



## Bioactive Compounds from Plants for Cardiovascular Therapy: Phytochemical Mechanisms, Molecular Targets, and Translational Potential in Preventive and Therapeutic Interventions

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### Abstract

Cardiovascular diseases (CVDs) remain the leading global cause of mortality, despite major advances in conventional pharmacotherapy. Limitations such as adverse drug reactions, incomplete risk reduction, and variable patient responses highlight the need for complementary therapeutic approaches. Plant-derived bioactive compounds have gained significant attention due to their multi-targeted actions, favorable safety profiles, and potential synergistic benefits alongside standard cardiovascular drugs. This review summarizes the cardiovascular therapeutic potential of key phytochemical classes, including flavonoids, polyphenols, alkaloids, terpenoids, saponins, and phenolic acids. These compounds exert protective effects through modulation of oxidative stress and inflammatory pathways (Nrf2 activation, NF- $\kappa$ B inhibition), improvement of endothelial function via enhanced nitric oxide bioavailability, regulation of lipid metabolism through LDL receptor and AMPK signaling, and suppression of atherosclerotic progression. Evidence from mechanistic studies, preclinical models, and emerging clinical trials supports the promise of compounds such as berberine, resveratrol, EGCG, and *Salvia miltiorrhiza* constituents. Challenges including poor bioavailability, extract variability, and clinical translation gaps are discussed to guide future research.

### DOI:

**Keywords:** Plant Bioactives, Cardiovascular Protection, Oxidative Stress, Inflammation, Lipid Modulation, Endothelial Function

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### Introduction

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, accounting for approximately 17.9 million deaths annually and representing 32% of all deaths worldwide <sup>[1]</sup>. Despite significant advances in pharmacotherapy, including statins, angiotensin-converting enzyme inhibitors, and antiplatelet agents, CVDs continue to impose substantial health and economic burdens <sup>[2]</sup>. Current therapeutic approaches face limitations including adverse effects, variable patient responses, and incomplete risk reduction, necessitating the exploration of alternative and complementary strategies <sup>[3]</sup>.

Plant-derived bioactive compounds have emerged as promising candidates for cardiovascular therapy, offering multi-targeted mechanisms, favorable safety profiles, and synergistic effects when combined with conventional treatments <sup>[4]</sup>. The pharmacological potential of phytochemicals extends beyond symptomatic management to address fundamental pathophysiological mechanisms underlying CVDs, including oxidative stress, chronic inflammation, endothelial dysfunction, and aberrant lipid metabolism <sup>[5]</sup>. Epidemiological evidence consistently demonstrates inverse associations between dietary

intake of plant bioactives and cardiovascular risk, while preclinical studies have elucidated specific molecular targets and signaling pathways [6, 7].

This review examines the cardiovascular therapeutic potential of major plant-derived bioactive compound classes, focusing on their molecular mechanisms, cellular targets, and translational applications. We critically evaluate evidence from phytochemical characterization, mechanistic studies, and clinical investigations to identify compounds with robust cardiovascular protective effects and discuss challenges in translating phytochemical research into clinical interventions.

## Phytochemical Classes for Cardiovascular Therapy

### Flavonoids and Polyphenols

Flavonoids represent the most extensively studied class of cardiovascular-active phytochemicals, comprising over 6,000 structurally diverse compounds categorized into flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, and isoflavones [8]. These compounds exhibit potent antioxidant properties through multiple mechanisms including direct free radical scavenging, metal chelation, and upregulation of endogenous antioxidant enzymes [9]. Quercetin, a ubiquitous flavonol found in onions, apples, and berries, demonstrates significant cardioprotective effects through activation of endothelial nitric oxide synthase (eNOS), inhibition of NADPH oxidase-mediated reactive oxygen species (ROS) generation, and modulation of nuclear factor erythroid 2-related factor 2 (Nrf2) signaling [10].

Epigallocatechin gallate (EGCG), the predominant catechin in green tea, exhibits multi-targeted cardiovascular benefits including LDL cholesterol reduction, inhibition of vascular smooth muscle cell proliferation, and suppression of platelet aggregation [11]. Clinical trials demonstrate that EGCG supplementation significantly reduces systolic and diastolic blood pressure, with meta-analyses reporting mean reductions of 2.6 mmHg and 1.8 mmHg, respectively [12]. Resveratrol, a stilbenoid polyphenol abundant in grapes and red wine, activates sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK), promoting mitochondrial biogenesis, enhancing insulin sensitivity, and exerting anti-atherosclerotic effects through modulation of inflammatory pathways [13].

### Alkaloids and Terpenoids

Alkaloids constitute a diverse group of nitrogen-containing compounds with significant cardiovascular pharmacological activities. Berberine, an isoquinoline alkaloid isolated from *Berberis* species, demonstrates remarkable lipid-lowering effects comparable to statins through multiple mechanisms including upregulation of hepatic LDL receptor expression, inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), and activation of AMPK [14]. Clinical studies reveal that berberine supplementation (1.0-1.5 g/day) reduces total cholesterol by 16-29%, LDL cholesterol by 21-25%, and triglycerides by 22-35% [15]. Additionally, berberine improves endothelial function through enhanced nitric oxide bioavailability and exhibits anti-arrhythmic properties via modulation of cardiac ion channels [16].

Terpenoids, including diterpenes and triterpenes, demonstrate cardiovascular protective mechanisms through anti-inflammatory and antioxidant pathways. Tanshinone IIA, a diterpene quinone from *Salvia miltiorrhiza*, inhibits nuclear factor-kappa B (NF-κB) activation, reduces

expression of adhesion molecules, and prevents myocardial ischemia-reperfusion injury through mitochondrial protection [17]. Ginsenosides, triterpene saponins from *Panax ginseng*, exhibit cardioprotective effects including improved cardiac contractility, reduced myocardial infarct size, and enhanced angiogenesis through vascular endothelial growth factor (VEGF) signaling [18].

### Saponins and Phenolic Acids

Saponins represent amphipathic glycosides with diverse cardiovascular activities. Astragaloside IV, derived from *Astragalus membranaceus*, demonstrates cardioprotective effects through activation of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling, inhibition of apoptosis, and promotion of cardiac progenitor cell differentiation [19]. Preclinical studies indicate that astragaloside IV reduces myocardial fibrosis, improves left ventricular function, and attenuates adverse cardiac remodeling in heart failure models [20].

Phenolic acids, including hydroxycinnamic and hydroxybenzoic acid derivatives, contribute significantly to cardiovascular protection. Salvianolic acid B from *Salvia miltiorrhiza* exhibits potent antioxidant activity, inhibits platelet aggregation, and prevents atherosclerotic lesion formation through suppression of oxidized LDL uptake by macrophages [21]. Caffeic acid phenethyl ester demonstrates anti-inflammatory properties by inhibiting lipoxygenase and cyclooxygenase pathways, reducing production of pro-inflammatory eicosanoids implicated in atherosclerosis progression [22].

### Molecular Mechanisms and Cardiovascular Targets Antioxidant and Anti-inflammatory Pathways

Oxidative stress and chronic inflammation represent fundamental mechanisms underlying CVD pathogenesis, creating a compelling rationale for antioxidant and anti-inflammatory interventions [23]. Plant bioactives exert antioxidant effects through multiple complementary mechanisms beyond direct ROS scavenging. Activation of the Nrf2-Kelch-like ECH-associated protein 1 (Keap1) pathway represents a critical mechanism whereby phytochemicals induce expression of phase II detoxifying enzymes and antioxidant proteins including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and glutathione S-transferase [24].

Suppression of pro-inflammatory signaling constitutes another major cardioprotective mechanism. Flavonoids and polyphenols inhibit NF-κB activation through multiple mechanisms including prevention of inhibitor of κB (IκB) phosphorylation and degradation, direct modulation of upstream kinases, and interference with DNA binding [25]. This results in reduced expression of inflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein, and adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [26]. Additionally, several phytochemicals modulate inflammasome activation, particularly the NLRP3 inflammasome, which plays a crucial role in atherosclerosis and myocardial injury [27].

### Lipid Modulation and Anti-atherosclerotic Effects

Dyslipidemia represents a major modifiable risk factor for atherosclerotic CVD, and numerous plant bioactives

demonstrate significant lipid-modulating effects through diverse mechanisms [28]. Inhibition of intestinal cholesterol absorption represents one important mechanism, exemplified by plant sterols and stanols which compete with cholesterol for incorporation into mixed micelles, reducing absorption by approximately 30-50% [29]. Hepatic cholesterol metabolism modulation occurs through multiple pathways including upregulation of LDL receptor expression, inhibition of HMG-CoA reductase, activation of cholesterol 7 $\alpha$ -hydroxylase (the rate-limiting enzyme in bile acid synthesis), and suppression of PCSK9 expression [30].

Anti-atherosclerotic effects extend beyond lipid lowering to include prevention of LDL oxidation, inhibition of foam cell formation, and stabilization of atherosclerotic plaques [31]. Polyphenolic compounds prevent copper-mediated LDL oxidation through antioxidant mechanisms and metal chelation, reducing the formation of oxidized phospholipids and oxidized cholesteryl esters that promote macrophage uptake [32]. Furthermore, plant bioactives inhibit macrophage scavenger receptors including CD36 and scavenger receptor A, reducing foam cell formation, and suppress matrix metalloproteinase expression, contributing to plaque stabilization [33].

### **Endothelial Protection, Vasorelaxation, and Antihypertensive Effects**

Endothelial dysfunction, characterized by reduced nitric oxide bioavailability, increased oxidative stress, and impaired vasodilation, represents an early event in atherosclerosis and hypertension [34]. Plant bioactives protect endothelial function through multiple mechanisms including enhanced eNOS expression and activity, increased nitric oxide production, and prevention of nitric oxide degradation by reducing oxidative stress [35]. Phosphorylation of eNOS at activating sites (Ser1177) and dephosphorylation at inhibitory sites (Thr495) represent important regulatory mechanisms influenced by flavonoids through activation of PI3K/Akt signaling [36].

Vasorelaxant effects occur through both endothelium-dependent and endothelium-independent mechanisms. Endothelium-dependent vasodilation involves enhanced nitric oxide and prostacyclin production, while endothelium-independent mechanisms include direct effects on vascular smooth muscle cells through modulation of calcium channels, potassium channels, and phosphodiesterase activity [37]. Several alkaloids and flavonoids demonstrate calcium channel blocking activity comparable to synthetic calcium antagonists, contributing to blood pressure reduction and anti-arrhythmic effects [38]. Additionally, inhibition of angiotensin-converting enzyme (ACE) by various plant polyphenols provides antihypertensive effects through reduced angiotensin II formation and increased bradykinin availability [39].

### **Therapeutic Applications**

#### **Hypertension Prevention and Management**

Hypertension affects over 1.28 billion adults globally and represents a primary risk factor for stroke, myocardial infarction, and chronic kidney disease [40]. Multiple plant bioactives demonstrate clinically significant blood pressure-lowering effects through diverse mechanisms. Flavanol-rich cocoa products reduce systolic blood pressure by 3-4 mmHg and diastolic pressure by 2-3 mmHg, effects attributed to improved endothelial function and enhanced nitric oxide

bioavailability [41]. Hibiscus sabdariffa extracts, rich in anthocyanins and organic acids, demonstrate antihypertensive effects comparable to low-dose captopril in clinical trials, reducing systolic pressure by 7-13 mmHg through ACE inhibition and diuretic effects [42].

Garlic preparations containing allicin and organosulfur compounds reduce blood pressure through hydrogen sulfide-mediated vasorelaxation and modulation of the renin-angiotensin-aldosterone system [43]. Meta-analyses of randomized controlled trials indicate that garlic supplementation reduces systolic blood pressure by 8-10 mmHg in hypertensive individuals, with effects most pronounced in those with baseline systolic pressure exceeding 140 mmHg [44]. Celery seed extracts containing 3-n-butylphthalide demonstrate antihypertensive effects through calcium channel blockade and direct vasodilatory actions [45].

#### **Anti-atherosclerotic and Lipid-lowering Effects**

Plant bioactives offer significant potential for atherosclerosis prevention and lipid management. Berberine demonstrates lipid-lowering efficacy approaching that of statins while exhibiting a favorable safety profile, with clinical trials showing 20-30% reductions in LDL cholesterol and 15-25% reductions in triglycerides [46]. Combination therapy of berberine with statins allows dose reduction of statins while maintaining therapeutic efficacy, potentially reducing statin-associated muscle symptoms [47]. Red yeast rice, containing naturally occurring lovastatin, reduces LDL cholesterol by 15-25% and demonstrates cardiovascular event reduction in secondary prevention trials [48].

Curcumin from *Curcuma longa* exhibits pleiotropic anti-atherosclerotic effects including lipid lowering, anti-inflammatory activity, and inhibition of vascular smooth muscle cell proliferation [49]. Clinical studies demonstrate that curcumin supplementation improves endothelial function, reduces inflammatory markers, and decreases arterial stiffness in patients with metabolic syndrome and diabetes [50]. Pomegranate polyphenols, particularly punicalagins, reduce atherosclerotic lesion size in animal models and decrease carotid intima-media thickness in human studies through antioxidant and anti-inflammatory mechanisms [51].

#### **Cardioprotection in Ischemic and Heart Failure Conditions**

Myocardial ischemia-reperfusion injury and chronic heart failure represent significant causes of morbidity and mortality, and several plant bioactives demonstrate cardioprotective effects in these conditions. Salvianolic acids and tanshinones from *Salvia miltiorrhiza* reduce myocardial infarct size, preserve left ventricular function, and improve survival in experimental myocardial infarction through multiple mechanisms including antioxidant effects, mitochondrial protection, and anti-apoptotic signaling. Clinical trials in patients with coronary artery disease demonstrate that *Salvia miltiorrhiza* preparations improve exercise tolerance, reduce anginal episodes, and decrease biomarkers of myocardial injury.

Hawthorn (*Crataegus* species) extracts, containing flavonoids and oligomeric procyanidins, improve cardiac contractility, increase coronary blood flow, and demonstrate positive inotropic effects through inhibition of phosphodiesterase and modulation of intracellular calcium. Meta-analyses of clinical trials in heart failure patients

indicate that hawthorn extracts significantly improve exercise capacity, reduce symptoms, and enhance quality of life with excellent tolerability. Astragaloside IV demonstrates potential in heart failure therapy through promotion of angiogenesis, inhibition of cardiomyocyte apoptosis, and attenuation of adverse cardiac remodeling.

### Challenges and Translational Perspectives

#### Bioavailability, Metabolism, and Pharmacokinetics

Poor bioavailability represents a major challenge limiting the therapeutic potential of many plant bioactives. Polyphenolic compounds typically exhibit low oral bioavailability due to limited intestinal absorption, extensive first-pass metabolism, and rapid elimination. Conjugation reactions including glucuronidation, sulfation, and methylation occur in intestinal and hepatic tissues, generating metabolites with altered biological activities compared to parent compounds. The gut microbiota plays a crucial role in phytochemical metabolism, converting parent compounds and conjugates into bioactive metabolites that may contribute significantly to observed cardiovascular effects.

Strategies to enhance bioavailability include structural modification, formulation optimization, and combination with absorption enhancers. Nanoparticle delivery systems, including liposomes, solid lipid nanoparticles, and polymeric nanoparticles, demonstrate improved bioavailability and tissue distribution for poorly soluble compounds like curcumin and resveratrol. Co-administration with piperine, a bioavailability enhancer from black pepper, increases curcumin bioavailability by up to 2000% through inhibition of hepatic and intestinal glucuronidation. Understanding the pharmacokinetic-pharmacodynamic relationships of plant bioactives and their metabolites remains essential for rational dose selection and optimization of therapeutic regimens.

#### Standardization and Quality Control of Plant Extracts

Variability in phytochemical composition due to genetic factors, environmental conditions, harvesting practices, and processing methods poses significant challenges for therapeutic applications. Standardization to specific marker compounds or compound classes provides consistency in phytochemical content but may not fully capture the complexity of multi-component extracts where synergistic interactions contribute to biological activity. Comprehensive chemical fingerprinting using chromatographic and spectroscopic techniques enables quality control while preserving the chemical complexity of plant extracts.

Adulteration, contamination with heavy metals or pesticides, and batch-to-batch variability represent additional quality control concerns requiring robust analytical methods and regulatory oversight. Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP) provide frameworks for ensuring quality and consistency of botanical products. Development of standardized extraction protocols, validated analytical methods, and authenticated botanical reference materials remains essential for advancing clinical translation of plant-derived cardiovascular therapeutics.

### Preclinical to Clinical Translation Gaps

Despite extensive preclinical evidence supporting cardiovascular benefits of plant bioactives, clinical translation faces several challenges. Discrepancies between preclinical and clinical findings may arise from differences in dosing (often higher in animal studies), bioavailability variations across species, and the use of pure compounds versus complex extracts. Many preclinical studies employ intravenous or intraperitoneal administration, achieving plasma concentrations unattainable through oral dosing in humans. Furthermore, animal models may not fully recapitulate the complexity of human CVD, particularly chronic conditions involving multiple risk factors and comorbidities.

Clinical trials of plant bioactives frequently suffer from methodological limitations including small sample sizes, short duration, heterogeneous study populations, and inadequate characterization of interventions. Large-scale, long-duration trials with hard cardiovascular endpoints (myocardial infarction, stroke, cardiovascular mortality) are necessary to definitively establish clinical efficacy but require substantial resources and coordinated efforts. Personalized medicine approaches considering genetic polymorphisms affecting phytochemical metabolism, individual gut microbiota composition, and baseline cardiovascular risk profiles may optimize therapeutic responses and facilitate successful translation.

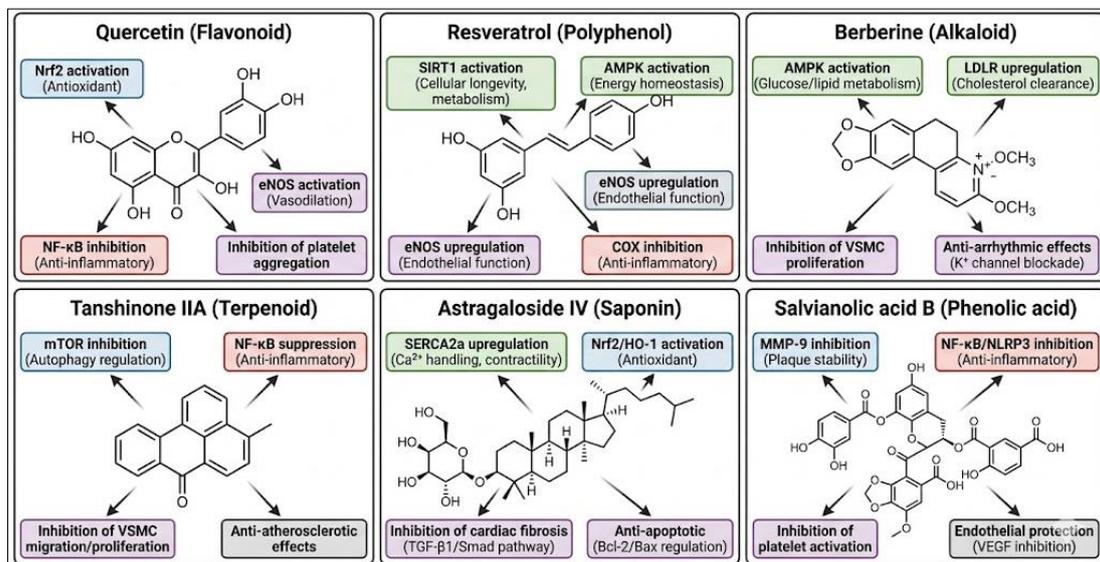
### Conclusion

Plant-derived bioactive compounds demonstrate significant cardiovascular therapeutic potential through multi-targeted mechanisms addressing fundamental pathophysiological processes including oxidative stress, inflammation, dyslipidemia, endothelial dysfunction, and pathological vascular remodeling. Flavonoids, alkaloids, terpenoids, saponins, and phenolic acids exert cardioprotective effects supported by robust mechanistic evidence and promising clinical data. Berberine, resveratrol, EGCG, and *Salvia miltiorrhiza* constituents represent particularly well-characterized compounds with established molecular targets and demonstrated clinical efficacy.

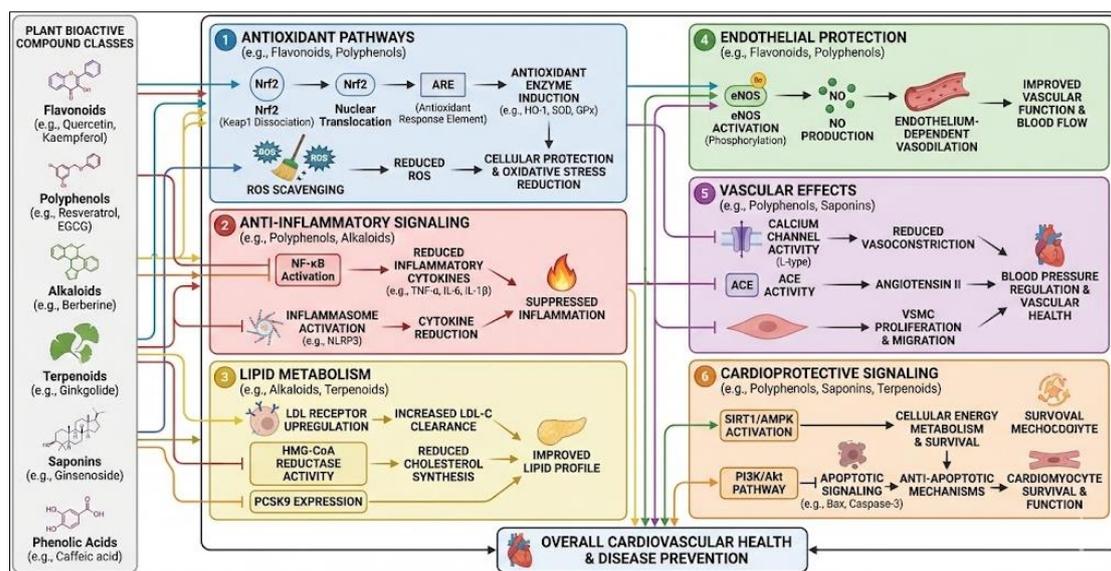
However, translation of phytochemical research into mainstream cardiovascular therapeutics requires addressing critical challenges including bioavailability optimization, rigorous standardization and quality control, and comprehensive clinical validation through adequately powered trials with cardiovascular endpoints. Integration of advanced drug delivery systems, systems pharmacology approaches, and precision medicine strategies will facilitate optimal utilization of plant bioactives in cardiovascular prevention and therapy. Future research should prioritize mechanistic studies elucidating compound-specific molecular targets, pharmacokinetic-pharmacodynamic investigations informing rational dosing strategies, and collaborative clinical trials establishing definitive cardiovascular benefits. Plant-derived bioactives offer promising complementary and alternative approaches for cardiovascular disease management, with potential to reduce the global burden of these devastating conditions.

**Table 1:** Selected Medicinal Plants, Key Bioactive Compounds, Mechanisms, and Cardiovascular Applications

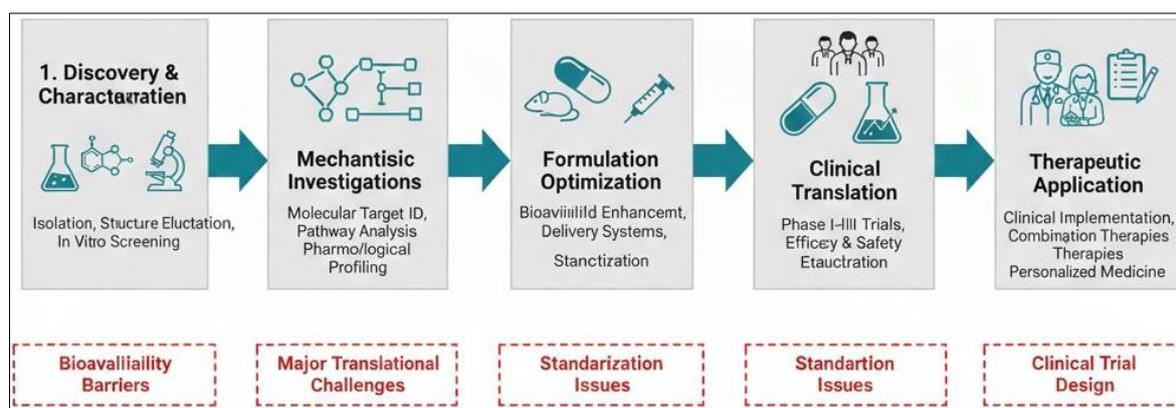
Plant Species	Key Bioactive Compounds	Primary Molecular Mechanisms	Cardiovascular Applications
Camellia sinensis	EGCG, catechins	eNOS activation, ROS scavenging, VSMC proliferation inhibition	Hypertension, atherosclerosis, lipid lowering
Vitis vinifera	Resveratrol, anthocyanins	SIRT1 activation, AMPK activation, NF-κB inhibition	Cardioprotection, anti-atherosclerotic, anti-inflammatory
Berberis spp.	Berberine	LDL receptor upregulation, PCSK9 inhibition, AMPK activation	Dyslipidemia, hypertension, diabetes
Salvia miltiorrhiza	Tanshinone IIA, salvianolic acids	Mitochondrial protection, anti-apoptotic, antioxidant	Myocardial ischemia, angina, heart failure
Crataegus spp.	Flavonoids, procyanidins	Phosphodiesterase inhibition, positive inotropy, coronary vasodilation	Heart failure, coronary insufficiency
Allium sativum	Allicin, organosulfur compounds	H <sub>2</sub> S-mediated vasodilation, ACE inhibition, antithrombotic	Hypertension, atherosclerosis prevention
Panax ginseng	Ginsenosides	VEGF signaling, cardiac contractility enhancement, cardioprotection	Heart failure, ischemia-reperfusion injury
Astragalus membranaceus	Astragaloside IV	PI3K/Akt activation, anti-fibrotic, angiogenesis promotion	Heart failure, cardiac remodeling
Curcuma longa	Curcumin	NF-κB inhibition, Nrf2 activation, anti-inflammatory	Atherosclerosis, endothelial dysfunction, dyslipidemia
Hibiscus sabdariffa	Anthocyanins, organic acids	ACE inhibition, diuretic effects, antioxidant	Hypertension



**Fig 1:** Major Plant-Derived Bioactive Compounds for Cardiovascular Therapy



**Fig 2:** Molecular Mechanisms and Pathways of Cardiovascular Protection by Plant Bioactives



**Fig 3:** Translational Pipeline from Plant Bioactives to Clinical Cardiovascular Interventions

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