunction can also aggravate each other. Persistent oxidative stress damages the endothelium, while endothelial dysfunction can further increase oxidative and inflammatory signalling. Redox-sensitive pathways, such as the Nrf2 pathway, are therefore relevant to cardiovascular protection. The effects of phytochemicals in this setting are not limited to direct scavenging of free radicals; many act by modifying cellular pathways that regulate antioxidant defence, inflammation, and endothelial function [3,4].

2.2 Inflammation and Innate Immune Signalling

Chronic low-grade inflammation contributes to several stages of cardiovascular disease. In atherosclerosis, endothelial activation promotes leukocyte recruitment, while retained and modified lipoproteins stimulate macrophage activation and foam-cell formation. Persistent inflammation also affects vascular smooth muscle cells and extracellular matrix turnover, contributing to plaque growth and instability. NF-κB and the NLRP3 inflammasome are among the major signalling systems involved in these responses [8,9].

Inflammatory signalling is also involved in myocardial injury, ventricular remodelling, cardiac fibrosis, and heart failure. NLRP3 inflammasome activation has been implicated in both ischaemic and non-ischaemic myocardial injury, as well as in subsequent inflammatory responses and adverse cardiac remodelling [9]. This overlap between vascular and myocardial disease helps explain why modulation of NF-κB, NLRP3, and related pathways has received considerable attention in studies of cardiovascular phytochemicals [3,8,9].

2.3 Metabolic Dysfunction and Mitochondrial Impairment

Metabolic disorders such as dyslipidaemia, insulin resistance, obesity, and diabetes increase cardiovascular risk, in part, through their effects on oxidative stress, inflammation, endothelial function, and cellular metabolism [1,2]. Mitochondrial dysfunction contributes to this burden by disrupting energy production, redox homeostasis, calcium homeostasis, and cellular survival. These effects are particularly important in the myocardium, where energy demand is high and normal mitochondrial function is essential for contractility and cellular homeostasis [10].

Several signalling pathways connect metabolic status with mitochondrial and cardiovascular function. AMPK regulates cellular energy balance, while sirtuins and PI3K/Akt participate in metabolic adaptation, stress responses, and cell survival. Their interactions with inflammatory and redox pathways provide a biological basis for the broad cardiovascular effects reported for several phytochemicals [3,10].

2.4 Interaction of Cardiovascular Pathways

The major pathological processes in CVD can be viewed as a connected sequence:

Metabolic dysfunction → oxidative stress and mitochondrial impairment → endothelial dysfunction → lipid retention and modification → inflammatory-cell recruitment and foam-cell formation → NF-κB/NLRP3 activation → vascular remodelling and plaque progression → plaque instability and thrombosis → cardiovascular events [2,8–10].

This sequence is not strictly linear. Oxidative stress can promote inflammation, which can further increase ROS production, and both can worsen endothelial and mitochondrial function. Similarly, metabolic abnormalities can affect multiple stages simultaneously. These interactions create self-reinforcing cycles that contribute to disease progression [2,8,10].

This interconnected biology also helps explain why some phytochemicals affect more than one cardiovascular process. A compound acting on redox regulation, inflammatory signalling, endothelial function, or cellular metabolism may influence several components of the disease network. The following section, therefore, examines the main molecular targets through which plant-derived compounds have been studied in cardiovascular disease [3].

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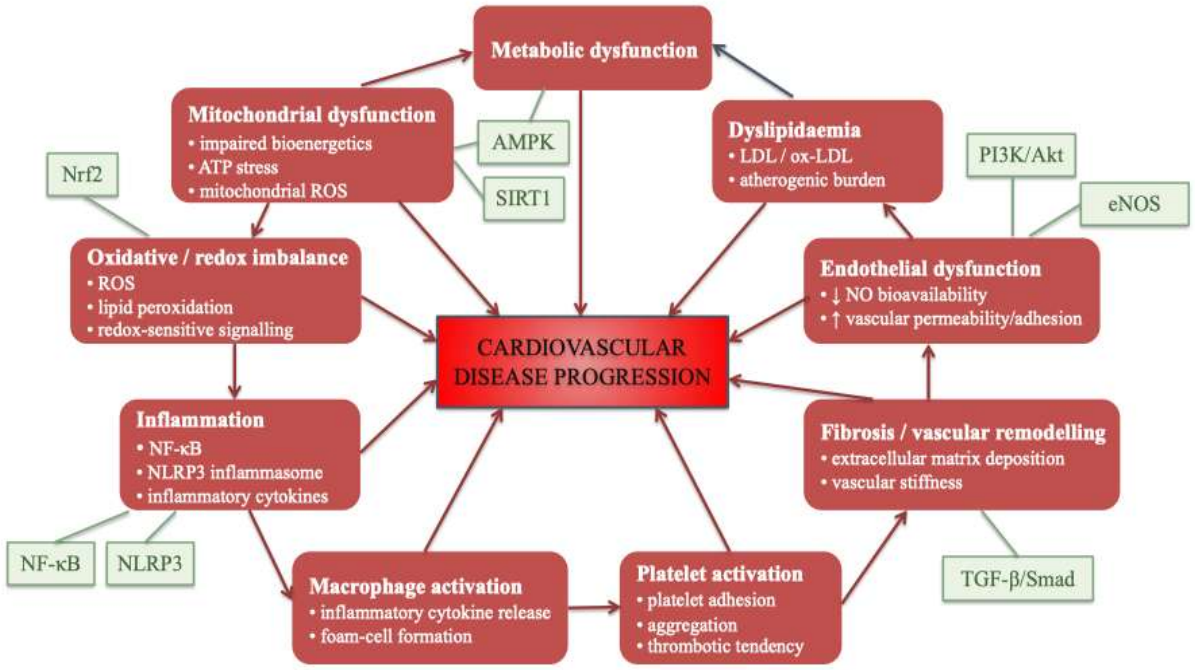


Figure 1. Integrated cardiovascular pathophysiology and molecular targets of phytochemicals. Cardiovascular disease involves interconnected changes in endothelial function, redox balance, inflammatory signalling, lipid and metabolic regulation, mitochondrial function, cardiac remodelling, and platelet activity. Representative phytochemicals may act on several of these processes through pathways including Nrf2, endothelial nitric oxide synthase (eNOS), AMPK, sirtuin 1 (SIRT1), PI3K/Akt, NF-κB, NLRP3, and TGF-β/Smad. Interactions among these pathways contribute to the development and progression of atherosclerosis, hypertension, myocardial ischaemia/reperfusion injury, heart failure, and thrombosis. Arrows indicate representative relationships between molecular pathways and cardiovascular processes rather than exclusive mechanisms of action.

3. MOLECULAR TARGETS OF PHYTOCHEMICALS IN CARDIOVASCULAR DISEASE

Plant-derived bioactive compounds include chemically diverse groups such as polyphenols, flavonoids, alkaloids, terpenoids, saponins, carotenoids, phytosterols, organosulfur compounds, and phenolic acids. Despite their structural diversity, many act through biological processes common to cardiovascular disease, including oxidative stress, inflammation, endothelial dysfunction, altered lipid and glucose metabolism, mitochondrial dysfunction, and platelet activation [3,11].

3.1 Major Molecular Pathways

The Nrf2/antioxidant response element (ARE) pathway is an important regulator of cellular defence against oxidative and electrophilic stress. Activation of Nrf2 induces genes involved in glutathione metabolism, antioxidant defence, and cellular stress responses. Several phytochemicals have been reported to activate Nrf2 signalling in endothelial cells, cardiomyocytes, and vascular tissues, potentially helping limit oxidative injury [11,12].

Inflammatory pathways are another major target. NF-κB regulates the expression of cytokines, chemokines, and adhesion molecules involved in vascular inflammation, while Toll-like receptor and MAPK signalling can contribute to its activation. The NLRP3 inflammasome links cellular stress with the maturation of inflammatory cytokines and has been implicated in atherosclerosis, myocardial injury, and cardiac remodelling [8,9]. Several phytochemicals have been reported to suppress NF-κB- and NLRP3-associated inflammatory responses in experimental models [3,11,12].

Metabolic regulation is closely linked to cardiovascular function. AMPK is a major sensor of cellular energy status and influences glucose and lipid metabolism, mitochondrial function, and cellular stress responses. SIRT1 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) also participate in metabolic adaptation and mitochondrial regulation. Berberine has been widely studied for its effects on AMPK-related pathways, while several

polyphenols have been linked to AMPK, SIRT1, and mitochondrial signalling [11,13].

Other relevant pathways include PI3K/Akt and eNOS/NO signalling, which contribute to endothelial function and cell survival, and TGF-β signalling, which is closely associated with fibrosis and cardiac remodelling. MAPKs participate in inflammatory and stress responses, while pathways controlling mitochondrial biogenesis, dynamics, mitophagy, and apoptosis are particularly relevant to myocardial injury and heart failure [10,11]. The overlap among these pathways helps explain why a single phytochemical may affect several cardiovascular processes.

3.2 Mechanism-Based Classification

In cardiovascular research, it is often more useful to group phytochemicals by their primary biological actions rather than by chemical structure alone. They may therefore be considered broadly as redox modulators, anti-inflammatory agents, metabolic regulators, endothelial-protective compounds, mitochondrial modulators, lipid-modifying agents, or antithrombotic compounds. These groups overlap because many phytochemicals act on multiple pathways [3,11].

Table 1. Major phytochemical classes and molecular targets relevant to cardiovascular disease

Phytochemical class	Representative compounds	Principal molecular targets/pathways	Potential cardiovascular relevance	Major translational consideration	References
Polyphenols	Resveratrol, curcumin, epigallocatechin gallate (EGCG)	Nrf2, NF-κB, AMPK, SIRT1	Redox regulation, inflammatory modulation, endothelial and mitochondrial effects	Low or variable oral bioavailability and extensive metabolism may limit exposure to parent compounds	[3,11,12]
Flavonoids	Quercetin, catechins, anthocyanins	Nrf2/ Heme oxygenase-1, NF-κB, PI3K/Akt, eNOS	Modulation of endothelial function, oxidative stress, and inflammatory signalling	Extensive intestinal and hepatic metabolism can produce substantial differences between ingested compounds and circulating metabolites	[3,12]
Alkaloids	Berberine	AMPK, SIRT1, NF-κB, lipid- and glucose-regulatory pathways	Effects on lipid and glucose metabolism, inflammation, and vascular function	Low oral bioavailability and extensive metabolism complicate translation from experimental concentrations	[13]
Terpenoids	Ginsenosides, triterpenoids	PI3K/Akt, AMPK, Nrf2 and mitochondrial/stress-response	Experimental cardioprotective, vascular, metabolic, and anti-inflammatory	Most mechanistic evidence remains preclinical; dose, preparation, metabolism, and clinical	[14]

		pathways	effects	standardisation remain important limitations	
Saponins	Ginsenosides and related saponins	PI3K/Akt, AMPK and redox-related signalling	Experimental cardioprotective, vascular and metabolic effects	Chemical composition and biological activity vary among ginseng species, extracts, and individual ginsenosides	[14]
Carotenoids	Lycopene, β-carotene, lutein	Oxidative-stress and inflammatory pathways	Associations with vascular health and modulation of oxidative and inflammatory markers	Bioavailability varies considerably, and cardiovascular findings from supplementation studies are not uniformly consistent	[15]
Phytosterols	β-Sitosterol, campesterol	Reduction of intestinal cholesterol absorption and modulation of sterol handling	Reduction in LDL cholesterol and apolipoprotein B	Improvement in lipid biomarkers should not be assumed to represent a reduction in cardiovascular events	[16,17]
Organosulfur compounds	Allicin and related garlic constituents	Oxidative-stress, inflammatory, vascular and platelet-related pathways	Experimental and clinical evidence for effects on vascular function and cardiovascular risk factors	Allicin is chemically unstable, and biological activity can vary with garlic preparation and processing	[18]
Phenolic acids	Caffeic acid, ferulic acid, chlorogenic acid	Inflammatory, redox and metabolic pathways	Anti-inflammatory and other experimental cardioprotective effects, including effects on blood pressure, lipid metabolism and cardiac remodelling	Absorption and metabolism influence circulating forms and may affect biological activity	[19]

3.3 From Molecular Activity to Cardiovascular Relevance

Evidence that a phytochemical activates or inhibits a molecular pathway does not by itself establish a therapeutic effect. Experimental studies may use concentrations that are difficult to achieve in humans, and intestinal or hepatic metabolism may substantially alter the compounds that reach the circulation. In some cases, metabolites rather than the parent phytochemical may account for part of the biological activity [3,5].

A useful way to examine the evidence is to follow the compound from administration to clinical effect:

Phytochemical exposure → achievable systemic or tissue concentration → target engagement → biomarker change → physiological response → clinical outcome.

This distinction is also important when comparing purified compounds with whole-plant preparations or standardised extracts. Botanical preparations contain multiple constituents, and their biological effects may depend on more than one compound or metabolite. At the same time, this chemical complexity can lead to differences in composition, exposure, safety, and herb-drug interactions between preparations [5,6].

For this reason, the number of pathways affected by a phytochemical is less important than the strength of the evidence supporting a relevant cardiovascular effect. The following sections examine this evidence in specific cardiovascular conditions.

4. CARDIOVASCULAR APPLICATIONS OF PHYTOMEDICINE

Phytochemicals have been investigated across a range of cardiovascular conditions because they can influence vascular function, lipid metabolism, inflammation, mitochondrial homeostasis, cardiac remodelling, and haemostasis. Their potential cardiovascular relevance, however, varies considerably depending on the compound or preparation, disease context, and the strength of the available experimental and clinical evidence [3,11].

4.1 Endothelial Dysfunction and Hypertension

The vascular endothelium plays an important role in the regulation of vascular tone, permeability, inflammation, thrombosis, and vascular smooth muscle function. Nitric oxide (NO) is particularly important in maintaining vascular homeostasis through its vasodilatory, anti-inflammatory, and antithrombotic actions. Reduced NO bioavailability is a characteristic feature of endothelial dysfunction and is closely associated with cardiovascular disorders, including hypertension and atherosclerosis [20].

Reduced NO availability is central to endothelial dysfunction. Endothelial NO synthase (eNOS) produces NO from L-arginine, and NO subsequently activates soluble guanylyl cyclase in vascular smooth muscle, increasing cyclic guanosine monophosphate (cGMP) and promoting vasodilation. NO also contributes to the inhibition of platelet activation, leukocyte adhesion, and vascular smooth muscle proliferation. Increased oxidative stress can impair this system by reducing NO bioavailability and promoting eNOS uncoupling, in which eNOS generates superoxide rather than NO, thereby further increasing vascular oxidative stress [20].

Several phytochemicals influence pathways involved in endothelial function. Polyphenols and flavonoids have been reported to affect Nrf2-dependent antioxidant responses, PI3K/Akt/eNOS signalling, and NF-κB-mediated inflammation [3,11,12]. These actions may improve NO availability and reduce endothelial activation, including the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Their vascular effects, therefore, appear to involve changes in redox regulation, NO signalling, and inflammation rather than simple free-radical scavenging.

Evidence from human studies supports some of these vascular effects. A 2024 systematic review and dose-response meta-analysis of eight randomised controlled trials involving 596 participants reported that citrus flavonoid supplementation improved flow-mediated dilation (FMD), with a pooled increase of approximately 2.75 percentage points compared with control (95% confidence interval, 1.29-4.20). However, substantial heterogeneity was present (I^2 = 87.3%), indicating considerable variation among studies [21].

A larger 2025 systematic review and meta-analysis of 109 publications comprising 145 randomised controlled trials and 5,205

participants evaluated flavan-3-ol-rich interventions. Repeated consumption reduced office systolic and diastolic blood pressure by approximately 2.8 and 2.0 mmHg, respectively, and also improved FMD. The magnitude of the effects varied according to baseline blood pressure and intervention characteristics, indicating that responses are not uniform across populations [22].

Hypertension and endothelial dysfunction can reinforce each other. Sustained high blood pressure increases mechanical stress, oxidative injury, inflammation, and vascular remodelling, whereas impaired endothelial function increases vascular resistance and can further raise blood pressure [20]. Plant-derived compounds have therefore been studied for effects on NO-dependent vasodilation, vascular smooth muscle function, oxidative stress, and the renin-angiotensin system. Dietary nitrate and nitrate-rich plant foods provide a relatively well-defined example, as nitrate-derived NO signalling may contribute to reductions in blood pressure. A 2025 systematic review and dose-response meta-analysis of 75 randomised controlled trials involving 1,823 participants found dose-dependent reductions in blood pressure and improvements in vascular measures, including FMD and pulse-wave velocity, following dietary nitrate supplementation [23].

Flow-mediated dilation, pulse-wave velocity, peripheral arterial tonometry, circulating adhesion molecules, and NO-related metabolites are commonly used to assess vascular responses in clinical studies. These measures are useful for detecting changes in endothelial function, but they should be interpreted according to what they actually measure. In particular, an improvement in FMD indicates better endothelial responsiveness but does not by itself demonstrate a reduction in myocardial infarction, stroke, or cardiovascular mortality [21,22].

Current evidence therefore supports endothelial function and blood pressure regulation as relevant targets for phytomedicine. Human studies provide evidence of improvements in vascular and haemodynamic measures, particularly with certain flavonoid- and nitrate-rich interventions, but evidence for the prevention of major cardiovascular events remains limited [21–23].

4.2 Atherosclerosis and Dyslipidaemia

Atherosclerosis is a progressive vascular disease characterised by the accumulation of atherogenic lipoproteins, inflammatory cells, extracellular matrix, and cellular debris within the arterial wall. Retention of apolipoprotein B-containing lipoproteins is an important early event, whereas disease progression involves endothelial activation, monocyte recruitment, macrophage foam cell formation, vascular smooth muscle cell responses, chronic inflammation, and changes in plaque structure that can ultimately lead to plaque disruption and thrombosis [8,24]. Dyslipidaemia, particularly elevated low-density lipoprotein cholesterol (LDL-C) and other apolipoprotein B-containing lipoproteins, is therefore an important causal driver of atherosclerotic cardiovascular disease [24].

Phytochemicals have been studied for their effects on several of these processes, including cholesterol absorption and metabolism, lipoprotein modification, macrophage cholesterol handling, inflammatory signalling, and endothelial function. The evidence, however, differs considerably among compounds and preparations [3,11,13].

4.2.1 Lipoprotein Modification, Inflammation, and Macrophage Cholesterol Handling

Following retention in the arterial wall, LDL particles can undergo oxidative and other modifications that promote endothelial activation and monocyte recruitment. Macrophages take up modified lipoproteins through scavenger receptors, leading to intracellular cholesterol accumulation and foam-cell formation. Cholesterol efflux pathways, including those involving ATP-binding cassette transporters A1 and G1, help remove excess cholesterol from macrophages and are important components of cellular cholesterol homeostasis.

Curcumin, quercetin, resveratrol, EGCG, and other phytochemicals have been studied for effects on oxidative stress and inflammatory signalling associated with these processes. Nrf2, NF-κB, AMPK, peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and SIRT1 are among the pathways implicated in experimental studies [3,11,12]. These mechanistic observations provide possible explanations for the anti-atherogenic effects reported in experimental models, but they do not, by themselves, demonstrate plaque regression or the prevention of cardiovascular events in humans.

The NLRP3 inflammasome provides an additional connection between lipid accumulation and vascular inflammation. Cholesterol crystals and other cellular stress signals can activate NLRP3 in atherosclerotic lesions, promoting the maturation of inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18) [9,25]. Experimental studies suggest that

some phytochemicals can modulate NLRP3-associated inflammatory signalling, although the clinical importance of this mechanism for phytomedicine remains uncertain.

4.2.2 Clinical Evidence for Lipid-Modifying Phytomedicines

Among individual phytochemicals, berberine has a comparatively substantial body of human evidence for lipid modification. Its proposed actions include regulation of AMPK and pathways involved in hepatic lipid and cholesterol metabolism [13]. A systematic review and meta-analysis of 18 randomised placebo-controlled trials involving 1,788 adults found that berberine reduced LDL-C by 0.46 mmol/L, total cholesterol by 0.48 mmol/L, triglycerides by 0.34 mmol/L, and apolipoprotein B by 0.25 g/L, although most included studies were conducted in mainland China or Hong Kong and treatment duration ranged from 4 to 24 weeks [26].

Phytosterols provide a more clearly defined plant-derived approach to cholesterol lowering. β-Sitosterol and campesterol are among the major dietary plant sterols. Plant sterols and stanols reduce intestinal cholesterol absorption and thereby lower circulating LDL-C [16]. A 2024 meta-analysis of 28 randomised controlled trials involving 1,777 participants found significant reductions in total cholesterol, LDL-C, and apolipoprotein B following phytosterol supplementation [17]. These findings provide comparatively strong evidence for an effect on lipid biomarkers, although evidence that phytosterol supplementation itself reduces cardiovascular events is insufficient [16,17].

Garlic has also been studied for lipid-modifying effects. A 2024 meta-analysis of 21 randomised controlled trials in patients with dyslipidaemia found reductions in total cholesterol, triglycerides, and LDL-C following garlic consumption. The pooled reductions were 0.64 mmol/L in total cholesterol, 0.17 mmol/L in triglycerides, and 0.44 mmol/L in LDL-C [27]. Considerable heterogeneity was present, and subgroup analyses indicated that effects varied by the type of garlic preparation, reinforcing the importance of treating garlic oil, powder, extracts, and other preparations as pharmacologically non-equivalent interventions [27].

Other phytochemicals, including curcumin, resveratrol, quercetin, and catechins, have extensive experimental evidence supporting their involvement in redox, inflammatory, and metabolic pathways [3,11,12]. However, evidence from mechanistic or preclinical studies should be distinguished from evidence demonstrating reproducible lipid modification or prevention of atherosclerotic cardiovascular events in humans.

4.2.3 Clinical Relevance

The clinical evidence reviewed here is strongest for changes in lipid biomarkers. Phytosterols show consistent LDL-C-lowering effects [16,17], while berberine and garlic also have meta-analytic evidence for improvements in lipid measures [26,27]. These effects are clinically relevant as changes in established cardiovascular risk factors. Still, they should not automatically be interpreted as evidence that the interventions reduce atherosclerotic plaque burden or prevent myocardial infarction, stroke, or cardiovascular death.

This distinction is particularly important when evaluating phytomedicines. Evidence of LDL-C reduction, changes in inflammatory biomarkers, or modulation of an atherosclerosis-related molecular pathway represents a different level of evidence from demonstration of improved patient-important clinical outcomes. At present, selected phytomedicines have stronger evidence for lipid-modifying effects than for the prevention of major cardiovascular events. They should not be regarded as substitutes for established lipid-lowering therapies in the absence of appropriate clinical outcome evidence.

4.3 Myocardial Ischaemia/Reperfusion Injury

Myocardial ischaemia/reperfusion injury (MIRI) occurs when restoration of blood flow to ischaemic myocardium, although essential for tissue survival, causes additional cellular injury. Reperfusion is accompanied by a rapid increase in reactive oxygen species (ROS), calcium overload, mitochondrial dysfunction, inflammatory activation, and cardiomyocyte death. These processes can increase infarct size and impair subsequent ventricular function [28,29].

Mitochondria play a central role in MIRI. Reoxygenation can lead to a rapid increase in mitochondrial ROS, while calcium overload and loss of mitochondrial membrane potential favour the opening of the mitochondrial permeability transition pore. The resulting impairment of ATP production and mitochondrial integrity contributes to cardiomyocyte injury and death. Mitochondrial quality control, including the regulation of mitochondrial dynamics and mitophagy, is therefore an important

target in experimental studies of cardioprotection [28–30].

Several phytochemicals have been investigated for their effects on these processes. Activation of Nrf2-dependent antioxidant responses may strengthen endogenous cellular defences, while AMPK, SIRT1, and PI3K/Akt signalling may support metabolic adaptation and cell survival. Plant-derived compounds have also been reported to affect mitochondrial fusion and fission, as well as PINK1/Parkin-mediated mitophagy [12,30,31].

Ferroptosis has received increasing attention as another form of cell death involved in MIRI. It is characterised by iron-dependent lipid peroxidation and failure of cellular antioxidant defences [31]. Kaempferol has been reported to reduce experimental reperfusion injury through Nrf2/GPX4-associated mechanisms [32], while dihydromyricetin has been linked to PPARα signalling and regulation of ferroptotic injury [33]. These studies suggest that control of lipid peroxidation and iron-dependent cell death may contribute to the cardioprotective actions of some phytochemicals [32,33].

Other natural compounds have been studied for their effects on mitochondrial and cell death pathways. Carnosic acid has been associated with mitofusin-2-related mitochondrial signalling [34], whereas sinomenine has been investigated for its effects on inflammatory and regulated cell death pathways [35]. Although these findings broaden the range of possible mechanisms, evidence for these compounds remains largely experimental.

Quercetin and resveratrol have a larger preclinical evidence base. Studies on quercetin have reported reductions in infarct size and oxidative injury across various experimental models [36]. Resveratrol has been studied for effects on oxidative stress, inflammation, mitochondrial function, and apoptosis, and a systematic review and meta-analysis of preclinical studies provides broader support for its cardioprotective effects than individual animal experiments alone [37].

Despite these findings, evidence for the use of phytochemicals in MIRI remains predominantly preclinical [31–37]. Most studies measure infarct size, oxidative and inflammatory markers, mitochondrial function, or histological injury in experimental models. These outcomes are useful for identifying possible mechanisms but do not establish whether treatment improves survival, preserves long-term ventricular function, prevents heart failure, or reduces recurrent cardiovascular events after myocardial infarction.

Clinical development in this area will therefore require evidence that effective concentrations can be achieved in myocardial tissue and that the proposed molecular effects are accompanied by meaningful changes in cardiac injury and function. At present, phytochemicals targeting mitochondrial dysfunction, oxidative injury, ferroptosis, and inflammation remain promising experimental approaches rather than established treatments for myocardial reperfusion injury.

4.4 Heart Failure and Cardiac Remodelling

Heart failure (HF) is a complex clinical syndrome arising from ischaemic heart disease, hypertension, cardiomyopathies, metabolic disorders, and other forms of myocardial injury. Its progression involves cardiomyocyte hypertrophy and death, neurohormonal activation, oxidative stress, mitochondrial dysfunction, chronic inflammation, extracellular-matrix remodelling, and myocardial fibrosis. These changes gradually alter cardiac structure and function, contributing to progressive ventricular dysfunction [38,39].

Pathological hypertrophy may initially develop as an adaptive response to pressure or volume overload, but becomes harmful when the underlying stress persists. Prolonged hypertrophic signalling increases myocardial oxygen demand, alters calcium handling, and contributes to metabolic and mitochondrial dysfunction. AMPK, PI3K/Akt, MAPK, mechanistic target of rapamycin (mTOR), NF-κB, and redox-sensitive pathways participate in cardiac hypertrophic signalling [38,39]. Ginsenosides have shown antihypertrophic effects in experimental models, although evidence in humans remains limited [40].

Myocardial fibrosis is another important feature of adverse cardiac remodelling. Persistent fibroblast activation and differentiation into myofibroblasts increase the deposition of collagen and other extracellular-matrix proteins. Progressive fibrosis increases myocardial stiffness, impairs relaxation, and can disturb electrical conduction. TGF-β/Smad signalling is a major regulator of cardiac fibrosis, with additional contributions from neurohormonal, inflammatory, and redox-sensitive pathways [41]. Plant-derived compounds, including curcumin and ginsenosides, have demonstrated antifibrotic effects in experimental studies by modulating fibrosis-associated signalling pathways [40,41].

Mitochondrial dysfunction is also closely linked to HF progression. The failing myocardium may show impaired ATP

production, altered substrate utilisation, increased ROS generation, disturbed calcium handling, and abnormalities in mitochondrial quality control [38]. Resveratrol and ginsenosides have been investigated for effects on mitochondrial and metabolic regulatory pathways, including sirtuin-, AMPK-, and redox-associated signalling [14,40]. The objective in this setting is not complete elimination of ROS, which also participate in physiological signalling, but restoration of redox homeostasis.

Autophagy contributes to the removal of damaged proteins and organelles and interacts closely with mitochondrial quality control and cardiomyocyte survival. Both insufficient and excessive autophagic activity can contribute to cardiac dysfunction. Autophagy-related pathways, including AMPK/mTOR and PI3K/Akt signalling, are involved in myocardial stress responses and cardiomyocyte survival [42]. Phytochemicals may influence these regulatory pathways, thereby affecting autophagy-related responses during cardiac stress. Interpretation nevertheless requires caution because changes in individual markers such as microtubule-associated protein 1 light chain 3-II or Beclin-1 do not, by themselves, establish changes in autophagic flux [42].

Human evidence for plant-derived interventions in HF is beginning to emerge. A 2025 network meta-analysis of 20 studies involving 2,077 patients reported improvements in selected functional, biomarker, and cardiac measures with several plant extracts, including six-minute walk distance, B-type natriuretic peptide (BNP), quality of life, left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) functional class, depending on the intervention evaluated [43]. A 2026 systematic review and network meta-analysis involving 28 studies and 3,650 patients similarly reported improvements in LVEF, NYHA functional class, quality of life, and six-minute walk distance with selected plant extracts [44]. Considerable variation in the botanical interventions and limitations in the underlying trials, however, restrict the certainty and generalisability of these findings [43,44].

Ginsenosides illustrate an important problem in interpreting this literature. Individual ginsenosides have shown experimental effects on myocardial energy metabolism, oxidative stress, inflammation, fibrosis, and cardiomyocyte survival, while ginseng-containing preparations have also been evaluated clinically [14,40,43]. Purified ginsenosides, standardised ginseng extracts, and complex herbal formulations are not equivalent interventions, however, and evidence obtained with one preparation should not automatically be extrapolated to another.

Current evidence suggests that phytomedicines may influence several processes involved in HF and cardiac remodelling, particularly hypertrophy, fibrosis, mitochondrial dysfunction, oxidative stress, and inflammation [40–42]. Human studies provide some evidence of improvements in cardiac function and functional capacity with selected preparations [43,44], but evidence for effects on HF hospitalisation and cardiovascular mortality remains insufficient. Phytomedicines should therefore be investigated as possible adjunctive interventions rather than considered substitutes for established guideline-directed HF treatment.

4.5 Thrombosis and Platelet Dysfunction

Thrombosis is a major cause of acute cardiovascular events following vascular injury or disruption of an atherosclerotic plaque. Platelet adhesion, activation, and aggregation initiate arterial thrombus formation, while activation of the coagulation cascade generates thrombin and fibrin, which stabilise the developing clot. Endothelial dysfunction, inflammation, and oxidative stress can further promote a prothrombotic state [45].

Platelet activation is regulated by several agonists, including adenosine diphosphate (ADP), thromboxane A_2, thrombin, and collagen. Plant-derived compounds have been studied for their effects on platelet aggregation, intracellular calcium signalling, nitric oxide pathways, oxidative stress, and arachidonic acid metabolism [45]. Most of this evidence comes from experimental studies, and the magnitude of platelet inhibition varies among compounds and preparations [45].

Garlic (*Allium sativum*) is among the botanicals investigated for possible antiplatelet effects. A systematic review of 12 randomised controlled trials involving 595 participants found that six trials reported reductions in platelet aggregation, whereas the remaining trials reported inconsistent findings. The authors concluded that heterogeneity and the limited number of trials prevented a firm conclusion regarding the antithrombotic effect of garlic [46]. Differences among garlic preparations should also be considered because their chemical composition and pharmacological properties are not necessarily equivalent [18,46].

Resveratrol and curcumin have also been investigated for antiplatelet activity. Experimental evidence indicates that these and

other polyphenolic phytochemicals can influence agonist-induced platelet activation and platelet signalling pathways [45]. However, evidence for modulation of platelet-related mechanisms should not be equated with evidence that these compounds prevent clinical thrombotic events.

A broader range of phytochemicals, including flavonoids, phenolic compounds, terpenoids, and organosulfur compounds, has been investigated for effects on haemostatic and platelet-related mechanisms [45]. These findings are of mechanistic interest, but the available evidence does not justify using such compounds as alternatives to established antiplatelet or anticoagulant therapy.

Safety requires particular attention when phytomedicines are used together with cardiovascular medicines. Herb-drug interactions may be pharmacodynamic, through additive effects on haemostasis, or pharmacokinetic, through effects on drug-metabolising enzymes and transporters [6,47]. Reported interactions involving herbal products and anticoagulant or antiplatelet drugs underscore the need to carefully assess concomitant medication use, although the strength of clinical evidence varies substantially across specific herb-drug combinations [47].

Overall, phytochemicals can influence platelet activation and other haemostatic processes [45,46]. However, the evidence is substantially stronger for mechanistic and platelet-related outcomes than for patient-important outcomes such as myocardial infarction or stroke. At present, these compounds are more appropriately investigated as potential adjunctive interventions than regarded as substitutes for established antiplatelet or anticoagulant treatment.

5. TRANSLATIONAL BARRIERS IN CARDIOVASCULAR PHYTOMEDICINE

Experimental studies show that phytochemicals can influence many processes involved in cardiovascular disease. Demonstrating biological activity, however, is only an early step in evaluating a potential treatment. The composition of the preparation, absorption, metabolism, tissue exposure, safety, and reproducibility all determine whether an experimental effect is likely to be relevant in humans [3,5,48].

5.1 Bioavailability and Pharmacokinetics

Many phytochemicals have limited or highly variable bioavailability due to factors such as aqueous solubility, intestinal absorption, metabolism, and elimination. Consequently, concentrations that produce biological effects in cultured cells may not correspond to exposures achieved in humans after oral administration. Phytochemicals may also undergo extensive metabolic transformation, producing conjugated or microbiota-derived metabolites that can differ pharmacologically from the parent compound [3,48].

The administered dose, therefore, provides only limited information about pharmacologically relevant exposure. Plasma concentrations and, where feasible, tissue exposure are more informative when relating an intervention to its proposed mechanism. This is particularly important when interpreting in vitro experiments and extrapolating findings from animal studies to humans, because administered dose alone does not establish comparable systemic exposure [48].

Pharmacokinetic measurements can help determine whether concentrations associated with biological activity are achieved in humans. Where sufficient data are available, pharmacokinetic-pharmacodynamic analysis can also relate exposure to parent compounds or metabolites to changes in relevant biological or physiological measures [48].

5.2 Metabolism and Active Metabolites

Metabolism does more than eliminate phytochemicals from the body. It can determine which chemical species are present in the circulation and which contribute to biological activity. Phase I and phase II metabolism can substantially alter the parent compound, while intestinal microorganisms may generate additional metabolites with different absorption and biological properties [7,48].

This distinction is important when studying mechanisms of action. A molecular effect attributed to an orally administered parent compound may instead be produced partly or predominantly by one or more circulating metabolites. Studies should therefore identify the chemical species present at biologically relevant concentrations whenever possible [48].

The issue is more complex for botanical extracts that contain multiple constituents with distinct absorption and metabolic profiles. The activity of such preparations may not be adequately represented by the concentration of a single marker

compound. Similarly, findings obtained with a purified phytochemical cannot automatically be applied to a crude or standardised botanical extract [49,50].

5.3 Standardisation and Reproducibility

Reliable clinical evaluation requires a clearly defined and reproducible botanical intervention. The chemical composition of plant preparations can vary with species or chemotype, geographic origin, cultivation conditions, harvesting season, plant part, drying and storage conditions, extraction procedures, and manufacturing methods. These differences can alter both biological activity and safety [49,50].

Reporting only the botanical name and administered dose is therefore insufficient. Studies should provide information on botanical authentication, the plant part used, extraction method, chemical composition, relevant marker compounds, and batch-to-batch consistency. Chromatographic fingerprinting and quantitative analysis of selected constituents can improve the description and reproducibility of complex preparations. For some products, characterisation of several markers may be more informative than reliance on a single compound [49,50].

Quality control should also include appropriate testing for contaminants and adulterants [51]. Dietary plants, traditional preparations, standardised extracts, purified phytochemicals, and modified formulations should be treated as distinct interventions rather than interchangeable forms of the same product [49,50].

5.4 Safety, Contamination, and Adulteration

Natural origin does not guarantee safety. Herbal medicinal products may be contaminated or adulterated with microorganisms, toxic metals, pesticides, mycotoxins, residual solvents, or undeclared pharmaceutical substances [51]. Such contamination or adulteration can result in clinically important toxicity [5,51].

Safety assessment should extend beyond short-term tolerability. Depending on the intervention and its expected pharmacological actions, assessment may include hepatic and renal function, haematological parameters, blood pressure, heart rate, bleeding events, metabolic effects, and other relevant safety measures. Long-term safety is particularly important when a botanical intervention is intended for chronic cardiovascular prevention or treatment [5,50].

Safety also depends on the biological action of the product. A compound that lowers blood pressure, inhibits platelet activation, reduces heart rate, or alters glucose concentrations may be beneficial in one setting but produce excessive effects when combined with conventional medicines [5,6].

5.5 Herb-Drug Interactions

Herb-drug interactions are especially relevant in cardiovascular disease because many patients receive several medications simultaneously. Interactions may be pharmacodynamic, through additive effects on blood pressure, heart rate, platelet function, coagulation, glucose, or electrolytes, or pharmacokinetic, through changes in drug absorption, metabolism, transport, or elimination. Cytochrome P450 enzymes and drug transporters such as P-glycoprotein may contribute to some of these interactions [6].

The clinical importance of an interaction depends on the strength of the evidence. Findings from enzyme assays or in vitro experiments should not be treated as equivalent to interactions demonstrated in controlled human studies. This distinction is important when considering possible interactions with statins, digoxin, antihypertensive drugs, antiplatelet agents, and anticoagulants [6].

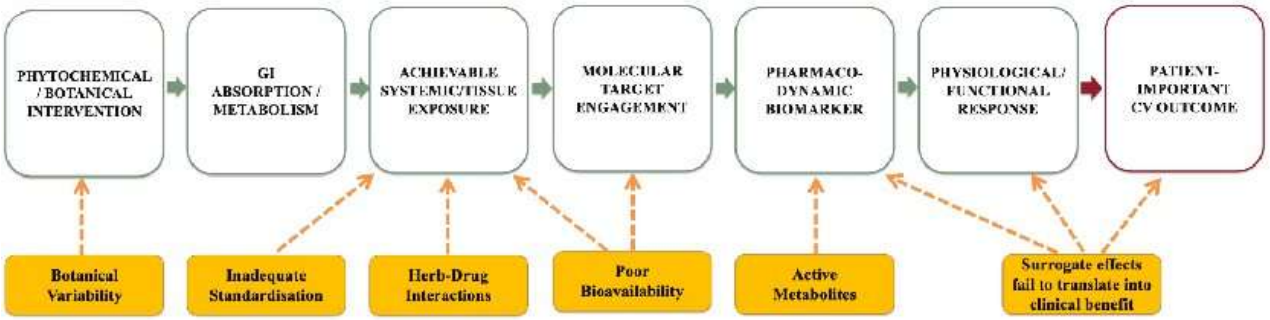
Particular caution is required when botanicals with possible antiplatelet or anticoagulant activity are used with aspirin, P2Y12 inhibitors, or anticoagulants. Clinical studies should document concomitant medication use and assess bleeding and other adverse events rather than assuming that a botanical product is pharmacologically inactive when added to conventional treatment [5,6].

5.6 Developing a Reproducible Botanical Intervention

For a phytomedicine to be evaluated reliably, the product used in experimental and clinical studies must be sufficiently characterised to allow reproduction. This begins with authenticated botanical material and controlled extraction or manufacturing, followed by chemical characterisation, contaminant testing, and assessment of batch consistency [49,50].

Pharmacokinetic studies can then determine what compounds or metabolites reach the circulation and at what concentrations [48].

Evidence of biological activity should then be linked to relevant pharmacodynamic effects and, ultimately, to clinical efficacy and safety. Continued safety assessment may also be necessary as a product progresses to wider, longer-term clinical use [50].



A practical development sequence is:

Authenticated botanical material → controlled extraction/manufacturing → chemical characterisation → contaminant and adulterant testing → batch consistency → pharmacokinetic assessment → confirmation of the proposed biological effect → clinical efficacy and safety → post-marketing surveillance [48–51].

The central question is therefore straightforward: can a well-characterised botanical intervention produce a reproducible biological effect at an achievable and safe exposure, and does that effect lead to a clinically meaningful benefit?

6. FROM LABORATORY EVIDENCE TO CLINICAL TRANSLATION

Experimental research has identified numerous phytochemicals that affect pathways involved in cardiovascular disease. The strength of this mechanistic evidence, however, is often greater than the evidence from well-designed human studies. A common pattern is progression from biochemical or cellular activity to animal studies, then to relatively small clinical trials, with much less evidence of effects on major cardiovascular outcomes [3,5]. A clear distinction between these levels of evidence is therefore necessary when assessing the therapeutic value of phytomedicines.

Figure 2. Translational pathway for cardiovascular phytomedicine. The pathway illustrates the progression from a phytochemical or botanical intervention to a patient-important cardiovascular outcome. Translation depends on gastrointestinal absorption and metabolism, sufficient systemic or tissue exposure, molecular target engagement, changes in pharmacodynamic biomarkers, and measurable physiological or functional responses. Botanical variability, inadequate standardisation, poor bioavailability, active metabolites, herb–drug interactions, and failure of surrogate effects to translate into clinical benefit may limit progression at different stages.

6.1 Levels of Evidence

Evidence for cardiovascular phytomedicine can be considered at five levels:

1. Chemical evidence: interaction with a molecular target or demonstration of biochemical activity.

2. Cellular evidence: reproducible modulation of a relevant pathway in cardiovascular, metabolic, or inflammatory cells.

3. Preclinical evidence: demonstration of biological or physiological effects in appropriate and reproducible animal models.

4. Clinical pharmacological evidence: demonstration of human exposure, relevant biological activity, pharmacodynamic response, and safety.

5. Clinical outcome evidence: evidence of benefit in patient-important outcomes such as cardiovascular morbidity, hospitalisation, major adverse cardiovascular events, or mortality.

For broader interpretation, chemical and cellular findings can be considered mechanistic evidence, followed by preclinical evidence, clinical pharmacological evidence, and clinical outcome evidence. These levels should not be treated as equivalent.

For example, inhibition of NF-κB in cultured macrophages suggests a potential anti-inflammatory mechanism but does not confer protection against myocardial infarction. Similarly, increased antioxidant enzyme activity in an animal model does not demonstrate reduced cardiovascular mortality.

The value of an intervention, therefore, depends not only on whether it affects a molecular pathway but also on whether that effect can be demonstrated under clinically relevant conditions and eventually linked to meaningful patient benefit [52].

6.2 Biomarkers, Physiological or Functional Outcomes, and Patient-Important Clinical Outcomes

Clinical studies of cardiovascular phytomedicines use endpoints that provide different levels of information and should be interpreted according to what they measure. These can be considered broadly as biomarkers → physiological or functional outcomes → patient-important clinical outcomes [53].

Biomarkers can provide evidence of biological activity and include measures such as LDL-C, apolipoprotein B, C-reactive protein and other inflammatory markers, BNP or N-terminal proBNP, cardiac troponins, and platelet reactivity measures. Physiological or functional outcomes include blood pressure, flow-mediated dilation, LVEF, exercise capacity, and relevant imaging measures of cardiovascular structure or function. Patient-important clinical outcomes include symptoms, quality of life, HF hospitalisation, myocardial infarction, stroke, and cardiovascular mortality [53].

These categories serve different purposes. A reduction in LDL-C indicates an effect on lipid metabolism, while improved flow-mediated dilation indicates a change in endothelial responsiveness. Neither finding alone demonstrates a reduction in myocardial infarction, stroke, HF hospitalisation, or cardiovascular mortality. Clinical interpretation should therefore reflect the type of endpoint evaluated and avoid presenting improvement in a biomarker or physiological measure as evidence of clinical benefit that has not been directly demonstrated [52,53].

6.3 Designing More Informative Clinical Trials

Clinical trials of phytomedicines require the same attention to intervention quality, dose, safety, and outcome selection expected in other areas of pharmacological research. The botanical preparation should be authenticated and chemically characterised, and the manufacturing process should be sufficiently controlled to ensure that participants receive a reproducible intervention [49].

Early clinical studies can help determine an appropriate dose, describe pharmacokinetics, identify relevant biological effects, and establish initial safety. Dose selection should be supported by evidence rather than being based solely on traditional use or arbitrary supplement doses. Where possible, early studies should also determine whether the proposed biological target is affected at concentrations achieved in humans [49,52].

Later trials should use adequate sample sizes, clinically relevant treatment durations, predefined outcomes, and systematic safety assessment. Comparator selection should reflect the intended clinical role of the intervention. When a phytomedicine is being evaluated as an adjunct, placebo-controlled studies conducted alongside guideline-directed therapy are generally more informative than comparisons with no treatment [49,54].

Trials should also distinguish clearly among dietary exposure, supplementation, purified phytochemicals, standardised botanical extracts, and complex herbal formulations. Evidence obtained with one type of intervention should not automatically be attributed to another [49].

6.4 Real-World Evidence and Long-Term Evaluation

Randomised controlled trials remain the principal method for establishing efficacy, but they cannot answer every question about long-term use. Observational cohorts, registries, electronic health records, and pharmacovigilance systems may provide additional information on adherence, uncommon adverse events, herb-drug interactions, effectiveness in routine practice, and outcomes in patient groups underrepresented in clinical trials [55].

Such evidence requires careful interpretation. Patients receiving an intervention in routine practice may differ systematically from non-users in health behaviours, socioeconomic characteristics, healthcare utilisation, comorbidities, and concomitant treatments. These differences can introduce confounding and affect observed cardiovascular outcomes independently of the intervention [55]. Real-world evidence should therefore complement rather than automatically replace randomised evidence

when treatment efficacy is being assessed.

6.5 Regulatory Considerations and Clinical Integration

Clinical development also requires appropriate standards for product quality, manufacturing, safety, and evidence of efficacy. Regulatory approaches to botanical products recognise that their chemical complexity and variability create challenges that differ from those associated with conventional single-molecule drugs. Evaluation, therefore, needs to consider botanical identity, chemical characterisation, manufacturing controls, batch consistency, safety, and clinical evidence [49].

For cardiovascular disease, the likely role of many phytomedicines is currently adjunctive rather than substitutive [5]. Botanical interventions should not replace therapies with established cardiovascular benefits unless adequate comparative clinical evidence supports such use. Their integration into clinical care requires evidence that the preparation is reproducible, sufficiently safe, compatible with concomitant medication, and capable of providing clinically relevant benefit [5,6,49].

6.6 A Staged Approach to Clinical Development

A practical development pathway for cardiovascular phytomedicines can be organised into the following stages:

Stage 1 - Discovery: identify reproducible cardiovascular activity.

Stage 2 - Mechanistic validation: confirm the molecular or cellular processes responsible for the observed effect.

Stage 3 - Pharmacokinetic characterisation: determine absorption, metabolism, relevant metabolites, distribution, and achievable exposure.

Stage 4 - Human biological activity: establish whether the proposed mechanism is affected at clinically realistic exposure.

Stage 5 - Biomarker and physiological evaluation: identify changes that are consistent with the proposed cardiovascular action.

Stage 6 - Early clinical evaluation: establish safety, dose, pharmacokinetics, and preliminary evidence of benefit.

Stage 7 - Confirmatory randomised trials: determine whether the intervention improves predefined patient-important clinical outcomes.

Stage 8 - Clinical integration: evaluate its role alongside established therapy and identify patient groups most likely to benefit.

Stage 9 - Long-term surveillance: assess uncommon adverse events, interactions, adherence, effectiveness, and long-term outcomes.

This staged approach allows ineffective or poorly characterised interventions to be identified before they progress to large clinical trials. It also separates promising experimental activity from the level of evidence required for clinical use [49,52,54].

7. FUTURE PERSPECTIVES

Future progress in cardiovascular phytomedicine will depend less on identifying additional compounds with general antioxidant or anti-inflammatory activity and more on determining which interventions produce reproducible effects in defined clinical settings. Important areas for further research include differences in individual response, phytochemical metabolism, the gut microbiome, improved delivery systems, computational approaches, and the development of reproducible multi-component botanical preparations [3,7,49].

7.1 Precision and Metabolite-Informed Phytomedicine

Individuals may respond differently to the same phytomedicine because of variation in genetics, metabolism, gut microbiota, hepatic and renal function, concomitant medications, and cardiovascular disease phenotype. These factors can influence both systemic exposure and biological response. In addition, metabolites formed through hepatic or microbial transformation may contribute substantially to activity and, in some cases, may be more relevant than the administered parent compound [7,48].

Combining pharmacokinetic and metabolomic measurements with clinical phenotyping could help identify factors associated with treatment response. Genomic information may also be useful when genetic variation affects relevant enzymes, transporters, receptors, or disease pathways. Such studies may eventually improve dose selection and help identify patient groups in whom a particular intervention is most likely to be useful [56].

7.2 Gut Microbiome and Cardiovascular Response

The relationship between phytochemicals and the gut microbiome is bidirectional. Plant-derived compounds can alter microbial composition and metabolic activity, while intestinal microorganisms can convert phytochemicals into metabolites with different absorption and biological properties [7]. Short-chain fatty acids, bile-acid metabolism, trimethylamine/trimethylamine-N-oxide (TMA/TMAO), tryptophan metabolites, intestinal permeability, and inflammatory signalling may all contribute to cardiovascular effects [57].

Studies combining microbiome analysis with pharmacokinetic and cardiovascular measurements may help explain interindividual differences in response to phytochemical interventions [7,57]. However, associations between microbial profiles and cardiovascular outcomes require mechanistic and clinical validation before they can guide treatment decisions.

7.3 Targeted Delivery and Improved Formulations

Poor solubility, chemical instability, limited absorption, and extensive metabolism can restrict the systemic exposure of some phytochemicals [48]. Delivery approaches, including liposomes, nanoemulsions, lipid-based carriers, micelles, phytosomes, and polymeric systems, have been investigated to improve solubility, stability, bioavailability, or tissue delivery of plant-derived bioactive compounds [58].

An important goal is to determine whether delivery systems can increase exposure at relevant cardiovascular sites without producing unacceptable systemic exposure or toxicity. Such formulations require evaluation of physicochemical stability, release characteristics, biodistribution, safety, and manufacturing reproducibility [58]. Improved delivery or bioavailability should not, by itself, be regarded as evidence of improved clinical efficacy.

7.4 Computational Approaches and Multi-Omics

Transcriptomic, proteomic, metabolomic, lipidomic, microbiome, and pharmacological datasets can be used to investigate the complex actions of phytochemicals. Computational and network-based methods may help identify candidate targets, metabolites, combinations, or patient subgroups and can assist in prioritising compounds for experimental study [59].

Artificial intelligence can also support natural-product drug discovery through the analysis of complex chemical and biological datasets, the prediction of molecular properties and interactions, and the prioritisation of compounds or targets [59]. Such predictions should be regarded as hypotheses requiring experimental validation rather than evidence of biological or clinical efficacy. The principal value of these approaches is therefore to guide experimental prioritisation and hypothesis generation rather than replace experimental and clinical evidence [59].

7.5 Multi-Component Botanical Preparations

The chemical complexity of botanical preparations presents both opportunities and difficulties. Several constituents may act on different but related pathways, and some effects may depend on interactions among compounds. At the same time, complex mixtures make it more difficult to determine dose, pharmacokinetics, active constituents, batch consistency, and the source of a biological effect [49].

Research should clearly distinguish traditional preparations, standardised extracts, enriched fractions, purified phytochemicals, and modified formulations. Claims of synergy should be supported experimentally rather than inferred from the presence of multiple constituents. For complex preparations intended for clinical use, reproducible composition and evidence of biological and clinical activity remain essential [49].

7.6 Phytochemicals as Sources for Cardiovascular Drug Discovery

Plant-derived natural products can provide biologically active chemical scaffolds and starting points for conventional drug discovery, including situations in which the original natural product itself is unsuitable for direct therapeutic use [60]. Structural modification and medicinal-chemistry optimisation can be used to improve properties such as potency, selectivity, stability, and pharmacokinetic behaviour.

This distinction broadens the value of phytomedicine research. A phytochemical does not necessarily need to become a botanical medicine itself to contribute to therapeutics; it may instead identify a biologically relevant target or provide a lead structure for subsequent drug development [60].

7.7 Sustainability and Responsible Development

Greater demand for medicinal plants can place pressure on wild plant populations and biodiversity, particularly where medicinal species are collected unsustainably. Sustainable cultivation, traceability, conservation of medicinal-plant resources, and reliable supply chains should therefore be considered during product development [61]. Appropriate recognition and protection of traditional knowledge are also important where such knowledge contributes to the identification or use of medicinal plants [61].

Long-term development will also require consistent standards for botanical authentication, chemical characterisation, manufacturing quality, clinical evidence, pharmacovigilance, and assessment of herb-drug interactions [6,49,61]. These considerations should be addressed throughout development rather than only after a product reaches clinical testing.

Future cardiovascular phytomedicine research should therefore focus on well-characterised interventions, biologically plausible mechanisms, individual variation in exposure and response, and clinically relevant outcomes. The central aim is not simply to identify more bioactive plant compounds, but to determine which plant-derived interventions can provide reproducible and meaningful cardiovascular benefit.

8. CONCLUSION

Phytomedicine offers a diverse source of bioactive compounds with potential relevance to cardiovascular disease. Experimental studies show that plant-derived compounds can influence oxidative stress, inflammation, endothelial function, lipid and glucose metabolism, mitochondrial function, cardiac remodelling, and platelet activity [3,11,12]. Human studies also provide evidence of beneficial effects of selected interventions, particularly on biomarkers and physiological or functional outcomes, including lipid parameters, blood pressure, endothelial function, and measures of cardiac function [17,21–23,26,27,43,44]. However, the strength of clinical evidence varies considerably among phytochemicals and botanical preparations.

A major challenge is the gap between biological activity demonstrated in experimental models and therapeutic effects that can be reproduced in humans. Limited or variable bioavailability, extensive metabolism, formation of active metabolites, differences in botanical composition, and inconsistent manufacturing can all influence exposure and response [48,49]. Safety is equally important, particularly in cardiovascular patients receiving antiplatelet agents, anticoagulants, lipid-lowering drugs, antihypertensive therapies, and other medications [5,6]. These factors make adequate botanical characterisation, pharmacokinetic assessment, and evaluation of herb-drug interactions essential components of clinical development [6,48,49].

Clinical interpretation should also reflect the available level of evidence. Changes in molecular pathways or biomarkers can support biological plausibility, but they should not be presented as evidence of reduced myocardial infarction, stroke, HF hospitalisation, or cardiovascular mortality unless these outcomes have been directly evaluated [52,53]. At present, clinical evidence for many phytomedicines remains stronger for biomarkers and physiological or functional outcomes than for patient-important clinical outcomes [5]. Evidence for major clinical cardiovascular outcomes, including myocardial infarction, stroke, HF hospitalisation, and cardiovascular mortality, remains particularly limited for many interventions [5,16,21–23,26,27,43,44].

Progress in this field will therefore depend on the study of well-characterised and reproducible interventions using clinically relevant doses, appropriate safety assessment, rigorous trial designs, and outcomes appropriate to the stage of clinical development. Precision approaches, metabolite and microbiome studies, improved delivery systems, and computational methods may help refine future research, but their value will ultimately depend on experimental and clinical validation. Phytomedicines should currently be viewed mainly as potential adjuncts to established cardiovascular therapy. Their wider clinical role will depend on whether specific interventions can demonstrate reproducible efficacy and acceptable safety in appropriately designed human studies.

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Author Contributions

Satyabrata Acharya: Conceptualisation, Literature Search, Selection of Bibliographic Sources, Investigation, Formal Analysis, Visualisation, Writing-Original Draft, Writing-Review & Editing.

Conflict of Interest

The author declares no conflict of interest with respect to the research, authorship, and/or publication of this article.

Ethics Statement

Ethical approval was not required for this review article, as it did not involve human participants, animals, or the collection of primary data.

Data Availability Statement

The information used in this review is publicly available from the published sources cited in the article. Additional information related to the review may be obtained from the author upon reasonable request.

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