Check for updates

Phytotherapy Research

WILEY

REVIEW OPEN ACCESS

Integrative Approaches in Cardiovascular Disease: The Role of Nutraceuticals in Heart Failure, Atrial Fibrillation, and Related Conditions

Laura Beatrice Mattioli[1,2] | Ivan Corazza[2,3] | Roberta Budriesi[1] | Luca Camarda[1] | Maria Carelli[4] | Alberto Spadotto[3] | Igor Diemberger[2,3,4]

[1]Department of Pharmacy and Biotechnology (FaBiT), Food Chemistry and Nutraceutical Lab, Alma Mater Studiorum-University of Bologna, Bologna, Italy | [2]Health Sciences and Technologies-Interdepartmental Center for Industrial Research (CIRI-SDV), Alma Mater Studiorum-University of Bologna, Bologna, Italy | [3]Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum-University of Bologna, Bologna, Italy | [4]Cardiology Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy

Correspondence: Laura Beatrice Mattioli (laurabeatrice.mattioli@unibo.it) | Ivan Corazza (ivan.corazza@unibo.it)

Received: 26 October 2025 | **Revised:** 29 June 2026 | **Accepted:** 23 August 2026

Keywords: atrial fibrillation | food chemistry | heart failure | integrative medicine in cardiology | natural compounds | nutraceuticals

ABSTRACT

Heart failure (HF) and atrial fibrillation (AF) are among the most prevalent cardiovascular diseases, often coexisting and sharing common pathophysiological pathways such as systemic inflammation, oxidative stress, mitochondrial dysfunction, and endothelial impairment. Despite substantial progress in pharmacological treatment, including renin–angiotensin–aldosterone system (RAAS) inhibitors, beta-blockers, sodium–glucose cotransporter 2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists (MRAs), diuretics, and antiarrhythmic drugs, many patients continue to experience residual symptoms and drug-related adverse effects. Nutraceuticals have emerged as potential adjuncts to conventional therapy due to their ability to modulate key biological processes involved in HF and AF. Polyphenols from *Olea europaea*, *Hibiscus sabdariffa*, *Camellia sinensis*, and *Vitis vinifera* (resveratrol) exhibit antioxidant, anti-inflammatory, and vasoprotective effects. Omega-3 fatty acids and astaxanthin contribute to inflammation control and redox balance, while *Orthosiphon stamineus* and *Taraxacum officinale* show mild diuretic activity. Moreover, anthocyanins, ursolic acid, and *Rhodiola crenulata* may exert antifibrotic and antiarrhythmic properties. This review provides a mechanistic comparison between pharmacological agents and nutraceuticals with overlapping mechanisms of action, highlighting their potential role in integrative cardiovascular care. While nutraceuticals are not substitutes for established therapies, emerging evidence supports their complementary use in improving treatment response, reducing side effects, and enhancing patient outcomes. Future research should focus on large-scale trials, improved bioavailability, standardized formulations, and the development of personalized therapeutic strategies. Challenges related to dosage consistency, clinical validation, and regulatory oversight are also addressed to guide innovation in integrative cardiology.

1 | Introduction

Cardiovascular diseases represent one of the leading causes of mortality and morbidity worldwide, with a significant impact on both patients' quality of life and healthcare systems (WHO's Team 2025; Di Cesare et al. 2024; Murray et al. 2020). Among these, heart failure (HF) and atrial fibrillation (AF) emerge as two conditions of utmost clinical relevance, characterized by

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2026 The Author(s). *Phytotherapy Research* published by John Wiley & Sons Ltd.

complex management and often interconnected progression (Kotecha and Piccini 2015; McDonagh et al. 2021).

HF is a heterogeneous clinical syndrome defined by the heart's inability to provide a cardiac output sufficient to meet the body's metabolic demands. This condition can result from structural or functional alterations that impair the heart's contractile ability or filling capacity (McDonagh et al. 2021; Heidenreich et al. 2022). The main symptoms include dyspnea and fatigue, while common clinical signs comprise fluid retention, peripheral edema, and pulmonary congestion. HF can be classified into two primary forms: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Among these, HFpEF is a remarkably heterogeneous condition with less clearly defined treatment strategies than HFrEF. HF with mildly reduced ejection fraction (HFmrEF) also deserves attention, as evidence suggests a potentially earlier functional improvement in these patients, although guidelines for its management are still evolving. The underlying causes are often multifactorial and include ischemic heart disease, arterial hypertension, and cardiomyopathies (McDonagh et al. 2021).

On the other hand, AF is the most common sustained cardiac arrhythmia in the general population, characterized by disorganized atrial electrical activity leading to ineffective atrial contraction (Hindricks et al. 2021). This arrhythmia is associated with a high risk of severe complications, including ischemic stroke, HF, and cardiovascular mortality. Recent evidence also points to a possible link between AF and cognitive impairment, potentially independent of thromboembolic events, suggesting a more complex interplay that warrants further investigation. The main predisposing factors include advanced age, hypertension, valvular diseases, metabolic dysfunctions, and chronic inflammatory status (Lee et al. 2024; Manolis et al. 2025).

HF and AF share numerous risk factors and often coexist in the same patient, further complicating clinical management (Kotecha and Piccini 2015; Santhanakrishnan et al. 2016; Anter et al. 2009). These two conditions are interconnected through shared pathophysiological mechanisms, such as systemic inflammation, oxidative stress, and endothelial dysfunction, which mutually reinforce each other and contribute to disease progression (Kotecha and Piccini 2015; Anter et al. 2009).

Despite advances in conventional pharmacological therapy, the management of these cardiovascular diseases remains a challenge. This has driven research toward innovative and complementary strategies, including nutraceuticals and natural compounds. These substances are gaining increasing attention for their potential to modulate inflammatory, oxidative, and metabolic processes, which underlie the development and progression of these diseases. Notably, their protective role has also been explored in inflammatory cardiac conditions such as myocarditis, further supporting their relevance in cardiovascular disease management (Enayati et al. 2022).

A growing body of evidence supports this integrative approach: nutraceuticals, including polyphenols, sterols, and other bioactive compounds, have demonstrated beneficial effects on cardiovascular risk factors, such as dyslipidemia, hypertension, and insulin resistance, with promising results in prevention strategies, as summarized by Sosnowska et al. (Sosnowska et al. 2017). Nutraceuticals may play an adjunctive role by enhancing the effectiveness of conventional therapies, reducing their side effects, and offering additional benefits in prevention and long-term disease management (Klein et al. 2000; Ansari 2021). A significant advantage of nutraceuticals is their safety profile, which is generally superior to conventional drugs, making them particularly promising for prevention and long-term treatment in chronic diseases (Newell et al. 2023; Vettorazzi et al. 2020; Puri et al. 2022).

In this context, exploring adjunctive therapies that target the same pathophysiological mechanisms as conventional treatments is especially relevant to optimizing patient-centered care. This review showcases the conventional pharmacological therapies used to manage HF and AF, analyzing the main mechanisms of action of the drugs employed. It introduces the nutraceuticals characterized by similar mechanisms of action, emphasizing their potential adjunctive and supportive role in conventional treatment. By presenting scientific evidence from molecular, preclinical, and clinical studies, we demonstrate the therapeutic potential of nutraceuticals to complement pharmacological therapy, thereby enhancing efficacy and improving patient outcomes. Overall, using an evidence-based overview, we assess whether and how nutraceuticals can be integrated into clinical practice to support conventional therapies and improve outcomes for patients with cardiovascular diseases.

This framework is intended as a conceptual model to support mechanistic interpretation and translational understanding, rather than a prescriptive clinical tool, and is primarily addressed to researchers and clinicians interested in integrative and mechanism-based approaches in cardiovascular disease. In this context, it enables a structured integration of nutraceuticals with established pharmacological targets within shared pathophysiological networks, providing a basis for interpreting their potential multi-target and complementary roles in cardiovascular disease management in line with the multicomponent–multitarget paradigm described in phytocomplex-based approaches (Mattioli, Frosini, et al. 2024).

1.1 | Criteria for Nutraceutical Selection in Cardiovascular Applications

This review focuses on a selection of nutraceuticals and natural compounds with potential cardiovascular relevance, particularly in the context of HF and AF. The selection was guided by the following criteria: (1) their traditional use for cardiovascular or systemic health; (2) their availability as food supplements or herbal preparations that comply with national and European safety standards (EFSA, n.d.); and (3) the presence of preclinical and/or clinical data supporting mechanisms of action that may overlap with those of conventional drugs; and (4) when available, a well-characterized qualitative and quantitative chemical composition, allowing a more reliable interpretation of their biological activity.

Studies were included based on their relevance to HF and AF, the presence of mechanistic and/or clinical evidence, and their alignment with the pharmacodynamic targets of conventional

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

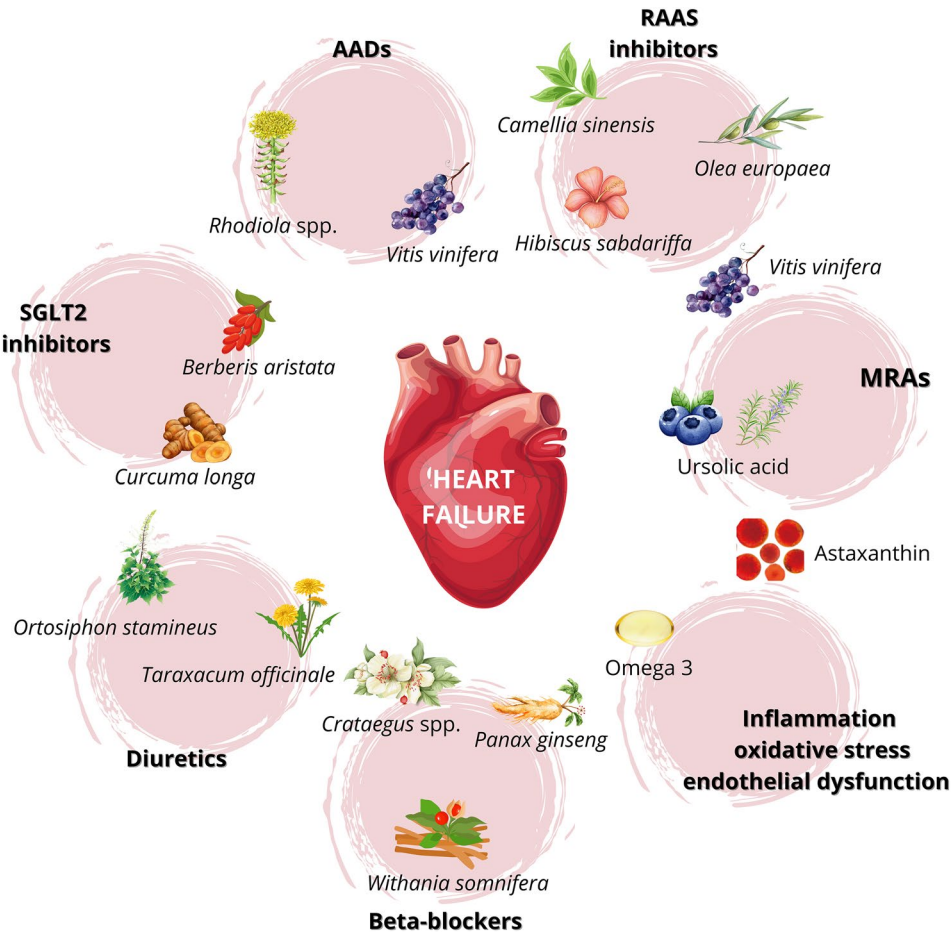

FIGURE 1 | Schematic overview of nutraceuticals with potential supportive roles in heart failure.

cardiovascular therapies. Studies not directly related to cardiovascular mechanisms or lacking sufficient biological plausibility were generally not considered.

Traditional use was considered as an initial selection criterion, but inclusion was ultimately based on mechanistic plausibility and available preclinical and/or clinical evidence.

A comprehensive literature search was conducted using PubMed, Scopus, ScienceDirect, Google Scholar, without language restrictions, covering studies published up to February 2025 with selected updates added during revision. Relevant guidelines and web resources were also consulted (last access on April, 2026). More than 450 records were screened during the preparation and the revision of this review, of which 232 sources were selected and cited. Among these, approximately 170 specifically addressed nutraceuticals, natural compounds, or bioactive extracts with cardiovascular relevance. Search terms included combinations such as "heart failure", "atrial fibrillation", "nutraceuticals", "natural compounds", "oxidative stress", "RAAS", "diuretics", "SGLT2 inhibitors", "MRAs", and "antiarrhythmic drugs", as well as specific plant or compound names (e.g., *Olea europaea*, *Vitis vinifera*, *Camellia sinensis*, *Haematococcus pluvialis*).

Given the narrative nature of this review, no formal systematic review protocol was used; however, emphasis was placed on selecting studies with the highest relevance and overall scientific quality from the existing literature.

Special emphasis was placed on compounds whose biological mechanisms are relatively well characterized and closely aligned with the pharmacodynamic targets of standard cardiovascular therapies, including RAAS inhibitors, beta-blockers, diuretics, SGLT2 inhibitors, mineralocorticoid receptor antagonists (MRAs), and antiarrhythmic drugs (AADs). While this review does not propose nutraceuticals as alternatives to established pharmacotherapies, it aims to present a mechanistic, evidence-based framework for their potential integration as adjuncts to conventional treatment, with a focus on efficacy, tolerability, and synergistic effects in HF and AF.

Priority was given to studies with well-characterized mechanisms of action and, when available, to clinical studies, while preclinical data were interpreted with appropriate caution.

The main nutraceuticals explored in this review for their relevance in HF are summarized in Figure 1. The figure provides a schematic overview of the proposed integrative framework, illustrating the relationship between major pharmacological classes used in cardiovascular therapy and nutraceuticals with overlapping or complementary mechanisms of action. This representation highlights how natural compounds may be

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

conceptually aligned with specific therapeutic targets, supporting their potential role as adjuncts in HF management.

2 | Conventional Pharmacological Therapy and Adjunctive Nutraceuticals in Heart Failure and Atrial Fibrillation

The conventional pharmacological therapy for HF and AF is based on multimodal approaches that target different pathophysiological mechanisms to improve patient prognosis and quality of life. Optimizing therapy requires careful monitoring and individualized treatment tailored to the patient's clinical characteristics.

Despite significant advances in cardiovascular pharmacology, the management of these diseases remains complex and is often associated with side effects that may limit adherence to therapy (Boutari et al. 2016; Stange et al. 2013). In this context, the role of complementary therapies, such as nutraceuticals, is emerging as a promising option due to their ability to modulate key pathophysiological processes involved in disease progression (Pallavi et al. 2022; Agrawal et al. 2024). However, further large-scale, randomized controlled trials are needed to validate their efficacy and safety.

Traditional drugs improve symptoms, slow disease progression, and reduce mortality. However, some natural compounds have been reported to exhibit biological effects that may overlap with or complement those of drugs used in clinical practice, as they can modulate conserved molecular pathways and pharmacological targets (Puri et al. 2022; Maitra et al. 2022). The supporting evidence for these compounds varies, as many findings were derived from preclinical or small-scale clinical studies. For this reason, this section will accompany each pharmacological class with a description of nutraceuticals with similar pharmacodynamic actions. The description will highlight the available scientific evidence, particularly clinical trials supporting their efficacy.

The objective is to provide a comparative framework between conventional pharmacological strategies and nutraceutical alternatives, evaluating their potential complementary role in managing HF and AF.

The mechanistic parallels discussed in this review are intended to highlight partial overlaps in biological pathways and should not be interpreted as direct pharmacological equivalence. In particular, these comparisons do not imply receptor-level interactions or target selectivity comparable to conventional drugs, but rather reflect broader modulation of interconnected pathophysiological processes.

2.1 | Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS) and Related Nutraceuticals

The RAAS is central to blood pressure regulation and fluid-electrolyte homeostasis, playing a crucial role in HF pathophysiology. RAAS inhibitors are a cornerstone in treating HFrEF, targeting different pathways to reduce vasoconstriction, sympathetic activation, and fluid retention (Hartnett and Dawn 2023).

2.1.1 | Angiotensin-Converting Enzymes Inhibitors (ACE Inhibitors)

ACE inhibitors, including enalapril, ramipril, and lisinopril, block the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. By reducing vascular resistance and aldosterone secretion, these drugs promote vasodilation, decrease sympathetic activity, and enhance sodium excretion, ultimately alleviating ventricular remodeling and reducing cardiac workload. Clinical trials have demonstrated their ability to improve ventricular function, reduce symptoms, and significantly decrease mortality in patients with HFrEF (Katragadda and Arora 2010).

2.1.2 | Angiotensin II Receptor Blockers (ARBs)

Angiotensin II receptor blockers (ARBs) such as valsartan, losartan, and candesartan provide an effective alternative to ACE inhibitors for patients who do not tolerate them. By selectively blocking the AT1 receptor (AT1R), ARBs prevent the vasoconstrictive and pro-inflammatory effects of angiotensin II while preserving the beneficial activation of the AT2 receptor (AT2R). Their use is associated with a lower risk of HF progression and reduced hospitalizations, offering a well-tolerated alternative for patients who cannot use ACE inhibitors (McMurray 2022).

2.1.3 | Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

Among the most innovative approaches to HF treatment, angiotensin receptor-neprilysin inhibitors (ARNI), such as sacubitril/valsartan, have demonstrated greater efficacy than ACE inhibitors in improving survival and reducing hospital admissions (Krum 2015). This dual-action therapy combines the AT1R blockade of valsartan with neprilysin inhibition, increasing the levels of natriuretic peptides. These peptides, primarily atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), enhance diuresis, natriuresis, and vasodilation, providing additional hemodynamic benefits beyond traditional RAAS inhibition (McMurray 2022; Bhushan et al. 2024).

Inhibiting the RAAS is a key strategy in managing HF, primarily through drugs that block the production or action of angiotensin II. This reduces vasoconstriction, sympathetic activation, and fluid retention. Similarly, certain natural compounds have been shown to modulate the RAAS through various mechanisms, potentially providing cardiovascular benefits. Below, we analyze key nutraceuticals with RAAS-modulating activity, supported by preclinical and clinical evidence.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2.1.4 | *Olea europaea* (Hydroxytyrosol, Tyrosol, Oleuropein)

Several studies have explored the cardioprotective properties of polyphenols from extra-virgin olive oil (EVOO) derived from *Olea europaea*, particularly their interaction with RAAS pathways. These compounds, including hydroxytyrosol, tyrosol, and oleuropein, have been demonstrated to reduce ACE expression and increase NO bioavailability, resulting in vasodilation and antihypertensive effects. A review of the role of polyphenols in cardiovascular disease highlights how *Olea europaea* polyphenols contribute to RAAS and ACE regulation, helping to lower hypertension and arterial stiffness by improving endothelial function and increasing NO levels (Goto 2024). In addition to olive oil polyphenols, extracts from *Olea europaea leaves* have also shown cardiovascular benefits, particularly when combined with *Hibiscus sabdariffa*. Recent studies suggest leaf extracts act as L-type calcium channel (LTCC) blockers, modulating vascular tone and contributing to blood pressure regulation, reinforcing their potential in cardiovascular health applications (Mattioli et al. 2022). In support of this, another study links their antihypertensive potential to RAAS modulation and ACE inhibition, which reduces vascular stiffness (Medina-Remón et al. 2013).

Preclinical studies reinforce these findings, particularly for hydroxytyrosol, which has demonstrated cardioprotective effects in isoproterenol-induced myocardial injury in rats. Hydroxytyrosol administration reduced cardiac damage markers, restored hemodynamic function, and inhibited ACE activity, preventing cardiac hypertrophy and remodeling (Mnafgui et al. 2016). Additionally, EVOO phenols have been shown to promote vasodilation in rat mesenteric arteries, further supporting their potential role in blood pressure regulation (D'Agostino et al. 2021).

These benefits extend to in vivo models of hypertension, where a phenolic-rich EVOO formulation significantly lowered systolic blood pressure and plasma angiotensin II levels in spontaneously hypertensive rats. This suggests a direct modulatory effect on RAAS, reinforcing the antihypertensive properties of EVOO polyphenols (Vazquez et al. 2019).

Clinical studies have confirmed the cardioprotective effects of high-polyphenol EVOO. In healthy individuals, its consumption was associated with reduced systolic blood pressure and downregulation of ACE expression, supporting a role in blood pressure regulation (Martín-Peláez et al. 2017). Serapis et al. reported a significant reduction in peripheral and central systolic blood pressure following high-polyphenol EVOO intake in hypertensive patients. However, no effects were observed on diastolic pressure or arterial stiffness (Sarapis et al. 2020). In a randomized, double-blind, placebo-controlled trial, Galvão Cândido et al. observed a -5.1 ± 1.6 mmHg decrease in diastolic pressure, particularly in women with excess body fat (Galvão Cândido et al. 2018). Hydroxytyrosol supplementation has been associated with favorable effects on selected cardiovascular-related parameters in high-risk individuals, while preclinical studies have also suggested reductions in infarct size and improvements in cardiac function (Christodoulou et al. 2024; Frumuzachi et al. 2024). Improvements in oxidative stress and inflammation markers have also been documented, such as decreased oxidized LDL and increased total antioxidant capacity (Sarapis et al. 2022; George et al. 2019).

Taken together, these findings support the potential role of EVOO polyphenols as promising nutraceuticals for cardiovascular health, acting through RAAS modulation, improving endothelial function, and promoting vasodilation.

Given their well-documented cardiovascular benefits, EVOO polyphenols may also play a role in AF prevention and management, primarily by counteracting oxidative stress and inflammation, key drivers of atrial remodeling and arrhythmogenesis. By mitigating these pathological processes, EVOO polyphenols may help preserve atrial function and reduce the susceptibility to AF.

Notably, the PREDIMED trial reported a lower incidence of AF in individuals following a Mediterranean diet enriched with EVOO compared to a control diet, suggesting a potential protective role (Martínez-González et al. 2014). While these findings highlight EVOO's cardioprotective potential, direct evidence linking its polyphenols to preventing AF remains limited. Further studies are needed to clarify its effects across different populations and risk profiles and establish its role in AF management.

2.1.5 | *Hibiscus sabdariffa*—Karkadè (Delphinidin-3-Sambubioside, Cyanidin-3-Sambubioside, Protocatechuic Acid, Quercetin)

Hibiscus sabdariffa has been widely studied for its antihypertensive effects, primarily attributed to its ability to inhibit ACE and modulate the RAAS. The presence of anthocyanins (particularly delphinidin-3-sambubioside and cyanidin-3-sambubioside), flavonoids such as quercetin and kaempferol, and phenolic acids like protocatechuic acid contribute to its blood pressure-lowering and antioxidant properties. Preclinical studies have confirmed that *H. sabdariffa* exhibits strong ACE inhibitory activity, reinforcing its potential as a natural antihypertensive agent (Ojeda et al. 2010). Additionally, it demonstrates competitive inhibition of ACE while exerting significant diuretic and natriuretic effects, further supporting its antihypertensive action (Sanou et al. 2024).

Clinical studies in patients with mild-to-moderate hypertension have shown that aqueous extracts of *H. sabdariffa* can reduce blood pressure and significantly decrease plasma aldosterone levels, with only modest effects on ACE activity, suggesting a potential modulation of the RAAS (Nwachukwu et al. 2015). Aqueous extracts effectively lower angiotensin II and aldosterone levels, with hot extracts displaying superior cardioprotective and antihypertensive activity due to their higher phenolic content (Salem et al. 2022).

Clinical investigations further validate these effects. In patients with Stage 1 hypertension, consuming *H. sabdariffa* in sour tea significantly reduced systolic and diastolic blood pressure, particularly when combined with lifestyle and

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

dietary modifications (Jalalyazdi et al. 2019). Similarly, a systematic review and meta-analysis of randomized controlled trials concluded that *Hibiscus sabdariffa* was effective in reducing both systolic and diastolic blood pressure in patients with mild-to-moderate hypertension. However, the analysis also reported that it was not effective in patients with metabolic syndrome and was not superior to conventional antihypertensive drugs (Abdelmonem et al. 2022). Another study on uncomplicated hypertension found that *H. sabdariffa* effectively reduced blood pressure, with results comparable to those observed with *Combretum micranthum* and captopril (Bourqui et al. 2021).

Clinical trials have shown that standardized extracts of *H. sabdariffa* can reduce blood pressure with efficacy comparable to ACE inhibitors such as captopril, supporting their potential role as complementary or adjunctive options rather than superior alternatives to conventional pharmacotherapy (Herrera-Arellano et al. 2004).

Due to its ACE-inhibitory, diuretic, and antioxidant properties, *H. sabdariffa* represents a promising natural approach for blood pressure control, with potential relevance also in HF-related settings. However, further research is required to fully elucidate its mechanisms of action and potential interactions with conventional antihypertensive drugs.

Beyond its antihypertensive properties, *H. sabdariffa* has also been explored for its potential role in AF management, owing to its impact on oxidative stress and autonomic regulation. Its polyphenol-rich extracts exhibit antioxidant activity, reducing oxidative stress markers such as malondialdehyde and NO, which may contribute to cardioprotective effects (Da-Costa-Rocha et al. 2014).

In addition to lowering blood pressure and heart rate—key factors in AF prevention—hibiscus extracts have been reported to influence autonomic regulation, potentially involving modulation of the sympathetic nervous system, which may contribute to a reduced arrhythmic risk (Aliyu et al. 2014; McKay et al. 2010).

Although *H. sabdariffa* shows promising cardioprotective effects, further investigation is needed to clarify its impact on AF management and potential interactions with conventional therapies.

2.1.6 | *Camellia sinensis*—Green Tea (Epigallocatechin Gallate)

Epigallocatechin gallate (EGCG), the most abundant catechin in green tea or *Camellia sinensis*, has been extensively studied for its cardiovascular benefits (Velayutham et al. 2008). While direct evidence of EGCG modulating aldosterone activity is limited (Parn et al. 2022), its influence on related systems suggests potential indirect effects. Studies indicate that EGCG reduces blood pressure and oxidative stress, which may intersect with aldosterone pathways.

A key target of RAAS modulation is the ACE, which converts angiotensin I to angiotensin II. EGCG metabolites, such as hydroxyphenyl valeric acids, have been shown to inhibit ACE activity in spontaneously hypertensive rats, resulting in significant reductions in systolic blood pressure (Takagaki and Nanjo 2015). In line with this, EGCG administration has been associated with reduced levels of angiotensin II and aldosterone in experimental models of HF, correlating with improved cardiac function and ventricular performance (Zhang et al. 2018; Wan et al. 2022).

EGCG also exerts antioxidant and endothelial-protective effects: it lowers systolic blood pressure and alleviates vascular dysfunction by reducing oxidative stress and enhancing NO bioavailability (Mohd Sabri et al. 2022). Furthermore, it enhances endothelial function by preventing eNOS uncoupling and restoring tetrahydrobiopterin levels, thereby further improving NO bioavailability (Mohd Sabri et al. 2022).

Additional mechanisms include inhibition of renin activity, mediated by its galloyl moiety and ortho-trihydroxy phenyl structures, which enhance binding affinity to renin (Li et al. 2013). In pressure-overload models, EGCG prevents hypertrophy and myocardial fibrosis via NF-κB inhibition, reduced inflammatory cell infiltration, and modulation of the TGF-β/Smad3 pathway (Cai et al. 2021; Chen et al. 2009). These antifibrotic actions may also be relevant at the atrial level, as myocardial fibrosis represents a key structural substrate for AF, suggesting a potential role for EGCG in modulating AF-related remodeling (Burstein and Nattel 2008).

Overall, these properties suggest that EGCG may have mechanistic relevance alongside RAAS-targeting therapies by potentially mitigating cardiac remodeling and supporting vascular function, although clinical confirmation is still limited (Parn et al. 2022; Takagaki and Nanjo 2015; Wan et al. 2022).

2.1.7 | Vitis Vinifera—Red Grapes (Resveratrol)

Resveratrol is a natural polyphenol in foods such as red grapes, red wine, and certain berries. It is widely recognized for its antioxidant, anti-inflammatory, and cardioprotective properties (Salehi et al. 2018). In recent years, scientific interest has increasingly focused on its potential role in modulating the RAAS.

Several studies suggest that resveratrol may influence RAAS activity by reducing oxidative stress, inhibiting ACE expression, and improving endothelial function (Dolinsky et al. 2013; Kim et al. 2018).

Resveratrol downregulates AT1R expression and decreases Angiotensin II levels in the heart, mitigating cardiac hypertrophy (Hashemizadeh et al. 2019; Ma et al. 2023). Additionally, it enhances the Angiotensin 1–7/Mas receptor (MasR) axis, which is known for its cardioprotective and anti-inflammatory effects. Thus, it potentially offers protection against ischemia/reperfusion injury (Soltan et al. 2021).

Beyond these effects, resveratrol reduces cardiomyocyte apoptosis, a pathological process exacerbated by RAAS dysregulation in HF. Additionally, its influence extends to vascular smooth muscle cells, where it alleviates angiotensin II-induced cellular senescence by upregulating the E2F1/SOD2 axis. This leads to

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

reduced oxidative stress and improved mitochondrial function (Liu et al. 2022).

Further evidence suggests that resveratrol enhances post-myocardial infarction recovery when combined with perindopril, demonstrating synergistic cardioprotective effects in a rat model (Raj et al. 2016).

Additionally, resveratrol shortens calcium transient duration at 90% repolarization (CaD90), improving cardiac function and indirectly modulating RAAS activity (Liu et al. 2024).

These mechanisms may be relevant to hemodynamic regulation in HF and could theoretically complement the effects of RAAS inhibitors, although direct clinical confirmation remains limited (Dyck et al. 2019).

At the molecular level, resveratrol exerts its cardioprotective effects through multiple pathways, including modulation of inflammatory, metabolic, and vascular mechanisms. It reduces inflammation by suppressing the expression of pro-inflammatory cytokines and inhibiting NF-κB signaling, thereby mitigating inflammation in RAAS-related diseases (Ma et al. 2023). Its activation of SIRT1, a key regulator of mitochondrial biogenesis and oxidative metabolism, further enhances its cardioprotective properties (Biala et al. 2010). Additionally, resveratrol stimulates AMPK, suppressing the RhoA/ROCK pathway, reducing vascular smooth muscle contraction, and improving vascular function (Cao et al. 2014). Emerging evidence suggests that resveratrol may work synergistically with ACE inhibitors, potentially enhancing their protective effects, though clinical validation is required (Restini et al. 2022).

The evidence to date points to a possible adjunctive role for resveratrol in HF, mainly supported by preclinical findings and limited clinical evidence. While further clinical studies are needed, available data suggest that resveratrol may complement standard RAAS inhibitors by reducing oxidative stress, modulating calcium homeostasis, and preventing cardiac remodeling. Its favorable safety profile makes it a promising candidate for integration into cardiovascular treatment strategies, although its clinical efficacy remains to be fully established.

Resveratrol's antioxidant, anti-inflammatory, and mitochondrial-modulating properties may contribute to AF prevention. While clinical evidence is limited, preclinical and mechanistic studies suggest that resveratrol may contribute to the modulation of mitochondrial dysfunction in AF, potentially through SIRT3-dependent pathways, oxidative stress and calcium overload, and preserving mitochondrial function (Fan et al. 2022; Yu et al. 2021; Wang et al. 2024; Cao et al. 2024). Although its direct role in AF treatment remains unclear, resveratrol's broader cardiovascular benefits suggest a potential protective effect (Gál et al. 2023).

2.2 | Beta-Blockers and Related Nutraceuticals

Beta-blockers represent a fundamental class of drugs in the management of heart failure with HFrEF, primarily due to their ability to modulate sympathetic nervous system activity, which is often hyperactivated in HF patients (Hjalmarson and Fagerberg 2000). In addition to their role in HF, beta-blockers are also essential in the management of AF, particularly for rate control, as recommended by both the European Society of Cardiology (ESC) guidelines and the ACC/AHA/ACCP/HRS guidelines on AF diagnosis and management (Gelder van et al. 2024). The excessive stimulation of β-adrenergic receptors leads to increased heart rate, myocardial workload, and oxygen consumption, all of which contribute to ventricular remodeling and disease progression.

Beta-blockers exert their therapeutic effects by antagonizing β-adrenergic receptors, predominantly β_1 in the heart and β_2 in the vasculature. This sympathetic inhibition reduces heart rate, myocardial contractility, and oxygen consumption, thereby alleviating myocardial stress, improving ventricular function, and slowing disease progression (Oliver et al. 2019). Among the most widely used beta-blockers in HF treatment are bisoprolol, carvedilol, metoprolol succinate, and nebivolol, all of which have demonstrated efficacy in improving cardiac function, alleviating symptoms, reducing cardiovascular mortality, and lowering the risk of hospitalizations in HFrEF patients (MERIT-HF Study Group 1999; CIBIS-II Investigators and Committees 1999).

Given their substantial impact on sympathetic modulation, beta-blockers are initiated at low doses and gradually titrated based on patient tolerance. According to the latest ESC guidelines on AF (ESC Guidelines for the Management of Atrial Fibrillation, n.d.), titration should follow a structured protocol, typically involving dose doubling every 2–4 weeks as tolerated, until guideline-directed target doses are achieved. A too-rapid reduction in sympathetic activity can lead to hypotension or worsening HF symptoms, making careful dose adjustment essential for treatment success (Allen and Fang 2017; Schurtz et al. 2023). While no natural compounds have been identified as direct β-adrenergic receptor antagonists, some nutraceuticals exhibit complementary effects, modulating adrenergic responses and autonomic tone through different mechanisms. These compounds may support cardiovascular function by reducing sympathetic overactivation, enhancing parasympathetic activity, or lowering stress-related neuroendocrine responses. As such, they may be of interest within an integrative cardiovascular framework, although they should not be considered substitutes for conventional beta-blockers. Below are the key nutraceuticals with sympatholytic or autonomic-modulating activity, with effects on sympathetic and autonomic regulation that partially overlap with the physiological pathways targeted by beta-blockers.

2.2.1 | *Crataegus* spp.—Hawthorn (Vitexin, Procyanidins)

Crataegus spp. (Hawthorn) is a medicinal plant traditionally used for cardiovascular support, particularly in the management of hypertension, arrhythmias, and HF (Tassell et al. 2010). Its bioactive compounds, including flavonoids (e.g., vitexin, quercetin, hyperoside) and procyanidins, contribute to its cardioprotective effects (Venskutonis 2018; Kim et al. 2000).

Among its bioactive constituents, vitexin and procyanidins have been identified as key contributors to its cardioprotective and antiarrhythmic properties.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Hawthorn has been shown to modulate adrenergic activity, primarily by enhancing coronary vasodilation, reducing myocardial oxygen demand, and improving left ventricular function (Lu et al. 2023; Chang et al. 2005). Although it does not act as a direct β-adrenergic receptor antagonist, it exerts negative chronotropic and inotropic effects, which mimic some actions of beta-blockers. These effects result from its ability to increase NO bioavailability, reduce sympathetic overactivation, and modulate calcium channels in cardiac myocytes (Wu et al. 2020; Ding et al. 2022). Early evidence suggested a potential benefit of hawthorn as an adjunctive therapy in chronic HF. An initial meta-analysis of randomized trials reported modest improvements in exercise capacity and selected hemodynamic parameters with standardized hawthorn extracts added to conventional treatment (Holubarsch et al. 2008). However, robust evidence on clinically relevant endpoints such as mortality and hospitalizations remains lacking.

Scientific evidence suggests that Hawthorn extract supplementation is associated with reduced blood pressure and improvements in cardiovascular function, including exercise tolerance in patients with HF (Orhan 2018; Walker et al. 2002; Szikora et al. 2025).

A large randomized clinical trial has shown that hawthorn extract is safe and may exert beneficial effects in selected subgroups of patients with chronic heart failure, supporting its potential adjunctive role (Holubarsch et al. 2008).

Furthermore, its antioxidant and anti-inflammatory properties contribute to endothelial protection and cardiovascular health (Lu et al. 2023; Chang et al. 2005).

Hawthorn has also been investigated for its potential anti-arrhythmic properties, attributed to its ability to modulate ion channels, reduce oxidative stress, and improve cardiac function.

Experimental and preclinical studies suggest that hawthorn extracts may influence cardiac electrophysiology, including modulation of nodal and myocardial refractory properties and anti-arrhythmic effects in different experimental models, which may help limit arrhythmia initiation and propagation (Pahlavan et al. 2018; Alp et al. 2016). Consistently, a large retrospective cohort study from German primary care reported an association between the use of hawthorn extract WS 1442 and a lower incidence of atrial fibrillation/flutter, tachycardia, and other cardiac arrhythmias compared with magnesium/potassium, suggesting a potential adjunctive role in arrhythmia prevention and management (Wyss et al. 2024). While these findings indicate a potential role for hawthorn in AF management, further clinical research is required to confirm its efficacy and safety in patients at risk for arrhythmic disorders (Holubarsch et al. 2018).

2.2.2 | *Withania somnifera*—Ashwagandha (Withaferin A, Withanolides)

Withania somnifera, commonly known as ashwagandha, is a traditional adaptogenic herb widely studied for its ability to mitigate stress-related physiological responses, including tachycardia and sympathetic activation (Della Porta et al. 2023). It primarily acts on the hypothalamic–pituitary–adrenal and sympathetic-adrenal medullary axes, helping to modulate stress-related physiological responses, including reductions in cortisol levels and potential effects on autonomic balance, as suggested by changes in heart rate variability (Speers et al. 2021; Smith et al. 2023).

Among its bioactive constituents, withaferin A and withanolides are the key molecules contributing to its anti-inflammatory, antioxidant, and cardioprotective effects.

Through these mechanisms, ashwagandha appears to exert a modulatory effect on the sympathetic nervous system, potentially contributing to a reduction in heart rate and improved autonomic balance.

Although ashwagandha does not directly block β-adrenergic receptors, available evidence suggests that it may influence autonomic balance and sympathetic activity, resulting in physiological effects that partially overlap with those of beta-blockade, although mediated through indirect neuroendocrine and catecholaminergic mechanisms rather than direct receptor antagonism, and therefore should not be considered pharmacological equivalents (Speers et al. 2021; Hore et al. 2013).

Clinical studies in healthy individuals suggest that ashwagandha supplementation may improve cardiorespiratory endurance and exercise capacity, as reflected by increases in maximal oxygen uptake (VO_2 max) and related performance parameters, with consistent findings across randomized trials and meta-analyses, although evidence remains limited to non-clinical populations (Bonilla et al. 2021; Tiwari et al. 2021).

Preclinical studies in rodent models of experimentally induced myocardial infarction have demonstrated cardioprotective effects of *Withania somnifera* supplementation, including improvements in hemodynamic parameters, reductions in oxidative stress, and preservation of myocardial tissue integrity (Mohanty et al. 2004; Khalil et al. 2015).

Available evidence suggests that ashwagandha supplementation may be associated with modest improvements in cardiovascular parameters, including potential reductions in blood pressure and systemic inflammation, supporting its possible relevance in cardiovascular care. However, clinical evidence in patients with established cardiac disease remains limited, and further well-designed clinical trials are needed to better define its therapeutic applicability (Wiciński et al. 2024).

While direct research on ashwagandha's effects on AF remains limited, its broader cardiovascular benefits suggest a potential role in heart health. Nevertheless, its specific impact on arrhythmic risk requires further investigation, particularly in individuals predisposed to AF.

2.2.3 | *Panax ginseng*—Ginseng (Ginsenoside Rb1, Ginsenoside Rg5)

Panax ginseng, commonly known as Korean ginseng, has been extensively investigated for its cardioprotective properties and

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

its potential to modulate multiple cardiovascular pathways, including vascular function, oxidative stress, inflammation, and metabolic regulation (Kim 2012; Tang et al. 2023). It does not act as a direct β-adrenergic receptor antagonist; its influence on vascular tone and autonomic regulation may produce effects that partially overlap with those of beta-blockers, particularly regarding blood pressure control and improvement of endothelial function (Zi-chang et al. 2024).

At the molecular level, ginsenosides—the bioactive components of ginseng—play a crucial role in myocardial energy metabolism, especially under ischemic conditions. Ginsenoside Rb1, for instance, has demonstrated protective effects against HF by enhancing mitochondrial energy metabolism, inhibiting excessive autophagy, and exerting antioxidant and anti-inflammatory actions, primarily through AMPK and PPAR signaling pathways (Zhou et al. 2024). Similarly, ginsenosides Rh4 and Rg5 modulate key cardioprotective pathways, such as phosphoinositide 3-kinase/protein kinase (PI3K-Akt) and calcium signaling, supporting their potential use in chronic HF treatment (Xie et al. 2024; Gao et al. 2024). These findings identify ginsenosides Rb1 and Rg5 as primary bioactive agents responsible for ginseng's cardioprotective potential in HF.

Another significant mechanism involves the inhibition of autophagy in myocardial cells, a process implicated in the progression of HF. Notably, preclinical studies have shown that ginseng enhances the efficacy of metoprolol—a widely used beta-blocker—by reducing myocardial autophagy via the PI3K/Akt/mTOR pathway, ultimately improving cardiac function and survival in murine models of chronic heart failure (Zi-chang et al. 2024). When studied in combination with conventional heart failure therapies, ginseng-containing preparations have been associated with improvements in selected functional and biomarker-based outcomes in patients with acute decompensated heart failure; however, the heterogeneity and overall quality of the included studies warrant cautious interpretation (Chen, Ma, et al. 2022).

Thanks to its multi-targeted action, ginseng addresses various aspects of HF pathophysiology, including inflammatory regulation and myocardial energy efficiency, reinforcing its potential as an adjunctive therapeutic strategy (Xie et al. 2024). However, it is essential to consider interindividual variability in response to ginseng supplementation. Further large-scale clinical trials are necessary to define standardized protocols and determine their long-term safety and efficacy in HF management.

The relationship between ginseng and AF is more complex. Ginseng has been observed to lower diastolic blood pressure, which may indirectly contribute to rhythm stabilization and improved cardiovascular control (Caron et al. 2002). Nonetheless, considering the delicate balance of cardiac electrophysiology, especially in patients predisposed to AF, its use warrants careful evaluation. Further clinical research is needed to fully understand its implications in this context and assess its therapeutic potential and safety profile in AF-prone individuals.

2.3 | Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors and Related Nutraceuticals

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, initially developed for glycemic control in Type 2 diabetes mellitus, have demonstrated significant cardiovascular and renal benefits that extend beyond their glucose-lowering effects (Cardoso et al. 2021). These agents, including dapagliflozin and empagliflozin, are now established therapeutic components in managing HF, particularly in patients with HFrEF and, more recently, those with HFpEF (Aguiar-Neves et al. 2023; Tomasoni et al. 2022).

SGLT2 inhibitors primarily act in the proximal renal tubules, reducing glucose and sodium reabsorption. This mechanism promotes natriuresis and osmotic diuresis, which decrease plasma volume, preload, and afterload, thereby enhancing ventricular loading conditions and their hemodynamic effects. SGLT2 inhibitors offer pleiotropic benefits, including favorable metabolic and anti-inflammatory actions, improved endothelial function, and modulation of myocardial energetics and fibrosis (Lopaschuk and Verma 2020). These combined effects help lower HF-related hospitalizations and cardiovascular mortality in both diabetic and non-diabetic populations (Cardoso et al. 2021).

Large-scale clinical trials, such as DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved, have provided strong evidence supporting the effectiveness of SGLT2 inhibitors, including their recommendation as first-line therapy in recent international guidelines for HFrEF and HFpEF (McMurray et al. 2019; Packer et al. 2020; Anker et al. 2021).

From a mechanistic perspective, SGLT2 inhibitors exhibit indirect antioxidant, anti-inflammatory, and antifibrotic properties, which may partially overlap with the biological actions of specific nutraceuticals. Although no natural compound currently reproduces the specific renal mechanism of SGLT2 inhibition, several nutraceuticals have demonstrated complementary actions, particularly in modulating metabolic, inflammatory, and endothelial pathways.

Therefore, the comparison is based on shared downstream pathways rather than direct mechanistic equivalence.

Notably, curcumin and berberine have been shown to improve insulin sensitivity, oxidative balance, endothelial function, and mitochondrial health. Among these, curcumin and berberine stand out for their partially overlapping downstream mechanisms with SGLT2 inhibitors and will be discussed in detail in the following sections.

Given their unique pharmacodynamic profile and broad clinical applicability, SGLT2 inhibitors represent one of the most promising therapeutic innovations in the current landscape of HF treatment.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2.3.1 | *Curcuma longa*—Turmeric (Curcumin)

Curcumin, the principal polyphenol derived from *Curcuma longa* (turmeric), exerts significant anti-inflammatory, antioxidant, and metabolic regulatory effects. Although it does not influence renal glucose handling, curcumin modulates key systemic pathways relevant to HF and metabolic syndrome, overlapping with the pleiotropic actions of SGLT2 inhibitors.

At the inflammatory level, curcumin inhibits the NF-κB signaling pathway, reducing the expression of pro-inflammatory cytokines such as TNF-α and IL-6, as well as circulating levels of C-reactive protein (CRP) and malondialdehyde (MDA) (Zamanian et al. 2024; Hussain et al. 2022; Lee and Kim 2024). These effects are particularly relevant in HF, where chronic inflammation contributes to disease progression.

Curcumin also enhances antioxidant defenses by increasing the activity of glutathione (GSH) and superoxide dismutase (SOD), while reducing oxidative stress markers and lipid peroxidation (Ebrahimzadeh et al. 2024; Cheng et al. 2025). These antioxidant actions support endothelial integrity and myocardial protection.

From a metabolic standpoint, curcumin has been shown to improve insulin sensitivity, reduce fasting glucose and HbA1c levels, and modulate hepatic gluconeogenesis via the PI3K-Akt-GSK3β pathway (Mo et al. 2025; Bozkurt et al. 2022; Feng et al. 2024). Additionally, curcumin has been reported to exert favorable effects on lipid profiles, including reductions in triglycerides and LDL cholesterol and potential increases in HDL levels (Bozkurt et al. 2022; Rafiee et al. 2021; Dehzad et al. 2023) which may be beneficial in patients with heart failure and concomitant metabolic disorders.

Although it does not replicate the renal mechanism of SGLT2 inhibition, curcumin targets many of the same inflammatory, oxidative, and metabolic pathways. These shared mechanisms suggest potential complementarity within integrative cardiovascular care, particularly at the mechanistic level, although clinical synergy with standard pharmacological therapy remains to be demonstrated.

2.3.2 | Berberis Aristata—Tree Turmeric (Berberine)

Berberine is an isoquinoline alkaloid extracted from *Berberis aristata* and related species, with notable cardiometabolic properties. Beyond its well-documented effects on glucose metabolism and lipid parameters—particularly reductions in triglycerides and LDL cholesterol— (Yin et al. 2008; Liu et al. 2025), berberine has demonstrated cardioprotective activity in preclinical studies. HF models include mitochondrial protection, anti-apoptotic effects, and potential synergistic interactions with SGLT2 inhibitors. Experimental studies suggest that berberine may enhance cardiomyocyte viability, reduce apoptosis, and improve mitochondrial function, primarily via activation of AMPK and regulation of PINK1/Parkin-mediated mitophagy—mechanisms that may contribute to preserving myocardial energetics and limiting adverse cardiac remodeling (Abudureyimu et al. 2020; Haftcheshmeh et al. 2022).

These effects are supported by experimental and mechanistic evidence showing that berberine attenuates oxidative stress, reduces cardiomyocyte apoptosis, and improves cardiac function in models of ischemia and HF (Feng et al. 2019).

Recent studies have explored the combination of berberine with dapagliflozin, showing synergistic benefits in cellular and animal models. The combined treatment significantly increased cardiomyocyte survival and reduced apoptosis by 72.7% compared to trastuzumab alone, while also suppressing IL-6 expression by over 86%, promoting an anti-inflammatory myocardial profile (Haftcheshmeh et al. 2022; Feng et al. 2019). These findings suggest that berberine may enhance the benefits of SGLT2 inhibitors in heart failure, particularly by reinforcing mitochondrial and anti-inflammatory pathways (Haftcheshmeh et al. 2022).

While SGLT2 inhibitors like dapagliflozin have proven beneficial in reducing NT-proBNP levels and improving left ventricular ejection fraction in chronic HF (Chen et al. 2024), the addition of berberine may represent a complementary therapeutic hypothesis requiring clinical validation. However, further clinical trials are needed to validate these findings, assess long-term safety, and define the translational potential of this combination in diverse patient populations.

2.4 | Mineralocorticoid Receptor Antagonists (MRAs) and Related Nutraceuticals

Mineralocorticoid receptor antagonists (MRAs) represent a cornerstone in treating HFrEF, due to their ability to counteract the deleterious effects of aldosterone. Beyond promoting sodium and water retention, aldosterone also drives myocardial and vascular fibrosis, endothelial dysfunction, and pathological cardiac remodeling, all of which contribute to the progression of heart failure and increase the risk of AF (Vizzardi et al. 2014).

By selectively blocking mineralocorticoid receptors, MRAs such as spironolactone and eplerenone reduce fluid overload, attenuate fibrotic processes, and improve endothelial function, contributing to improved clinical outcomes in patients with HFrEF (Ferreira et al. 2024). Their addition to standard therapy, including ACE inhibitors or ARNI and beta-blockers, has been shown to lower mortality and the risk of heart failure hospitalizations significantly. However, their use requires close monitoring of renal function and serum potassium levels, given the risk of hyperkalemia and renal impairment (Khan et al. 2020).

Since aldosterone plays a pivotal role in both ventricular and atrial remodeling, its regulation is essential to slow the progression of HF and reduce the substrate for AF development. In this context, interest has grown in natural compounds that modulate the mineralocorticoid axis. Specific nutraceuticals have demonstrated the ability to influence the RAAS, limit myocardial fibrosis, and counteract inflammation, thereby mimicking key aspects of MRA pharmacology. The following sections explore the main nutraceuticals with potential activity against mineralocorticoid-mediated cardiovascular remodeling.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2.4.1 | Ursolic Acid (From Apples, Basil, Blueberries, Rosemary)

Ursolic acid, a natural pentacyclic triterpenoid abundant in apples, basil, blueberries, and rosemary, has demonstrated promising properties targeting mineralocorticoid-driven cardiac remodeling (Majid et al. 2023). Although direct evidence of UA inhibiting aldosterone synthesis is still lacking, its modulatory effects on downstream fibrotic and mitochondrial pathways commonly activated by aldosterone are well documented.

One of the key mechanisms through which UA exerts cardioprotective effects is the inhibition of cardiac fibroblast activation, a critical step in myocardial fibrosis. This has been shown to occur through several pathways. UA downregulates miR-21 and suppresses ERK phosphorylation in cardiac fibroblasts, thus attenuating fibrotic signaling cascades (Dong et al. 2015). UA inhibits the expression of transforming growth factor-β (TGF-β), a central profibrotic cytokine, thereby reducing fibroblast-driven collagen deposition and myocardial fibrosis. Consistent with this, in experimental models of diabetic cardiomyopathy, UA administration has been shown to reduce hydroxyproline content, suppress TGF-β1 expression, and improve myocardial structure and function (Wang et al. 2018). These effects are further supported by evidence from isoproterenol-induced myocardial infarction models, in which UA downregulates the expression of TGF-β, collagen Type I, and α-smooth muscle actin, thus attenuating cardiac fibrosis (Radhiga et al. 2019).

Similarly, in pressure overload models such as transverse aortic constriction (TAC), UA attenuates pathological cardiac hypertrophy and fibrotic remodeling by inhibiting the miR-21/ERK pathway (Dong et al. 2015).

Importantly, UA also contributes to reducing ventricular stiffening, a consequence of chronic myocardial fibrosis. This is achieved not only by modulating extracellular matrix deposition but also by improving mitochondrial function. UA has been shown to enhance mitochondrial biogenesis and reduce oxidative stress, processes that are essential for preserving myocardial compliance (Roudi et al. 2025; Xu et al. 2023). By limiting both the biochemical drivers and structural consequences of fibrosis, UA appears, in preclinical models, to attenuate ventricular stiffening processes relevant to HFrEF (Dong et al. 2015; Radhiga et al. 2019).

Although further studies are warranted, particularly regarding its potential effect on aldosterone biosynthesis, existing evidence strongly supports the role of UA as a nutraceutical candidate capable of mimicking key antifibrotic and antistiffness actions of mineralocorticoid receptor antagonists. Furthermore, by mitigating ventricular and potentially atrial remodeling processes, UA may be of interest for broader cardiovascular protection strategies in HF- and AF-relevant settings, although clinical validation is lacking.

2.4.2 | Astaxanthin—From *Haematococcus pluvialis*

Astaxanthin (ASX) is a xanthophyll carotenoid derived primarily from the microalga *Haematococcus pluvialis*, known for its potent antioxidant and anti-inflammatory activity. Although direct modulation of the mineralocorticoid receptor by ASX has not been conclusively demonstrated, increasing evidence suggests that ASX targets multiple downstream consequences of mineralocorticoid activation, such as oxidative stress, mitochondrial dysfunction, and inflammatory signaling, as outlined below. In the following sections, experimental and preclinical studies are summarized to illustrate these mechanisms.

In animal models of hypertension, including the DOCA-salt rat model, ASX improved cardiovascular parameters by reducing oxidative stress and inflammation, thus protecting against hypertension-induced cardiac damage (Khodir et al. 2022).

In cardiomyocytes stimulated with angiotensin II, ASX reduced hypertrophic gene expression and cell size. This effect was mediated by modulation of a specific molecular pathway involving METTL3, circ_0078450, miR-338-3p, and GATA4, thereby supporting its role in preventing pathological cardiac remodeling (Zhang et al. 2024).

ASX protects cardiomyocytes from oxidative stress and mitochondrial damage induced by hydrogen peroxide and doxorubicin. This effect is largely mediated by inhibition of the Na^+/K^+-ATPase/Src/ROS signaling cascade, as well as the restoration of redox balance and mitochondrial function (Krestinin et al. 2024; Qu et al. 2020).

ASX has also demonstrated anti-apoptotic effects in myocardial cells exposed to hypoxia/reoxygenation injury. These protective actions appear to involve the modulation of microRNA expression and downstream inflammatory and apoptotic signaling pathways, suggesting potential relevance in the cellular response to ischemic and heart failure–related myocardial injury (Zhang et al. 2023).

In myocardial infarction models, ASX has been shown to reduce NF-κB expression, an inflammatory mediator upregulated in mineralocorticoid-driven oxidative stress, and to enhance mitochondrial biogenesis through the upregulation of PGC-1α and TFAM, two key regulators impaired in this context (Mahmoud et al. 2024).

Furthermore, a recent network pharmacology study identified AGE-RAGE and inflammatory signaling pathways as key targets of ASX in adriamycin-induced cardiotoxicity. While the study did not directly assess mineralocorticoid modulation, these pathways are well-recognized contributors to mineralocorticoid-driven diabetic cardiomyopathy (Zhu et al. 2024).

Preclinical models of myocardial infarction have shown that ASX reduces infarct size, attenuates adverse ventricular remodeling, and modulates inflammatory responses, partly by promoting an anti-inflammatory (M2) macrophage phenotype (Pan et al. 2020). In addition, clinical studies have confirmed the potent anti-inflammatory properties of ASX, including reductions in key cytokines such as IL-6 and TNF-α, supporting its role as a systemic antioxidant and immunomodulatory agent (Youssef et al. 2025).

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Clinically, ASX has shown a favorable safety profile in human studies, with no significant adverse effects reported. These studies have also demonstrated improvements in oxidative stress markers and blood rheology, supporting its role as a potent antioxidant with potential cardiovascular relevance (Fassett and Coombes 2009).

A broad review on the antioxidant and anti-inflammatory mechanisms of ASX in cardiovascular diseases highlighted its systemic benefits, although it did not explore mineralocorticoid receptor-specific modulation (Pereira et al. 2021).

Overall, while no study to date demonstrates a direct interaction between ASX and the mineralocorticoid receptor itself, substantial preclinical evidence indicates that ASX effectively targets mineralocorticoid-related downstream mechanisms, such as inflammation, oxidative stress, hypertrophy, and mitochondrial dysfunction. These findings support a functional overlap with the actions of MRAs and justify further research on ASX as a potential adjunct in mineralocorticoid-driven cardiovascular pathologies.

2.4.3 | *Vitis vinifera*—Red grapes (Resveratrol)

As discussed in Section 2.1 in the context of RAAS modulation, resveratrol—a polyphenolic compound found in *Vitis vinifera* (red grapes)—has been widely studied for its cardioprotective properties. Beyond its known effects on the angiotensin axis, resveratrol also exerts actions that overlap with mechanisms involved in mineralocorticoid receptor signaling, including antifibrotic, antioxidant, and anti-inflammatory effects.

Experimental studies have demonstrated that resveratrol attenuates pathological cardiac remodeling by reducing myocardial oxidative stress, inhibiting proinflammatory mediators, and limiting cardiomyocyte apoptosis (Fan et al. 2022; Gal et al. 2021).

In rodent models of myocardial infarction, resveratrol reduces infarct size and ventricular arrhythmias, effects attributed to its ability to induce pharmacological preconditioning and attenuate intracellular calcium overload (Das and Maulik 2006; Chen et al. 2008). This mechanism, which mimics the heart's adaptive response to brief ischemia, may also hold translational relevance for ischemic heart disease.

These preclinical findings have been further reinforced by a recent comprehensive review, which compiled evidence from multiple animal models of atherosclerosis, myocardial infarction, and heart failure. This analysis confirmed resveratrol's ability to improve cardiac structure and function, reduce infarct size, and modulate oxidative and inflammatory pathways, highlighting its therapeutic potential across various stages of ischemic heart disease and ventricular dysfunction (Raj et al. 2021).

Although clinical data remain limited, early-phase trials suggest that resveratrol supplementation may improve endothelial function and reduce oxidative stress markers. However, more robust and large-scale studies are required to confirm its therapeutic efficacy and to clarify its interaction with mineralocorticoid receptor signaling in humans (Kroon et al. 2010).

Overall, resveratrol shows compelling preclinical evidence of modulating key mechanisms implicated in mineralocorticoid-induced cardiac injury, including inflammation, fibrosis, oxidative stress, and calcium dysregulation. Its potential to complement the pharmacological actions of MRAs warrants further investigation in targeted experimental models and clinical studies.

2.5 | Antiarrhythmic Drugs (AADs) and Related Nutraceuticals

Given the current limited and heterogeneous evidence on nutraceuticals in AF, this section is intended to provide an exploratory and mechanistic overview rather than a comprehensive or clinically oriented analysis, reflecting the current stage of evidence in this field.

Antiarrhythmic drugs (AADs) are a key component of rhythm control in AF, particularly in symptomatic patients or those who fail rate control strategies. They exert their effects through modulation of cardiac electrophysiology to restore and maintain sinus rhythm, reduce arrhythmic burden, and prevent recurrences (Dan et al. 2018). The main drug classes include sodium channel blockers (Class Ic), potassium channel blockers (Class III), and agents with beta-blocking properties.

Class Ic agents (e.g., flecainide, propafenone) inhibit fast sodium channels and are effective in patients without structural heart disease, but carry proarrhythmic risk in myocardial damage. Class III agents (e.g., sotalol, amiodarone, dronedarone) prolong repolarization by blocking potassium channels. Amiodarone remains the most effective option, but it is limited by extracardiac toxicity. Dronedarone has a better safety profile but lower efficacy. Overall, AADs are limited by toxicity, proarrhythmic potential, and a lack of demonstrated mortality benefit (Tisdale et al. 2020).

Given these limitations, increasing attention has been paid to nutraceuticals that may modulate arrhythmic risk via non-ionotropic mechanisms. Although they do not replicate the ion channel–blocking actions of AADs, several plant-derived compounds have shown promise in modifying the arrhythmogenic substrate. Notably, resveratrol and EGCG exhibit antioxidant and antifibrotic effects that may attenuate atrial remodeling (Gál et al. 2023), while hawthorn (*Crataegus* spp.) influences cardiac electrophysiology through calcium and potassium current modulation (Chang et al. 2005).

Among the most studied are omega-3 fatty acids, which have been associated with membrane-stabilizing and anti-inflammatory actions that could reduce AF incidence (Khan et al. 2021)—a topic explored in detail in Section 2.7 on inflammation, oxidative stress, and endothelial dysfunction.

An emerging body of research continues to identify additional nutraceuticals capable of modulating key arrhythmogenic mechanisms, suggesting possible complementarity with rhythm

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

control strategies at a mechanistic level, particularly in patients with contraindications or intolerance to conventional AADs.

2.5.1 | *Rhodiola* spp.—Arctic Root (Rosea and Crenulata)

Rhodiola is a well-known adaptogenic genus traditionally used in Eastern and Northern medicine to enhance resistance to physical and emotional stress (Ivanova Stojcheva and Quintela 2022). Among its species, *Rhodiola rosea* and *Rhodiola crenulata* have been increasingly studied for their potential cardiovascular and antiarrhythmic effects, especially under conditions of sympathetic overactivity or autonomic stress.

Unlike conventional antiarrhythmic drugs, *Rhodiola* does not directly modulate cardiac ion channels. Instead, its effects appear to involve modulation of autonomic function, antioxidant activity, and neurohumoral regulation. Preclinical evidence suggests that these mechanisms may contribute to reduced susceptibility to stress-induced arrhythmias (Chen, Tang, et al. 2022).

Additional cardioprotective actions include anti-inflammatory and antioxidant effects. In a preclinical model of ischemic HF, *R. crenulata* significantly reduced IL-6, TNF-α, and IL-17 expression, thereby mitigating myocardial fibrosis and suppressing ventricular arrhythmias through inhibition of the MAPK signaling pathway (Hsiao et al. 2021). It also protects cardiomyocytes from hypoxia-induced oxidative damage by modulating NO signaling and restoring the balance between endothelial nitric oxide synthase (eNOS) and arginase-1 expression, attenuating ROS generation, and preserving mitochondrial function (Hsu et al. 2017).

Pharmacokinetic data indicate a delayed onset of action, suggesting a complex time–concentration–effect relationship between *Rhodiola*'s bioactive compounds and cardiac physiology (Jia et al. 2024). While human studies are currently lacking, these preclinical findings support further investigation of *Rhodiola*, particularly in stress-related arrhythmias and conditions characterized by autonomic dysregulation.

2.5.2 | *Vitis vinifera*—Red grapes (Resveratrol)

Resveratrol, a polyphenol abundant in red grapes, has already been discussed in Section 2.1 for its modulatory effects on the RAAS and in Section 2.4 for its relevance in mineralocorticoid-related mechanisms. In addition to these actions, resveratrol also exerts direct electrophysiological effects that support its classification as a potential antiarrhythmic agent.

Preclinical studies have shown that resveratrol modulates cardiac potassium and calcium channels while exerting antiarrhythmic effects in experimental arrhythmia models (Soltani et al. 2022). It acts through multiple mechanisms, including inhibition of Kv1.5 and late sodium currents, both implicated in atrial fibrillation pathogenesis (Baczko et al. 2014). Additionally, it activates ATP-sensitive potassium channels (KATP) and restores hERG channel trafficking in models of long QT syndrome, thereby contributing to action potential shortening and electrical stability (Buluc et al. 2007; Zhao et al. 2014).

Resveratrol enhances SERCA2a function via phospholamban oligomerization, facilitating calcium reuptake into the sarcoplasmic reticulum and reducing diastolic Ca^{2+} overload (Bai et al. 2016). These electrophysiological and calcium-handling effects may be further complemented by activation of the NO–cGMP–PKG signaling pathway, which in cardiac models has been associated with improved myocardial relaxation, stabilization of membrane potential, and protection against ischemia–reperfusion–induced injury (Numata and Takimoto 2022).

In vivo, resveratrol has been shown to reduce the incidence of ventricular arrhythmias and improve survival in models of ischemia–reperfusion injury, reinforcing its potential as an adjunct in arrhythmia prevention (Menezes-Rodrigues et al. 2021).

Despite this compelling mechanistic rationale, the clinical relevance of resveratrol in arrhythmia management remains largely hypothetical. Robust preclinical studies with detailed electrophysiological endpoints are limited, and clinical trials addressing its antiarrhythmic efficacy are virtually absent. Therefore, further investigation is required to validate its electrophysiological effects and determine its safety and therapeutic value in patients with atrial or ventricular arrhythmias.

The pharmacological classes discussed so far—including RAAS inhibitors, beta-blockers, SGLT2 inhibitors, MRAs, and antiarrhythmic drugs—represent the current pillars of HF and AF management. These agents are supported by strong clinical evidence and are associated with significant improvements in morbidity and mortality.

However, additional pharmacological strategies, such as diuretics, play an essential symptomatic role, particularly in controlling congestion and fluid overload, despite their lack of prognostic benefit (Magdy et al. 2022). In parallel, numerous nutraceuticals have shown mechanistic overlaps with these therapies, offering promising complementary approaches.

The following sections provide a concise overview of these adjunctive pharmacological classes and explore nutraceutical compounds that target inflammation, oxidative stress, and endothelial dysfunction—key processes involved in HF and AF progression.

2.6 | Diuretics and Related Nutraceuticals

Diuretics are an essential class of drugs in managing HF, primarily used to alleviate congestion by promoting sodium and water excretion. Unlike other pharmacological treatments, they do not directly impact mortality but provide rapid symptomatic relief in patients with fluid retention and dyspnea (Suri and Pamboukian 2021).

Their mechanism of action involves the inhibition of renal transporters responsible for sodium reabsorption, leading to

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

increased diuresis and a reduction in intravascular volume. Loop diuretics (e.g., furosemide, torasemide) act on the $Na^+/K^+/2Cl^-$ co-transporter in the loop of Henle, enhancing sodium and water excretion; in contrast, thiazide diuretics (e.g., Hydrochlorothiazide, Metolazone) inhibit the Na^+/Cl^- co-transporter in the distal tubule, often used in combination with loop diuretics for a synergistic effect (Li et al. 2021). Despite their efficacy in reducing pulmonary and peripheral congestion, diuretics do not directly improve prognosis in HF, as current evidence does not demonstrate a clear independent mortality benefit; their primary role remains the relief of congestion and improvement of symptoms (Cuthbert and Clark 2024).

Several natural compounds have been studied for their diuretic effects, offering potential complementary or alternative approaches to pharmacological diuretics. Below, the main nutraceuticals with diuretic effects are analyzed, highlighting the available scientific evidence and their possible clinical role.

2.6.1 | *Ortosiphon stamineus*—Java tea (Flavonoids)

Orthosiphon stamineus, commonly known as Java tea, has been traditionally used in Southeast Asia for its diuretic, antihypertensive, and antioxidant properties (Kalusalingam et al. 2024; Gimbun et al. 2019). Recent studies have explored its potential role in cardiovascular health, particularly in managing fluid retention associated with HF.

Java tea's diuretic effects are attributed to its rich phytochemical composition, which includes flavonoids such as eupatorium, sinensetin, and rosmarinic acid. These constituents have been shown in experimental models to support renal function and increase urinary excretion of water and electrolytes, thereby promoting mild fluid elimination (Adam et al. 2009). Additionally, compounds such as sinensetin and methylripariochromene A have been isolated and shown to contribute to increased urine output and sodium excretion, thereby reinforcing their diuretic potential (Hsu et al. 2010).

Clinical and pharmacological studies suggest that Java tea exerts aquaretic effects, promoting water elimination without significant electrolyte loss. This mechanism may be relevant to fluid homeostasis in HF, although direct clinical evidence in HF patients remains limited (Gimbun et al. 2019). This mechanism differentiates it from loop and thiazide diuretics, often leading to electrolyte imbalances. Furthermore, its antihypertensive properties may provide an additional cardiovascular benefit, supporting blood pressure regulation in HF patients (Ameer et al. 2012).

Regarding safety, Java tea is well-tolerated, with no significant toxicity reported in both in vitro and in vivo studies (Adam et al. 2009; Ameer et al. 2012). This favorable safety profile, together with its mild diuretic properties, highlights its potential as a complementary nutraceutical in HF management. However, further clinical research is needed to establish standardized dosages and evaluate its efficacy in combination with conventional diuretics (European Medicines Agency (EMA), n.d.).

2.6.2 | *Taraxacum officinale*—Dandelion (Sesquiterpenes, Flavonoids)

Taraxacum officinale, commonly known as dandelion, has long been used as a natural diuretic and is now being investigated for its potential applications in HF management. Its diuretic effects are primarily linked to its rich phytochemical composition, including sesquiterpenes, triterpenes, and flavonoids, which promote urine production and detoxification (Hao et al. 2024; Di Napoli and Zucchetti 2021).

A pilot study in humans reported that a hydroethanolic extract of dandelion leaves increased urinary frequency and excretion ratio, suggesting potential diuretic activity. Interestingly, unlike many conventional diuretics, it may contribute to potassium retention, lowering the risk of hypokalemia (Clare et al. 2009). Due to its high potassium content, dandelion may support electrolyte balance while promoting diuresis, distinguishing it from conventional diuretics that are often associated with potassium depletion. Additionally, preliminary evidence suggests antihypertensive and renal protective effects, although most available data focus on hypertension and chronic kidney disease rather than HF (Gunasekaran and Chamundeeswari 2025).

Dandelion exhibits promising diuretic properties, with potential benefits in managing fluid retention in HF. Its potassium-sparing effect differentiates it from conventional diuretics, but further clinical studies are needed to confirm its efficacy and establish its role as an adjunct to pharmacological therapy.

2.7 | Counteracting Inflammation, Oxidative Stress, and Endothelial Dysfunction in HF

Systemic inflammation, oxidative stress, and endothelial dysfunction are key contributors to HF progression, promoting ventricular remodeling, myocardial fibrosis, and vascular impairment (Wróbel-Nowicka et al. 2024). Chronic inflammation elevates pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), while oxidative stress exacerbates cellular damage, reducing NO bioavailability and impairing endothelial function.

These mechanisms are addressed in relation to specific pharmacological classes in the previous sections and are summarized here to provide a more integrated overview of their role in HF and AF pathophysiology.

Given their impact on cardiac function, nutraceuticals with anti-inflammatory, antioxidant, and cardioprotective properties have gained attention as potential adjuncts to conventional therapy. Among these, Omega-3 fatty acids and astaxanthin stand out for their ability to modulate inflammation, support endothelial health, and reduce oxidative stress.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

The following sections will explore their mechanisms of action and potential role in HF management.

2.7.1 | Omega-3 Fatty Acids—Fish Oils and Flax (EPA, DHA)

Omega-3 polyunsaturated fatty acids (PUFAs), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have gained significant attention in cardiovascular health due to their anti-inflammatory, endothelial-protective, and cardiometabolic benefits (Jump et al. 2012). Found in fatty fish (e.g., salmon, mackerel, and sardines) and plant sources (e.g., flaxseeds and walnuts), these essential fatty acids have been extensively studied for their potential to counteract the pathophysiological mechanisms underlying HF (Bernasconi et al. 2021).

Systemic inflammation is critical in HF progression, contributing to ventricular remodeling, myocardial fibrosis, and endothelial dysfunction (Daou et al. 2023). Elevated levels of inflammatory markers such as CRP, IL-6, and TNF-α are commonly observed in HF patients and correlate with worse clinical outcomes. Omega-3 fatty acids exert potent anti-inflammatory effects by modulating the production of specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins (Distefano et al. 2024; Maliha et al. 2024). These bioactive lipid mediators reduce cytokine production, limit leukocyte infiltration, and mitigate oxidative stress, potentially slowing the inflammatory cascade that exacerbates HF (Gutiérrez et al. 2019). Endothelial dysfunction, another major contributor to HF, is characterized by reduced NO bioavailability, increased oxidative stress, and vascular stiffness (Pacinella et al. 2022). EPA and DHA enhance endothelial function by promoting NO production, improving vasodilation, and increasing blood flow. They also help reduce oxidative stress by limiting lipid peroxidation and endothelial damage while modulating cell membrane composition to optimize receptor signaling and endothelial resilience (Yamagata 2020; Sherratt et al. 2024). Clinical studies suggest that Omega-3 supplementation lowers arterial stiffness, improves vascular reactivity, and enhances microvascular function, which is crucial for hemodynamic stability in HF patients (Chu et al. 2021; Tousoulis et al. 2014; Dzupina et al. 2024).

Chronic inflammation is a well-established factor in arterial stiffness, contributing to vascular remodeling and oxidative stress. Several studies have shown that Omega-3 supplementation reduces inflammatory markers such as CRP and interleukins, which are associated with improved arterial compliance and cardiovascular health (Ito et al. 2014; Takaki et al. 2011; Satoh et al. 2009). A Boston-based study found that individuals with a high Omega-3 index had a significantly lower risk of cardiovascular mortality (Harris et al. 2018). Conversely, a low Omega-3 index was associated with an increased risk of sudden cardiac death, whereas an elevated Omega-3 index reduced this risk by 90% (Harris 2007; Aarsetoey et al. 2011).

The VITAL trial, a randomized controlled study involving 25,871 U.S. adults, evaluated the effects of 1 g/day of Omega-3 supplementation over five years in the primary prevention of cardiovascular disease. The results showed a 28% reduction in myocardial infarction risk, with a more pronounced effect in individuals with low fish consumption (< 1.5 servings per week) (Manson et al. 2019).

Beyond HF, Omega-3 s have been investigated for their potential role in AF. Observational data indicate that a high dietary intake is associated with a lower risk of developing AF (He et al. 2013). At the same time, mechanistic and epidemiological studies suggest a possible anti-arrhythmic effect of EPA and DHA (von Schacky 2012).

Overall, Omega-3 fatty acids offer a multifaceted therapeutic approach in HF, counteracting inflammation, improving endothelial function, and supporting cardiac hemodynamics. Given their favorable safety profile and potential synergistic effects with conventional HF therapies, they represent a potentially valuable nutraceutical option for prevention and adjunctive management in HF and AF, although benefits may vary according to population, formulation, and dose.

2.7.2 | Astaxanthin—From *Haematococcus pluvialis*

As previously discussed in Section 2.4, ASX is a xanthophyll carotenoid with strong antioxidant, anti-inflammatory, and mitochondrial-protective properties relevant to mineralocorticoid-driven cardiac remodeling. Beyond those effects, ASX also shows promise in HF through broader cardiometabolic mechanisms. Its amphipathic structure allows ASX to span cell membranes and mitochondrial layers, ensuring broad-spectrum antioxidant protection without pro-oxidant effects (Budriesi et al. 2022).

Oxidative stress and chronic inflammation are key drivers of HF progression, contributing to myocardial fibrosis, endothelial dysfunction, and impaired mitochondrial function (Fonseka et al. 2025). ASX exerts cardioprotective effects by reducing ROS, suppressing pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), enhancing NO bioavailability, stabilizing mitochondrial function, and preventing lipid peroxidation (Davinelli et al. 2022; Chang and Xiong 2020). These mechanisms improve endothelial function, prevent ventricular remodeling, and protect against ischemia–reperfusion injury, crucial factors in managing HF (Pereira et al. 2021).

In addition to its anti-inflammatory and antioxidant properties, ASX enhances endothelial resilience by modulating oxidative balance, preventing lipid peroxidation, and maintaining vascular integrity (Sztretye et al. 2019). Stabilizing mitochondrial function supports cellular energy production, a particularly important factor in HF, where cardiomyocyte energy depletion is a key issue (Nishida et al. 2021; Krestinina et al. 2021).

A pilot study demonstrated that three months of ASX supplementation improved exercise tolerance and cardiac function in patients with left ventricular systolic dysfunction. This improvement was associated with a decrease in oxidative stress markers, suggesting a potential indirect role of ASX in supporting myocardial performance through oxidative stress suppression (Kato et al. 2020).

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | Comparative analysis of conventional drugs and nutraceuticals in heart failure, highlighting pharmacological treatments and nutraceutical compounds with partially overlapping or complementary mechanisms of action.

Pharmacological class	Main drugs	Mechanism of action	Nutraceuticals with similar mechanism of actions	Clinical evidence[a]	References
RAAS inhibitors (ACE-Is, ARBs, ARNIs)	Enalapril, Ramipril, Lisinopril, Losartan, Valsartan, Sacubitril/Valsartan.	RAAS inhibition reduces vasoconstriction, sympathetic drive, and fluid overload.	*Olea europaea*	Yes	(Goto 2024; Mattioli et al. 2022; Medina-Remón et al. 2013; Mnafgui et al. 2016; D'Agostino et al. 2021; Vazquez et al. 2019; Martín-Peláez et al. 2017; Sarapis et al. 2020, 2022; Galvão Cândido et al. 2018; Christodoulou et al. 2024; Frumuzachi et al. 2024; George et al. 2019; Martínez-González et al. 2014)
			Hibiscus sabdariffa	Moderate	(Ojeda et al. 2010; Sanou et al. 2024; Nwachukwu et al. 2015; Salem et al. 2022; Jalalyazdi et al. 2019; Abdelmonem et al. 2022; Bourqui et al. 2021; Herrera-Arellano et al. 2004; Da-Costa-Rocha et al. 2014; Aliyu et al. 2014; McKay et al. 2010)
			Camellia sinensis	Limited	(Velayutham et al. 2008; Parn et al. 2022; Takagaki and Nanjo 2015; Zhang et al. 2018; Wan et al. 2022; Mohd Sabri et al. 2022; Cai et al. 2021; Chen et al. 2009; Burstein and Nattel 2008)
			Vitis vinifera	Limited	(Dolinsky et al. 2013; Kim et al. 2018; Hashemizadeh et al. 2019; Ma et al. 2023; Soltan et al. 2021; Liu et al. 2022, 2024; Raj et al. 2016; Dyck et al. 2019; Biala et al. 2010; Cao et al. 2014, 2024; Restini et al. 2022; Fan et al. 2022; Yu et al. 2021; Wang et al. 2024; Gál et al. 2023)
Beta-blockers	Bisoprolol, Carvedilol, Metoprolol, Nebivolol.	Reduces sympathetic activation by blocking β-adrenergic receptors, lowering heart rate and myocardial workload	*Crataegus* spp.	Moderate	(Tassell et al. 2010; Venskutonis 2018; Lu et al. 2023; Chang et al. 2005; Wu et al. 2020; Ding et al. 2022; Holubarsch et al. 2008; Orhan 2018; Walker et al. 2002; Szikora et al. 2025; Pahlavan et al. 2018; Alp et al. 2016)
			Withania somnifera	Moderate	(Della Porta et al. 2023; Speers et al. 2021; Smith et al. 2023; Bonilla et al. 2021; Tiwari et al. 2021; Mohanty et al. 2004; Khalil et al. 2015)
			Panax ginseng	Limited	(Kim 2012; Tang et al. 2023; Zi-chang et al. 2024; Zhou et al. 2024; Xie et al. 2024; Gao et al. 2024; Chen, Ma, et al. 2022; Caron et al. 2002)

(Continues)

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Pharmacological class	Main drugs	Mechanism of action	Nutraceuticals with similar mechanism of actions	Clinical evidence[a]	References
SGLT2 inhibitors	Empagliflozin, Dapagliflozin.	Promotes glycosuria and natriuresis, reducing preload and improving cardiac metabolism	*Curcuma longa*	Moderate	(Zamanian et al. 2024; Hussain et al. 2022; Lee and Kim 2024; Ebrahimzadeh et al. 2024; Cheng et al. 2025; Mo et al. 2025; Bozkurt et al. 2022; Feng et al. 2024; Rafiee et al. 2021; Dehzad et al. 2023)
			Berberis aristata	Limited	(Yin et al. 2008; Liu et al. 2025; Abudureyimu et al. 2020; Haftcheshmeh et al. 2022; Feng et al. 2019)
MRAs	Spironolactone, Eplerenone.	Antagonizes aldosterone to reduce fibrosis and sodium retention	Ursolic acid	Limited	(Majid et al. 2023; Dong et al. 2015; Wang et al. 2018; Radhiga et al. 2019; Roudi et al. 2025; Xu et al. 2023)
			Astaxanthin	Moderate	(Khodir et al. 2022; Zhang et al. 2024, 2023; Krestinin et al. 2024; Qu et al. 2020; Mahmoud et al. 2024; Zhu et al. 2024; Pan et al. 2020; Youssef et al. 2025; Fassett and Coombes 2009; Pereira et al. 2021)
			Vitis vinifera	Moderate	(Fan et al. 2022; Gal et al. 2021; Das and Maulik 2006; Chen et al. 2008; Raj et al. 2021; Kroon et al. 2010)
AADs	Amiodarone, Flecainide, Dronedarone, Sotalol.	Modulates ion channels and autonomic tone to restore and maintain sinus rhythm	*Rhodiola* spp.	No	(Ivanova Stojcheva and Quintela 2022; Chen, Tang, et al. 2022; Hsiao et al. 2021; Hsu et al. 2017; Jia et al. 2024)
			Vitis vinifera	Limited	(Soltani et al. 2022; Baczko et al. 2014; Buluc et al. 2007; Zhao et al. 2014; Bai et al. 2016; Menezes-Rodrigues et al. 2021)
Diuretics	Furosemide, Torasemide, Hydrochlorothiazide.	Increases urinary sodium and water excretion to relieve volume overload	*Orthosiphon stamineus*	Limited	(Kalusalingam et al. 2024; Gimbun et al. 2019; Adam et al. 2009; Hsu et al. 2010; Ameer et al. 2012)
			Taraxacum officinale	Limited	(Hao et al. 2024; Di Napoli and Zucchetti 2021; Clare et al. 2009; Gunasekaran and Chamundeeswari 2025)

(Continues)

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Pharmacological class	Main drugs	Mechanism of action	Nutraceuticals with similar mechanism of actions	Clinical evidence[a]	References
Anti-inflammatory, antioxidant, endothelial protective agents	N/A	Counteracts inflammation, reduces oxidative stress, enhances endothelial function, stabilizes mitochondrial activity	Omega-3 fatty acids	Yes	(Jump et al. 2012; Bernasconi et al. 2021; Daou et al. 2023; Distefano et al. 2024; Maliha et al. 2024; Gutiérrez et al. 2019; Pacinella et al. 2022; Yamagata 2020; Sherratt et al. 2024; Chu et al. 2021; Tousoulis et al. 2014; Dzupina et al. 2024; Ito et al. 2014; Takaki et al. 2011; Satoh et al. 2009; Harris et al. 2018; Harris 2007; Aarsetoey et al. 2011; Manson et al. 2019; He et al. 2013)
			Astaxanthin	Yes	(Pereira et al. 2021; Budriesi et al. 2022; Fonseka et al. 2025; Davinelli et al. 2022; Chang and Xiong 2020; Sztretye et al. 2019; Nishida et al. 2021; Krestinina et al. 2021; Kato et al. 2020)

[a]Clinical evidence: This classification is intended as a qualitative, descriptive summary of the available evidence for each nutraceutical with respect to the pharmacological mechanism discussed, and does not constitute a validated grading system. The categories are defined as follows: Yes = Presence of clinical evidence from randomized controlled trials (RCTs) in humans addressing cardiovascular outcomes or related mechanisms. Moderate = Evidence from observational human studies or small non-randomized clinical trials with mechanistic and/or clinical relevance. Limited = Evidence restricted to preclinical studies (in vivo or in vitro) supporting the proposed mechanism of action. No = Absence of relevant or consistent evidence supporting the described effect.

ASX's multifaceted actions, including those highlighted in Section 2.4, reinforce its potential relevance as a complementary nutraceutical in HF, acting by counteracting oxidative stress, supporting vascular integrity, and stabilizing mitochondrial function.

A comparative overview of conventional pharmacological therapies and nutraceutical counterparts with similar mechanisms of action is provided in Table 1.

The level of evidence reported for each nutraceutical is intended as a qualitative, descriptive summary based on the available literature and should not be interpreted as a formal or validated evidence-grading system.

3 | Conclusion and Future Perspectives

HF and AF continue to represent significant challenges in cardiovascular medicine due to their high morbidity, complex management, and persistent burden on healthcare systems. While conventional pharmacological therapies have significantly improved patient outcomes, their limitations—including adverse effects, drug interactions, and patient-specific variability—highlight the need for more integrative and personalized strategies.

Nutraceuticals and natural compounds have emerged as promising adjuncts to standard care, thanks to their pleiotropic mechanisms targeting inflammation, oxidative stress, endothelial dysfunction, autonomic regulation, and metabolic derangements.

However, their incorporation into clinical practice is still limited by challenges such as inconsistent evidence, variable formulation quality, and a lack of regulatory standardization, as well as limited bioavailability, variability in extract composition, and insufficiently defined dose–response relationships, which may significantly affect the interpretation and generalizability of current evidence.

To advance this field, future research should prioritize well-designed randomized clinical trials assessing efficacy and safety, long-term outcomes, and interactions with conventional therapies.

This need is consistent with the conclusions of Sosnowska et al., who highlighted both the potential of nutraceuticals and the current paucity of robust evidence on clinical endpoints, especially regarding hard outcomes such as cardiovascular events and mortality (Sosnowska et al. 2017). Moreover, dose–response relationships must be clearly defined, especially considering that many natural compounds exhibit non-linear pharmacokinetics or narrow therapeutic windows.

Standardization of plant extracts, active principles, and delivery systems (e.g., nanoformulations, sustained-release preparations) is essential to ensure reproducibility and clinical reliability. In this context, chemistry provides a fundamental contribution through the qualitative and quantitative characterization of natural extracts. Accurate chemical analysis ensures reproducibility, supports the elucidation of molecular mechanisms of action,

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and allows the prediction of binding interactions with pharmacological targets. Moreover, structural similarities between secondary metabolites and conventional drugs can be identified, facilitating the rational development of complementary therapeutic strategies.

In line with this approach, recent experimental evidence has shown that well-characterized polyphenol-rich extracts derived from agro-food by-products can exert coordinated antioxidant, anti-inflammatory, and endothelial-protective effects, supporting their potential role as multitarget agents in cardiovascular prevention (Mattioli, Corazza, et al. 2024; Prata et al. 2025).

An essential and underexplored direction is integrating omics technologies (metabolomics, pharmacogenomics) to better understand individual variability in response to nutraceuticals. This could pave the way for precision nutraceutical approaches, tailoring supplementation based on patient genotype, phenotype, or comorbidities. In addition, developing validated biomarkers for nutraceutical efficacy would facilitate clinical monitoring and decision-making. Efforts should also be directed toward harmonizing regulatory frameworks across countries, enabling safer and more consistent use of nutraceuticals in cardiology.

From a practical perspective, nutraceuticals are best suited for prevention, early intervention, and long-term management rather than acute treatment. Their strong safety profile and ability to target multiple pathways make them good options for integrative approaches to improve quality of life, decrease polypharmacy, and support better adherence. However, despite their generally favorable safety profile, nutraceuticals are not devoid of potential risks, including adverse effects, variability in composition, clinically relevant herb–drug interactions (e.g., through modulation of cytochrome P450 isoenzymes), and potential contraindications, particularly in patients receiving complex pharmacological regimens, and should be carefully considered when evaluating their risk–benefit profile in cardiovascular settings.

In conclusion, nutraceuticals represent an exciting frontier in cardiovascular care. However, their full potential will only be realized through rigorous research, standardized practices, and a deeper understanding of their interaction with conventional medicine. A multidisciplinary approach—linking cardiologists, pharmacologists, nutritionists, chemists, and regulatory bodies—will be crucial to bringing these innovations into mainstream clinical practice.

Future research should focus on well-designed randomized controlled trials to evaluate the efficacy of nutraceuticals as adjuncts to standard pharmacological therapies in HF and AF, with particular attention to clinically relevant endpoints and long-term outcomes. In addition, standardization of extracts, optimization of bioavailability, and characterization of dose–response relationships represent key challenges for clinical translation. Particular attention should also be given to the evaluation of pharmacokinetic and pharmacodynamic interactions between nutraceuticals and conventional drugs.

Author Contributions

Igor Diemberger: conceptualization, methodology, supervision, writing – review and editing. **Ivan Corazza:** methodology, writing – original draft, supervision. **Alberto Spadotto:** visualization. **Laura Beatrice Mattioli:** conceptualization, methodology, writing – original draft, writing – review and editing, supervision. **Luca Camarda:** visualization. **Maria Carelli:** supervision, visualization. **Roberta Budriesi:** conceptualization, supervision.

Acknowledgments

During the preparation of this manuscript, the authors used Grammarly to revise and improve the English language of the review. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Funding

This work was supported by the REMEDY Project – Regione Emilia-Romagna, Italy, PR FESR (CUP: E97G22000630007).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

Aarsetoey, H., R. Aarsetoey, T. Lindner, H. Staines, W. S. Harris, and D. W. T. Nilsen. 2011. "Low Levels of the Omega-3 Index Are Associated With Sudden Cardiac Arrest and Remain Stable in Survivors in the Subacute Phase." *Lipids* 46: 151–161. https://doi.org/10.1007/s11745-010-3511-3.

Abdelmonem, M., M. A. Ebada, S. Diab, et al. 2022. "Efficacy of *Hibiscus sabdariffa* on Reducing Blood Pressure in Patients With Mild-To-Moderate Hypertension: A Systematic Review and Meta-Analysis of Published Randomized Controlled Trials." *Journal of Cardiovascular Pharmacology* 79: e64–e74. https://doi.org/10.1097/FJC.0000000000001161.

Abudureyimu, M., W. Yu, R. Y. Cao, Y. Zhang, H. Liu, and H. Zheng. 2020. "Berberine Promotes Cardiac Function by Upregulating PINK1/Parkin-Mediated Mitophagy in Heart Failure." *Frontiers in Physiology* 11: 565751. https://doi.org/10.3389/fphys.2020.565751.

Adam, Y., M. N. Somchit, M. R. Sulaiman, et al. 2009. "Diuretic Properties of *Orthosiphon stamineus benth*." *Journal of Ethnopharmacology* 124: 154–158. https://doi.org/10.1016/j.jep.2009.04.014.

Agrawal, M., M. Singhal, R. Gupta, et al. 2024. "Nutraceutical Herbs in Cardiovascular Diseases." In *Herbals as Nutraceuticals*. Apple Academic Press.

Aguiar-Neves, I., D. Santos-Ferreira, and R. Fontes-Carvalho. 2023. "SGLT2 Inhibition in Heart Failure With Preserved Ejection Fraction — The New Frontier." *Reviews in Cardiovascular Medicine* 24, no. 1: 1–18. https://doi.org/10.31083/j.rcm2401001.

Aliyu, B., Y. J. Oyeniyi, F. B. O. Mojiminiyi, S. A. Isezuo, and A. R. A. Alada. 2014. "The Aqueous Calyx Extract of *Hibiscus sabdariffa* Lowers Blood Pressure and Heart Rate via Sympathetic Nervous System Dependent Mechanisms." *Nigerian Journal of Physiological Sciences* 29: 131–136.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Allen, L. A., and J. C. Fang. 2017. "The Goldilocks Dilemma of Dose Titration in Heart Failure With Reduced Ejection Fraction: Too Little, Too Much, or Just Right?" *Circulation. Heart Failure* 10: e004406. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004406.

Alp, H., B. C. Soner, T. Baysal, and A. S. Şahin. 2016. "Protective Effects of Hawthorn (*Crataegus oxyacantha*) Extract Against Digoxin-Induced Arrhythmias in Rats." *Anatolian Journal of Cardiology* 15: 970–975. https://doi.org/10.5152/akd.2014.5869.

Ameer, O. Z., I. M. Salman, M. Z. Asmawi, Z. O. Ibraheem, and M. F. Yam. 2012. "Orthosiphon Stamineus: Traditional Uses, Phytochemistry, Pharmacology, and Toxicology." *Journal of Medicinal Food* 15: 678–690. https://doi.org/10.1089/jmf.2011.1973.

Anker, S. D., J. Butler, G. Filippatos, et al. 2021. "Empagliflozin in Heart Failure With a Preserved Ejection Fraction." *New England Journal of Medicine* 385: 1451–1461. https://doi.org/10.1056/NEJMoa2107038.

Ansari, S. 2021. "Chapter 12—Heart Health and Nutraceuticals." In *Preparation of Phytopharmaceuticals for the Management of Disorders*, edited by C. Egbuna, A. P. Mishra, and M. R. Goyal, 255–272. Academic Press.

Anter, E., M. Jessup, and D. J. Callans. 2009. "Atrial Fibrillation and Heart Failure." *Circulation* 119: 2516–2525. https://doi.org/10.1161/CIRCULATIONAHA.108.821306.

Baczko, I., D. Liknes, W. Yang, et al. 2014. "Characterization of a Novel Multifunctional Resveratrol Derivative for the Treatment of Atrial Fibrillation." *British Journal of Pharmacology* 171: 92–106. https://doi.org/10.1111/bph.12409.

Bai, T., X. Hu, Y. Zheng, S. Wang, J. Kong, and L. Cai. 2016. "Resveratrol Protects Against Lipopolysaccharide-Induced Cardiac Dysfunction by Enhancing SERCA2a Activity Through Promoting the Phospholamban Oligomerization." *American Journal of Physiology. Heart and Circulatory Physiology* 311: H1051–H1062. https://doi.org/10.1152/ajpheart.00296.2016.

Bernasconi, A. A., M. M. Wiest, C. J. Lavie, R. V. Milani, and J. A. Laukkanen. 2021. "Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials." *Mayo Clinic Proceedings* 96: 304–313. https://doi.org/10.1016/j.mayocp.2020.08.034.

Bhushan, S., X. Huang, F. Jiang, and Z. Xiao. 2024. "Impact of Angiotensin Receptor-Neprilysin Inhibition (ARNI) in Improving Ejection Fraction and Left and Right Ventricular Remodeling in Heart Failure." *Current Problems in Cardiology* 49: 102464. https://doi.org/10.1016/j.cpcardiol.2024.102464.

Biala, A., E. Tauriainen, A. Siltanen, et al. 2010. "Resveratrol Induces Mitochondrial Biogenesis and Ameliorates Ang II-Induced Cardiac Remodeling in Transgenic Rats Harboring Human Renin and Angiotensinogen Genes." *Blood Pressure* 19: 196–205. https://doi.org/10.3109/08037051.2010.481808.

Bonilla, D. A., Y. Moreno, C. Gho, J. L. Petro, A. Odriozola-Martínez, and R. B. Kreider. 2021. "Effects of Ashwagandha (*Withania somnifera*) on Physical Performance: Systematic Review and Bayesian Meta-Analysis." *Journal of Functional Morphology and Kinesiology* 6: 20. https://doi.org/10.3390/jfmk6010020.

Bourqui, A., E. A. B. Niang, B. Graz, et al. 2021. "Hypertension Treatment With Combretum Micranthum or *Hibiscus sabdariffa*, as Decoction or Tablet: A Randomized Clinical Trial." *Journal of Human Hypertension* 35: 800–808. https://doi.org/10.1038/s41371-020-00415-1.

Boutari, C., K. Stavropoulos, K. P. Imprialos, K. Petidis, and M. Doumas. 2016. "Antihypertensive Drug-Related Side Effects: Is It the Unique Indicator for Nonadherence?" *American Journal of Hypertension* 29: 662. https://doi.org/10.1093/ajh/hpw024.

Bozkurt, O., B. Kocaadam-Bozkurt, and H. Yildiran. 2022. "Effects of Curcumin, a Bioactive Component of Turmeric, on Type 2 Diabetes Mellitus and Its Complications: An Updated Review." *Food & Function* 13: 11999–12010. https://doi.org/10.1039/D2FO02625B.

Budriesi, R., M. Micucci, M. Daglia, I. Corazza, G. Biotti, and L. B. Mattioli. 2022. "Chemical Features and Biological Effects of Astaxanthin Extracted From *Haematococcus pluvialis* Flotow: Focus on Gastrointestinal System." *Biology and Life Sciences Forum* 12: 31. https://doi.org/10.3390/IECN2022-12376.

Buluc, M., M. Ayaz, B. Turan, and E. Demirel-Yilmaz. 2007. "Resveratrol-Induced Depression of the Mechanical and Electrical Activities of the Rat Heart Is Reversed by Glyburide: Evidence for Possible K(ATP) Channels Activation." *Archives of Pharmacal Research* 30: 603–607. https://doi.org/10.1007/BF02977655.

Burstein, B., and S. Nattel. 2008. "Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation." *Journal of the American College of Cardiology* 51: 802–809. https://doi.org/10.1016/j.jacc.2007.09.064.

Cai, Y., S. S. Yu, Y. He, et al. 2021. "EGCG Inhibits Pressure Overload-Induced Cardiac Hypertrophy via the PSMB5/Nmnat2/SIRT6-Dependent Signalling Pathways." *Acta Physiologica (Oxford, England)* 231: e13602. https://doi.org/10.1111/apha.13602.

Cao, X., T. Luo, X. Luo, and Z. Tang. 2014. "Resveratrol Prevents AngII-Induced Hypertension via AMPK Activation and RhoA/ROCK Suppression in Mice." *Hypertension Research* 37: 803–810. https://doi.org/10.1038/hr.2014.90.

Cao, Y., L. Cui, S. Tuo, H. Liu, and S. Cui. 2024. "Resveratrol Mediates Mitochondrial Function Through the Sirtuin 3 Pathway to Improve Abnormal Metabolic Remodeling in Atrial Fibrillation." *European Journal of Histochemistry* 68: 4004. https://doi.org/10.4081/ejh.2024.4004.

Cardoso, R., F. P. Graffunder, C. M. P. Ternes, et al. 2021. "SGLT2 Inhibitors Decrease Cardiovascular Death and Heart Failure Hospitalizations in Patients With Heart Failure: A Systematic Review and Meta-Analysis." *eClinicalMedicine* 36: 1–18. https://doi.org/10.1016/j.eclinm.2021.100933.

Caron, M. F., A. L. Hotsko, S. Robertson, L. Mandybur, J. Kluger, and C. M. White. 2002. "Electrocardiographic and Hemodynamic Effects of *Panax ginseng*." *Annals of Pharmacotherapy* 36: 758–763. https://doi.org/10.1345/aph.1A411.

Chang, M. X., and F. Xiong. 2020. "Astaxanthin and Its Effects in Inflammatory Responses and Inflammation-Associated Diseases: Recent Advances and Future Directions." *Molecules* 25: E5342. https://doi.org/10.3390/molecules25225342.

Chang, W.-T., J. Dao, and Z.-H. Shao. 2005. "Hawthorn: Potential Roles in Cardiovascular Disease." *American Journal of Chinese Medicine* 33: 1–10. https://doi.org/10.1142/S0192415X05002606.

Chen, D.-D., Y.-G. Dong, D. Liu, and J.-G. He. 2009. "Epigallocatechin-3-Gallate Attenuates Cardiac Hypertrophy in Hypertensive Rats in Part by Modulation of Mitogen-Activated Protein Kinase Signals." *Clinical and Experimental Pharmacology & Physiology* 36: 925–932. https://doi.org/10.1111/j.1440-1681.2009.05173.x.

Chen, J., C. Jiang, M. Guo, et al. 2024. "Effects of SGLT2 Inhibitors on Cardiac Function and Health Status in Chronic Heart Failure: A Systematic Review and Meta-Analysis." *Cardiovascular Diabetology* 23: 2. https://doi.org/10.1186/s12933-023-02042-9.

Chen, X., Y. Ma, J. Li, et al. 2022. "The Efficacy of Ginseng-Containing Traditional Chinese Medicine in Patients With Acute Decompensated Heart Failure: A Systematic Review and Meta-Analysis." *Frontiers in Pharmacology* 13: 1083001. https://doi.org/10.3389/fphar.2022.1083001.

Chen, Y., M. Tang, S. Yuan, et al. 2022. "*Rhodiola rosea*: A Therapeutic Candidate on Cardiovascular Diseases." *Oxidative Medicine and Cellular Longevity* 2022: 1348795. https://doi.org/10.1155/2022/1348795.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Chen, Y.-R., F.-F. Yi, X.-Y. Li, et al. 2008. "Resveratrol Attenuates Ventricular Arrhythmias and Improves the Long-Term Survival in Rats With Myocardial Infarction." *Cardiovascular Drugs and Therapy* 22: 479–485. https://doi.org/10.1007/s10557-008-6141-8.

Cheng, M., F. Ding, L. Li, et al. 2025. "Exploring the Role of Curcumin in Mitigating Oxidative Stress to Alleviate Lipid Metabolism Disorders." *Frontiers in Pharmacology* 16: 1517174. https://doi.org/10.3389/fphar.2025.1517174.

Christodoulou, A., P.-E. Nikolaou, L. Symeonidi, et al. 2024. "Cardioprotective Potential of Oleuropein, Hydroxytyrosol, Oleocanthal and Their Combination: Unravelling Complementary Effects on Acute Myocardial Infarction and Metabolic Syndrome." *Redox Biology* 76: 103311. https://doi.org/10.1016/j.redox.2024.103311.

Chu, Z., Y. Wei, Y. Hao, J. Wang, F. Huang, and M. Hou. 2021. "Clinical Effectiveness of Fish Oil on Arterial Stiffness: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *Nutrition, Metabolism, and Cardiovascular Diseases* 31: 1339–1348. https://doi.org/10.1016/j.numecd.2020.12.033.

CIBIS-II Investigators and Committees. 1999. "The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial." *Lancet* 353: 9–13. https://doi.org/10.1016/S0140-6736(98)11181-9.

Clare, B. A., R. S. Conroy, and K. Spelman. 2009. "The Diuretic Effect in Human Subjects of an Extract of *Taraxacum officinale* Folium Over a Single Day." *Journal of Alternative and Complementary Medicine* 15: 929–934. https://doi.org/10.1089/acm.2008.0152.

Cuthbert, J. J., and A. L. Clark. 2024. "Diuretic Treatment in Patients With Heart Failure: Current Evidence and Future Directions—Part I: Loop Diuretics." *Current Heart Failure Reports* 21: 101–114. https://doi.org/10.1007/s11897-024-00643-3.

Da-Costa-Rocha, I., B. Bonnlaender, H. Sievers, I. Pischel, and M. Heinrich. 2014. "*Hibiscus sabdariffa* L.—A Phytochemical and Pharmacological Review." *Food Chemistry* 165: 424–443. https://doi.org/10.1016/j.foodchem.2014.05.002.

D'Agostino, R., L. Barberio, M. Gatto, T. Tropea, M. De Luca, and M. Mandalà. 2021. "Extra Virgin Olive Oil Phenols Vasodilate Rat Mesenteric Resistance Artery via Phospholipase C (PLC)-Calcium Microdomains-Potassium Channels (BKCa) Signals." *Biomolecules* 11: 137. https://doi.org/10.3390/biom11020137.

Dan, G. A., A. Martinez-Rubio, S. Agewall, et al. 2018. "Antiarrhythmic Drugs–Clinical Use and Clinical Decision Making: A Consensus Document From the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, Endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP)." *EP Europace* 20: 731–732. https://doi.org/10.1093/europace/eux373.

Daou, D., T. G. Gillette, and J. A. Hill. 2023. "Inflammatory Mechanisms in Heart Failure With Preserved Ejection Fraction." *Physiology (Bethesda)* 38: 217–230. https://doi.org/10.1152/physiol.00004.2023.

Das, D. K., and N. Maulik. 2006. "Resveratrol in Cardioprotection: A Therapeutic Promise of Alternative Medicine." *Molecular Interventions* 6: 36–47. https://doi.org/10.1124/mi.6.1.7.

Davinelli, S., L. Saso, F. D'Angeli, V. Calabrese, M. Intrieri, and G. Scapagnini. 2022. "Astaxanthin as a Modulator of Nrf2, NF-κB, and Their Crosstalk: Molecular Mechanisms and Possible Clinical Applications." *Molecules* 27: 502. https://doi.org/10.3390/molecules27020502.

Dehzad, M. J., H. Ghalandari, M. R. Amini, and M. Askarpour. 2023. "Effects of Curcumin/Turmeric Supplementation on Lipid Profile: A GRADE-Assessed Systematic Review and Dose-Response Meta-Analysis of Randomized Controlled Trials." *Complementary Therapies in Medicine* 75: 102955. https://doi.org/10.1016/j.ctim.2023.102955.

Della Porta, M., J. A. Maier, and R. Cazzola. 2023. "Effects of *Withania somnifera* on Cortisol Levels in Stressed Human Subjects: A Systematic Review." *Nutrients* 15: 5015. https://doi.org/10.3390/nu15245015.

Di Cesare, M., P. Perel, S. Taylor, et al. 2024. "The Heart of the World." *Global Heart* 19, no. 11: 11. https://doi.org/10.5334/gh.1288.

Di Napoli, A., and P. Zucchetti. 2021. "A Comprehensive Review of the Benefits of *Taraxacum officinale* on Human Health." *Bulletin of the National Research Centre* 45: 110. https://doi.org/10.1186/s42269-021-00567-1.

Ding, J., J. Wu, H. Wei, et al. 2022. "Exploring the Mechanism of Hawthorn Leaves Against Coronary Heart Disease Using Network Pharmacology and Molecular Docking." *Frontiers in Cardiovascular Medicine* 9: 804801. https://doi.org/10.3389/fcvm.2022.804801.

Distefano, A., L. Orlando, S. Giallongo, et al. 2024. "Fish Oil Containing Pro-Resolving Mediators Enhances the Antioxidant System and Ameliorates LPS-Induced Inflammation in Human Bronchial Epithelial Cells." *Pharmaceuticals (Basel)* 17: 1066. https://doi.org/10.3390/ph17081066.

Dolinsky, V. W., S. Chakrabarti, T. J. Pereira, et al. 2013. "Resveratrol Prevents Hypertension and Cardiac Hypertrophy in Hypertensive Rats and Mice." *Biochimica et Biophysica Acta* 1832: 1723–1733. https://doi.org/10.1016/j.bbadis.2013.05.018.

Dong, X., S. Liu, L. Zhang, et al. 2015. "Downregulation of miR-21 Is Involved in Direct Actions of Ursolic Acid on the Heart: Implications for Cardiac Fibrosis and Hypertrophy." *Cardiovascular Therapeutics* 33: 161–167. https://doi.org/10.1111/1755-5922.12125.

Dyck, G. J. B., P. Raj, S. Zieroth, J. R. B. Dyck, and J. A. Ezekowitz. 2019. "The Effects of Resveratrol in Patients With Cardiovascular Disease and Heart Failure: A Narrative Review." *International Journal of Molecular Sciences* 20: 904. https://doi.org/10.3390/ijms20040904.

Dzupina, A., D. Pella, P. Zenuch, et al. 2024. "The Role of Omega-3 Polyunsaturated Fatty Acids in Patients With Metabolic Syndrome and Endothelial Dysfunction." *Medicina (Kaunas, Lithuania)* 61: 43. https://doi.org/10.3390/medicina61010043.

Ebrahimzadeh, A., S. Mohseni, M. Safargar, et al. 2024. "Curcumin Effects on Glycaemic Indices, Lipid Profile, Blood Pressure, Inflammatory Markers and Anthropometric Measurements of Non-Alcoholic Fatty Liver Disease Patients: A Systematic Review and Meta-Analysis of Randomized Clinical Trials." *Complementary Therapies in Medicine* 80: 103025. https://doi.org/10.1016/j.ctim.2024.103025.

EFSA. "Guidance on Scientific Principles and Data Requirements for the Safety and Relative Bioavailability Assessment of New Micronutrient Sources." Accessed March 21, 2025. https://www.efsa.europa.eu/en/efsajournal/pub/8946.

Enayati, A., M. Banach, T. Jamialahmadi, and A. Sahebkar. 2022. "Protective Role of Nutraceuticals Against Myocarditis." *Biomedicine & Pharmacotherapy* 146: 112242. https://doi.org/10.1016/j.biopha.2021.112242.

n.d. "ESC Guidelines for the Management of Atrial Fibrillation." Accessed April 23, 2025. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation.

European Medicines Agency (EMA). "Orthosiphonis Folium—Herbal Medicinal Product." Accessed April 24, 2026. https://www.ema.europa.eu/en/medicines/herbal/orthosiphonis-folium.

Fan, S., Y. Hu, Y. You, et al. 2022. "Role of Resveratrol in Inhibiting Pathological Cardiac Remodeling." *Frontiers in Pharmacology* 13: 924473. https://doi.org/10.3389/fphar.2022.924473.

Fassett, R. G., and J. S. Coombes. 2009. "Astaxanthin, Oxidative Stress, Inflammation and Cardiovascular Disease." *Future Cardiology* 5: 333–342. https://doi.org/10.2217/fca.09.19.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Feng, X., A. Sureda, S. Jafari, et al. 2019. "Berberine in Cardiovascular and Metabolic Diseases: From Mechanisms to Therapeutics." *Theranostics* 9: 1923–1951. https://doi.org/10.7150/thno.30787.

Feng, Y., Y. Ren, X. Zhang, et al. 2024. "Metabolites of Traditional Chinese Medicine Targeting PI3K/AKT Signaling Pathway for Hypoglycemic Effect in Type 2 Diabetes." *Frontiers in Pharmacology* 15: 1373711. https://doi.org/10.3389/fphar.2024.1373711.

Ferreira, J. P., B. Pitt, and F. Zannad. 2024. "Mineralocorticoid Receptor Antagonists in Heart Failure: An Update." *Circulation. Heart Failure* 17: e011629. https://doi.org/10.1161/CIRCHEARTFAILURE.124.011629.

Fonseka, O., S. R. Gare, X. Chen, et al. 2025. "Molecular Mechanisms Underlying Heart Failure and Their Therapeutic Potential." *Cells* 14: 324. https://doi.org/10.3390/cells14050324.

Frumuzachi, O., L. I. Gavrilaș, D. C. Vodnar, S. Rohn, and A. Mocan. 2024. "Systemic Health Effects of Oleuropein and Hydroxytyrosol Supplementation: A Systematic Review of Randomized Controlled Trials." *Antioxidants* 13: 1040. https://doi.org/10.3390/antiox13091040.

Gal, R., L. Deres, K. Toth, R. Halmosi, and T. Habon. 2021. "The Effect of Resveratrol on the Cardiovascular System From Molecular Mechanisms to Clinical Results." *International Journal of Molecular Sciences* 22: 10152. https://doi.org/10.3390/ijms221810152.

Gál, R., R. Halmosi, F. Gallyas, et al. 2023. "Resveratrol and Beyond: The Effect of Natural Polyphenols on the Cardiovascular System: A Narrative Review." *Biomedicine* 11: 2888. https://doi.org/10.3390/biomedicines11112888.

Galvão Cândido, F., F. Xavier Valente, L. E. da Silva, O. Gonçalves Leão Coelho, M. d. C. Gouveia Peluzio, and R. d. C. Gonçalves Alfenas. 2018. "Consumption of Extra Virgin Olive Oil Improves Body Composition and Blood Pressure in Women With Excess Body Fat: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial." *European Journal of Nutrition* 57: 2445–2455. https://doi.org/10.1007/s00394-017-1517-9.

Gao, K., D. Xu, F. Mu, et al. 2024. "Systems Pharmacology to Explore the Potential Mechanism of Ginseng Against Heart Failure." *Rejuvenation Research* 28: 54–66. https://doi.org/10.1089/rej.2024.0051.

van Gelder, I. C., M. Rienstra, K. V. Bunting, et al. 2024. "2024 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With the European Association for Cardio-Thoracic Surgery (EACTS): Developed by the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC), With the Special Contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO)." *European Heart Journal* 45, no. 36: 3314–3414. https://doi.org/10.1093/eurheartj/ehae176.

George, E. S., S. Marshall, H. L. Mayr, et al. 2019. "The Effect of High-Polyphenol Extra Virgin Olive Oil on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis." *Critical Reviews in Food Science and Nutrition* 59: 2772–2795. https://doi.org/10.1080/10408398.2018.1470491.

Gimbun, J., S. F. Pang, and M. M. Yusoff. 2019. "*Orthosiphon stamineus* (Java Tea)." In *Nonvitamin and Nonmineral Nutritional Supplements*, edited by S. M. Nabavi and A. S. Silva, 327–333. Academic Press.

Goto, K. 2024. "Chapter 2—Polyphenols: A Promising Nutritional Strategy for the Prevention and Treatment of Hypertension." In *Studies in Natural Products Chemistry*, edited by Atta-Ur Rahman, vol. 80, 15–54. Elsevier.

Gunasekaran, M., and D. Chamundeeswari. 2025. "Exploring Herbal Diuretics in Chronic Kidney Disease and Hypertension: Dandelion and *Hibiscus sabdariffa*'s Roles." In *Case Studies on Holistic Medical Interventions*. CRC Press.

Gutiérrez, S., S. L. Svahn, and M. E. Johansson. 2019. "Effects of Omega-3 Fatty Acids on Immune Cells." *International Journal of Molecular Sciences* 20: 5028. https://doi.org/10.3390/ijms20205028.

Haftcheshmeh, S. M., M. Abedi, K. Mashayekhi, et al. 2022. "Berberine as a Natural Modulator of Inflammatory Signaling Pathways in the Immune System: Focus on NF-κB, JAK/STAT, and MAPK Signaling Pathways." *Phytotherapy Research* 36: 1216–1230. https://doi.org/10.1002/ptr.7407.

Hao, F., X. Deng, X. Yu, et al. 2024. "Taraxacum: A Review of Ethnopharmacology, Phytochemistry and Pharmacological Activity." *American Journal of Chinese Medicine* 52: 183–215. https://doi.org/10.1142/S0192415X24500083.

Harris, W. S. 2007. "Omega-3 Fatty Acids and Cardiovascular Disease: A Case for Omega-3 Index as a New Risk Factor." *Pharmacological Research* 55: 217–223. https://doi.org/10.1016/j.phrs.2007.01.013.

Harris, W. S., N. L. Tintle, M. R. Etherton, and R. S. Vasan. 2018. "Erythrocyte Long-Chain Omega-3 Fatty Acid Levels Are Inversely Associated With Mortality and With Incident Cardiovascular Disease: The Framingham Heart Study." *Journal of Clinical Lipidology* 12: 718–727.e6. https://doi.org/10.1016/j.jacl.2018.02.010.

Hartnett, S., and B. Dawn. 2023. "Renin Angiotensin System Inhibitors in Heart Failure With Reduced Ejection Fraction: Clinical Evidence and Considerations for Use." In *The Renin Angiotensin System in Cardiovascular Disease*, edited by N. S. Dhalla, S. K. Bhullar, and A. K. Shah, 331–347. Springer International Publishing.

Hashemizadeh, T., A. Pedarzadeh, A. Naghedi, F. Dorri Mashhadi, J. Zavvar Reza, and F. Safari. 2019. "Resveratrol Suppresses Cardiac Renin Angiotensin System in the Late Phase of Left Ventricular Hypertrophy." *Research Journal of Pharmacognosy* 6: 25–37. https://doi.org/10.22127/rjp.2019.84316.

He, Z., L. Yang, J. Tian, K. Yang, J. Wu, and Y. Yao. 2013. "Efficacy and Safety of Omega-3 Fatty Acids for the Prevention of Atrial Fibrillation: A Meta-Analysis." *Canadian Journal of Cardiology* 29: 196–203. https://doi.org/10.1016/j.cjca.2012.03.019.

Heidenreich, P. A., B. Bozkurt, D. Aguilar, et al. 2022. "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." *Circulation* 145: e895–e1032. https://doi.org/10.1161/CIR.0000000000001063.

Herrera-Arellano, A., S. Flores-Romero, M. A. Chávez-Soto, and J. Tortoriello. 2004. "Effectiveness and Tolerability of a Standardized Extract From *Hibiscus sabdariffa* in Patients With Mild to Moderate Hypertension: A Controlled and Randomized Clinical Trial." *Phytomedicine* 11: 375–382. https://doi.org/10.1016/j.phymed.2004.04.001.

Hindricks, G., T. Potpara, N. Dagres, et al. 2021. "2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration With the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed With the Special Contribution of the European Heart Rhythm Association (EHRA) of the ESC." *European Heart Journal* 42: 373–498. https://doi.org/10.1093/eurheartj/ehaa612.

Hjalmarson, A., and B. Fagerberg. 2000. "MERIT-HF Mortality and Morbidity Data." *Basic Research in Cardiology* 95, no. Suppl 1: I98–I103. https://doi.org/10.1007/s003950070017.

Holubarsch, C. J. F., W. S. Colucci, and J. Eha. 2018. "Benefit-Risk Assessment of Crataegus Extract WS 1442: An Evidence-Based Review." *American Journal of Cardiovascular Drugs* 18: 25–36. https://doi.org/10.1007/s40256-017-0249-9.

Holubarsch, C. J. F., W. S. Colucci, T. Meinertz, W. Gaus, M. Tendera, and Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in CHF (SPICE Trial Study Group). 2008. "The Efficacy and Safety of Crataegus Extract WS 1442 in Patients With Heart Failure: The SPICE Trial." *European Journal of Heart Failure* 10: 1255–1263. https://doi.org/10.1016/j.ejheart.2008.10.004.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Hore, S. K., S. Choudhury, A. H. Ahmad, and S. K. Garg. 2013. "*Withania somnifera* Ameliorates Lead-Induced Augmentation of Adrenergic Response in Rat Portal Vein." *Indian Journal Of Pharmacology* 45: 563–568. https://doi.org/10.4103/0253-7613.121365.

Hsiao, Y.-W., Y.-N. Tsai, Y.-T. Huang, et al. 2021. "Rhodiola Crenulata Reduces Ventricular Arrhythmia Through Mitigating the Activation of IL-17 and Inhibiting the MAPK Signaling Pathway." *Cardiovascular Drugs and Therapy* 35: 889–900. https://doi.org/10.1007/s10557-020-07072-z.

Hsu, C.-L., B.-H. Hong, Y.-S. Yu, and G.-C. Yen. 2010. "Antioxidant and Anti-Inflammatory Effects of Orthosiphon Aristatus and Its Bioactive Compounds." *Journal of Agricultural and Food Chemistry* 58: 2150–2156. https://doi.org/10.1021/jf903557c.

Hsu, S.-W., T.-C. Chang, Y.-K. Wu, K.-T. Lin, L.-S. Shi, and S.-Y. Lee. 2017. "Rhodiola Crenulata Extract Counteracts the Effect of Hypobaric Hypoxia in Rat Heart via Redirection of the Nitric Oxide and Arginase 1 Pathway." *BMC Complementary and Alternative Medicine* 17: 29. https://doi.org/10.1186/s12906-016-1524-z.

Hussain, Y., H. Khan, G. Alotaibi, et al. 2022. "How Curcumin Targets Inflammatory Mediators in Diabetes: Therapeutic Insights and Possible Solutions." *Molecules* 27: 4058. https://doi.org/10.3390/molecules27134058.

Ito, R., N. Satoh-Asahara, H. Yamakage, et al. 2014. "An Increase in the EPA/AA Ratio Is Associated With Improved Arterial Stiffness in Obese Patients With Dyslipidemia." *Journal of Atherosclerosis and Thrombosis* 21: 248–260. https://doi.org/10.5551/jat.19976.

Ivanova Stojcheva, E., and J. C. Quintela. 2022. "The Effectiveness of *Rhodiola rosea* L. Preparations in Alleviating Various Aspects of Life-Stress Symptoms and Stress-Induced Conditions—Encouraging Clinical Evidence." *Molecules* 27: 3902. https://doi.org/10.3390/molecules27123902.

Jalalyazdi, M., J. Ramezani, A. Izadi-Moud, F. Madani-Sani, S. Shahlaei, and S. S. Ghiasi. 2019. "Effect of *Hibiscus sabdariffa* on Blood Pressure in Patients With Stage 1 Hypertension." *Journal of Advanced Pharmaceutical Technology & Research* 10: 107–111. https://doi.org/10.4103/japtr.JAPTR_402_18.

Jia, Z., G. Zou, Y. Xie, et al. 2024. "Pharmacokinetic-Pharmacodynamic Correlation Analysis of Rhodiola Crenulata in Rats With Myocardial Ischemia." *Pharmaceuticals* 17: 595. https://doi.org/10.3390/ph17050595.

Jump, D. B., C. M. Depner, and S. Tripathy. 2012. "Omega-3 Fatty Acid Supplementation and Cardiovascular Disease." *Journal of Lipid Research* 53: 2525–2545. https://doi.org/10.1194/jlr.R027904.

Kalusalingam, A., D. N. Hasnu, A. Khan, et al. 2024. "An Updated Review of Ethnobotany, Ethnopharmacology, Phytochemistry and Pharmacological Activities of Orthosiphon Stamineus Benth." *Malaysian Applied Biology* 53: 1–18. https://doi.org/10.55230/mabjournal.v53i1.2774.

Kato, T., T. Kasai, A. Sato, et al. 2020. "Effects of 3-Month Astaxanthin Supplementation on Cardiac Function in Heart Failure Patients With Left Ventricular Systolic Dysfunction-A Pilot Study." *Nutrients* 12: 1896. https://doi.org/10.3390/nu12061896.

Katragadda, S., and R. R. Arora. 2010. "Role of Angiotensin-Converting Enzyme Inhibitors in Vascular Modulation: Beyond the Hypertensive Effects." *American Journal of Therapeutics* 17: e11–e23. https://doi.org/10.1097/MJT.0b013e31815addd9.

Khalil, M. I., I. Ahmmed, R. Ahmed, et al. 2015. "Amelioration of Isoproterenol-Induced Oxidative Damage in Rat Myocardium by *Withania somnifera* Leaf Extract." *BioMed Research International* 2015: 624159. https://doi.org/10.1155/2015/624159.

Khan, M. S., M. S. Khan, A. Moustafa, A. S. Anderson, R. Mehta, and S. S. Khan. 2020. "Efficacy and Safety of Mineralocorticoid Receptor Antagonists in Patients With Heart Failure and Chronic Kidney Disease." *American Journal of Cardiology* 125: 643–650. https://doi.org/10.1016/j.amjcard.2019.11.014.

Khan, S. U., A. N. Lone, M. S. Khan, et al. 2021. "Effect of Omega-3 Fatty Acids on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis." *EClinicalMedicine* 38: 100997. https://doi.org/10.1016/j.eclinm.2021.100997.

Khodir, S. A., E. Sweed, M. Gadallah, and A. Shabaan. 2022. "Astaxanthin Attenuates Cardiovascular Dysfunction Associated With Deoxycorticosterone Acetate-Salt-Induced Hypertension in Rats." *Clinical and Experimental Hypertension* 44: 382–395. https://doi.org/10.1080/10641963.2022.2055764.

Kim, E. N., M. Y. Kim, J. H. Lim, et al. 2018. "The Protective Effect of Resveratrol on Vascular Aging by Modulation of the Renin-Angiotensin System." *Atherosclerosis* 270: 123–131. https://doi.org/10.1016/j.atherosclerosis.2018.01.043.

Kim, J.-H. 2012. "Cardiovascular Diseases and *Panax ginseng*: A Review on Molecular Mechanisms and Medical Applications." *Journal of Ginseng Research* 36: 16–26. https://doi.org/10.5142/jgr.2012.36.1.16.

Kim, S. H., K. W. Kang, K. W. Kim, and N. D. Kim. 2000. "Procyanidins in Crataegus Extract Evoke Endothelium-Dependent Vasorelaxation in Rat Aorta." *Life Sciences* 67: 121–131. https://doi.org/10.1016/s0024-3205(00)00608-1.

Klein, C., T. Sato, M. M. Meguid, and G. Miyata. 2000. "From Food to Nutritional Support to Specific Nutraceuticals: A Journey Across Time in the Treatment of Disease." *Journal of Gastroenterology* 35, no. Suppl 12: 1–6.

Kotecha, D., and J. P. Piccini. 2015. "Atrial Fibrillation in Heart Failure: What Should we Do?" *European Heart Journal* 36: 3250–3257. https://doi.org/10.1093/eurheartj/ehv513.

Krestinin, R., M. Kobyakova, Y. Baburina, L. Sotnikova, and O. Krestinina. 2024. "Astaxanthin Protects Against H_2O_2- and Doxorubicin-Induced Cardiotoxicity in H9c2 Rat Myocardial Cells." *Life* 14: 1409. https://doi.org/10.3390/life14111409.

Krestinina, O., Y. Baburina, and R. Krestinin. 2021. "Mitochondrion as a Target of Astaxanthin Therapy in Heart Failure." *International Journal of Molecular Sciences* 22: 7964. https://doi.org/10.3390/ijms22157964.

Kroon, P. A., A. Iyer, P. Chunduri, V. Chan, and L. Brown. 2010. "The Cardiovascular Nutrapharmacology of Resveratrol: Pharmacokinetics, Molecular Mechanisms and Therapeutic Potential." *Current Medicinal Chemistry* 17: 2442–2455. https://doi.org/10.2174/092986710791556032.

Krum, H. 2015. "Prospective Comparison of ARNi With ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF)." *Circulation* 131: 11–12. https://doi.org/10.1161/CIRCULATIONAHA.114.013887.

Lee, Y., J. H. Kim, and J.-K. Park. 2024. "Self-Rated Health and the Risk of Incident Atrial Fibrillation in General Population." *Scientific Reports* 14: 24651. https://doi.org/10.1038/s41598-024-76426-6.

Lee, Y.-M., and Y. Kim. 2024. "Is Curcumin Intake Really Effective for Chronic Inflammatory Metabolic Disease? A Review of Meta-Analyses of Randomized Controlled Trials." *Nutrients* 16: 1728. https://doi.org/10.3390/nu16111728.

Li, D. Y., Z. Wang, X. Jia, et al. 2021. "Loop Diuretics Inhibit Renal Excretion of Trimethylamine *N*-Oxide." *JACC: Basic to Translational Science* 6: 103–115. https://doi.org/10.1016/j.jacbts.2020.11.010.

Li, F., Y. Takahashi, and K. Yamaki. 2013. "Inhibitory Effect of Catechin-Related Compounds on Renin Activity." *Biomedical Research* 34: 167–171. https://doi.org/10.2220/biomedres.34.167.

Liu, D., H. Zhao, Y. Zhang, J. Hu, and H. Xu. 2025. "Efficacy and Safety of Berberine on the Components of Metabolic Syndrome: A Systematic

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Review and Meta-Analysis of Randomized Placebo-Controlled Trials." *Frontiers in Pharmacology* 16: 1572197. https://doi.org/10.3389/fphar.2025.1572197.

Liu, K., Y. Zhu, W. Gao, et al. 2024. "Resveratrol Alleviates Heart Failure by Activating Foxo3a to Counteract Oxidative Stress and Apoptosis." *Biomedicine & Pharmacotherapy* 181: 117716. https://doi.org/10.1016/j.biopha.2024.117716.

Liu, L., X. Yang, Y. Liao, C. Wang, and Y. Wang. 2022. "Resveratrol Alleviates Ang II-Induced Vascular Smooth Muscle Cell Senescence by Upregulating E2F1/SOD2 Axis." *Toxicology Research* 11: 831–840. https://doi.org/10.1093/toxres/tfac051.

Lopaschuk, G. D., and S. Verma. 2020. "Mechanisms of Cardiovascular Benefits of Sodium Glucose co-Transporter 2 (SGLT2) Inhibitors." *JACC Basic Transl Sci* 5: 632–644. https://doi.org/10.1016/j.jacbts.2020.02.004.

Lu, M., L. Zhang, J. Pan, H. Shi, M. Zhang, and C. Li. 2023. "Advances in the Study of the Vascular Protective Effects and Molecular Mechanisms of Hawthorn (*Crataegus anamesa* Sarg.) Extracts in Cardiovascular Diseases." *Food & Function* 14: 5870–5890. https://doi.org/10.1039/D3FO01688A.

Ma, E., C. Wu, J. Chen, et al. 2023. "Resveratrol Prevents Ang II-Induced Cardiac Hypertrophy by Inhibition of NF-κB Signaling." *Biomedicine & Pharmacotherapy* 165: 115275. https://doi.org/10.1016/j.biopha.2023.115275.

Magdy, J. S., J. McVeigh, and P. Indraratna. 2022. "Diuretics in the Management of Chronic Heart Failure: When and How." *Australian Prescriber* 45: 200–204. https://doi.org/10.18773/austprescr.2022.069.

Mahmoud, D. S. E., M. A. Kamel, I. E.-T. El-Sayed, et al. 2024. "Astaxanthin Ameliorated Isoproterenol Induced Myocardial Infarction via Improving the Mitochondrial Function and Antioxidant Activity in Rats." *Journal of Biochemical and Molecular Toxicology* 38: e23804. https://doi.org/10.1002/jbt.23804.

Maitra, U., C. Stephen, and L. M. Ciesla. 2022. "Drug Discovery From Natural Products—Old Problems and Novel Solutions for the Treatment of Neurodegenerative Diseases." *Journal of Pharmaceutical and Biomedical Analysis* 210: 114553. https://doi.org/10.1016/j.jpba.2021.114553.

Majid, A., F. O. Hassan, M. M. Hoque, J. O. Gbadegoye, and D. Lebeche. 2023. "Bioactive Compounds and Cardiac Fibrosis: Current Insight and Future Prospect." *Journal of Cardiovascular Development and Disease* 10: 313. https://doi.org/10.3390/jcdd10070313.

Maliha, A., M. Tahsin, T. Z. Fabia, S. M. Rahman, and M. M. Rahman. 2024. "Pro-Resolving Metabolites: Future of the Fish Oil Supplements." *Journal of Functional Foods* 121: 106439. https://doi.org/10.1016/j.jff.2024.106439.

Manolis, A. A., T. A. Manolis, and A. S. Manolis. 2025. "Current Strategies for Atrial Fibrillation Prevention and Management: Taming the Commonest Cardiac Arrhythmia." *Current Vascular Pharmacology* 23: 31–44. https://doi.org/10.2174/0115701611317504240910113003.

Manson, J. E., N. R. Cook, I.-M. Lee, et al. 2019. "Marine N-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer." *New England Journal of Medicine* 380: 23–32. https://doi.org/10.1056/NEJMoa1811403.

Martínez-González, M. Á., E. Toledo, F. Arós, et al. 2014. "Extravirgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation." *Circulation* 130: 18–26. https://doi.org/10.1161/CIRCULATIONAHA.113.006921.

Martín-Peláez, S., O. Castañer, V. Konstantinidou, et al. 2017. "Effect of Olive Oil Phenolic Compounds on the Expression of Blood Pressure-Related Genes in Healthy Individuals." *European Journal of Nutrition* 56: 663–670. https://doi.org/10.1007/s00394-015-1110-z.

Mattioli, L. B., I. Corazza, R. Budriesi, et al. 2024. "From Waste to Health: Olive Mill Wastewater for Cardiovascular Disease Prevention." *Nutrients* 16: 2986. https://doi.org/10.3390/nu16172986.

Mattioli, L. B., M. Frosini, R. Amoroso, et al. 2022. "Olea Europea L. Leaves and Hibiscus Sabdariffa L. Petals Extracts: Herbal Mix From Cardiovascular Network Target to Gut Motility Dysfunction Application." *Nutrients* 14: 463. https://doi.org/10.3390/nu14030463.

Mattioli, L. B., M. Frosini, I. Corazza, et al. 2024. "Long COVID-19 Gastrointestinal Related Disorders and Traditional Chinese Medicine: A Network Target-Based Approach." *Phytotherapy Research* 38: 2323–2346. https://doi.org/10.1002/ptr.8163.

McDonagh, T. A., M. Metra, M. Adamo, et al. 2021. "2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure." *European Heart Journal* 42: 3599–3726. https://doi.org/10.1093/eurheartj/ehab368.

McKay, D. L., C. Y. O. Chen, E. Saltzman, and J. B. Blumberg. 2010. "*Hibiscus sabdariffa* L. Tea (Tisane) Lowers Blood Pressure in Prehypertensive and Mildly Hypertensive Adults." *Journal of Nutrition* 140: 298–303. https://doi.org/10.3945/jn.109.115097.

McMurray, J. 2022. "Angiotensin Receptor Blockers and Angiotensin Receptor–Neprilysin Inhibitors." In *Oxford Textbook of Heart Failure*, edited by A. L. Clark, R. S. Gardner, T. A. McDonagh, A. L. Clark, R. S. Gardner, and T. A. McDonagh. Oxford University Press.

McMurray, J. J. V., S. D. Solomon, S. E. Inzucchi, et al. 2019. "Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction." *New England Journal of Medicine* 381: 1995–2008. https://doi.org/10.1056/NEJMoa1911303.

Medina-Remón, A., R. Estruch, A. Tresserra-Rimbau, A. Vallverdú-Queralt, and R. M. Lamuela-Raventos. 2013. "The Effect of Polyphenol Consumption on Blood Pressure." *Mini Reviews in Medicinal Chemistry* 13: 1137–1149. https://doi.org/10.2174/1389557511313080002.

Menezes-Rodrigues, F. S., P. R. Errante, E. A. Araújo, et al. 2021. "Cardioprotection Stimulated by Resveratrol and Grape Products Prevents Lethal Cardiac Arrhythmias in an Animal Model of Ischemia and Reperfusion." *Acta Cirúrgica Brasileira* 36: e360306. https://doi.org/10.1590/ACB360306.

MERIT-HF Study Group. 1999. "Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)." *Lancet* 353: 2001–2007. https://doi.org/10.1016/S0140-6736(99)04440-2.

Mnafgui, K., R. Hajji, F. Derbali, et al. 2016. "Protective Effect of Hydroxytyrosol Against Cardiac Remodeling After Isoproterenol-Induced Myocardial Infarction in Rat." *Cardiovascular Toxicology* 16: 147–155. https://doi.org/10.1007/s12012-015-9323-1.

Mo, L., S. Wan, T. Zékány-Nagy, X. Luo, and X. Yang. 2025. "The Effect of Curcumin on Glucolipid Metabolic Disorders: A Review." *Food Reviews International* 41: 543–577. https://doi.org/10.1080/87559129.2024.2405654.

Mohanty, I., D. S. Arya, A. Dinda, K. K. Talwar, S. Joshi, and S. K. Gupta. 2004. "Mechanisms of Cardioprotective Effect of *Withania somnifera* in Experimentally Induced Myocardial Infarction." *Basic & Clinical Pharmacology & Toxicology* 94: 184–190. https://doi.org/10.1111/j.1742-7843.2004.pto940405.x.

Mohd Sabri, N. A., S.-K. Lee, D. D. Murugan, and W. C. Ling. 2022. "Epigallocatechin Gallate (EGCG) Alleviates Vascular Dysfunction in Angiotensin II-Infused Hypertensive Mice by Modulating Oxidative Stress and eNOS." *Scientific Reports* 12: 17633. https://doi.org/10.1038/s41598-022-21107-5.

Murray, C., A. Aravkin, P. Zheng, et al. 2020. "Global Burden of 87 Risk Factors in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019." *Lancet* 396:

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

1223–1249. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30752-2/fulltext.

Newell, J., J. Nithura, J. Isaac, et al. 2023. "Clinical Application and Trials With Nutraceuticals." In *Nutraceuticals for Alzheimer's Disease: A Promising Therapeutic Approach*, edited by A. J. Thenmozhi and T. Manivasagam, 287–317. Springer Nature.

Nishida, Y., A. Nawaz, K. Hecht, and K. Tobe. 2021. "Astaxanthin as a Novel Mitochondrial Regulator: A New Aspect of Carotenoids, Beyond Antioxidants." *Nutrients* 14: 107. https://doi.org/10.3390/nu14010107.

Numata, G., and E. Takimoto. 2022. "Cyclic GMP and PKG Signaling in Heart Failure." *Frontiers in Pharmacology* 13: 792798. https://doi.org/10.3389/fphar.2022.792798.

Nwachukwu, D. C., E. Aneke, N. Z. Nwachukwu, L. F. O. Obika, U. I. Nwagha, and A. A. Eze. 2015. "Effect of *Hibiscus sabdariffa* on Blood Pressure and Electrolyte Profile of Mild to Moderate Hypertensive Nigerians: A Comparative Study With Hydrochlorothiazide." *Nigerian Journal of Clinical Practice* 18: 762–770. https://doi.org/10.4103/1119-3077.163278.

Ojeda, D., E. Jiménez-Ferrer, A. Zamilpa, A. Herrera-Arellano, J. Tortoriello, and L. Alvarez. 2010. "Inhibition of Angiotensin Converting Enzyme (ACE) Activity by the Anthocyanins Delphinidin- and Cyanidin-3-O-Sambubiosides From *Hibiscus sabdariffa*." *Journal of Ethnopharmacology* 127: 7–10. https://doi.org/10.1016/j.jep.2009.09.059.

Oliver, E., F. Mayor Jr., and P. D'Ocon. 2019. "Beta-Blockers: Historical Perspective and Mechanisms of Action." *Revista Española de Cardiología (English Edition)* 72: 853–862. https://doi.org/10.1016/j.rec.2019.04.006.

Orhan, I. E. 2018. "Phytochemical and Pharmacological Activity Profile of *Crataegus oxyacantha* L. (Hawthorn): A Cardiotonic Herb." *Current Medicinal Chemistry* 25: 4854–4865. https://doi.org/10.2174/0929867323666160919095519.

Pacinella, G., A. M. Ciaccio, and A. Tuttolomondo. 2022. "Endothelial Dysfunction and Chronic Inflammation: The Cornerstones of Vascular Alterations in Age-Related Diseases." *International Journal of Molecular Sciences* 23: 15722. https://doi.org/10.3390/ijms232415722.

Packer, M., S. D. Anker, J. Butler, et al. 2020. "Cardiovascular and Renal Outcomes With Empagliflozin in Heart Failure." *New England Journal of Medicine* 383: 1413–1424. https://doi.org/10.1056/NEJMoa2022190.

Pahlavan, S., M. S. Tousi, M. Ayyari, et al. 2018. "Effects of Hawthorn (*Crataegus pentagyna*) Leaf Extract on Electrophysiologic Properties of Cardiomyocytes Derived From Human Cardiac Arrhythmia-Specific Induced Pluripotent Stem Cells." *FASEB Journal* 32: 1440–1451. https://doi.org/10.1096/fj.201700494RR.

Pallavi, S., K. Vinod, K. Noopur, et al. 2022. "Cardiovascular Diseases and Nutraceuticals: Underlying Mechanism and Therapeutic Biomarkers." In *Advancements in Cardiovascular Research and Therapeutics: Molecular and Nutraceutical Perspectives*, 1–24. Bentham Science Publishers.

Pan, X., K. Zhang, C. Shen, X. Wang, L. Wang, and Y.-Y. Huang. 2020. "Astaxanthin Promotes M2 Macrophages and Attenuates Cardiac Remodeling After Myocardial Infarction by Suppression Inflammation in Rats." *Chinese Medical Journal* 133: 1786–1797. https://doi.org/10.1097/CM9.0000000000000814.

Parn, K. W., W. C. Ling, J. H. Chin, and S.-K. Lee. 2022. "Safety and Efficacy of Dietary Epigallocatechin Gallate Supplementation in Attenuating Hypertension via Its Modulatory Activities on the Intrarenal Renin-Angiotensin System in Spontaneously Hypertensive Rats." *Nutrients* 14: 4605. https://doi.org/10.3390/nu14214605.

Pereira, C. P. M., A. C. R. Souza, A. R. Vasconcelos, P. S. Prado, and J. J. Name. 2021. "Antioxidant and Anti-Inflammatory Mechanisms of Action of Astaxanthin in Cardiovascular Diseases (Review)." *International Journal of Molecular Medicine* 47: 37–48. https://doi.org/10.3892/ijmm.2020.4783.

Prata, C., C. Zalambani, F. Rossi, et al. 2025. "Nutrients and Nutraceuticals From *Vitis vinifera* L. Pomace: Biological Activities, Valorization, and Potential Applications." *Nutrients* 17: 583. https://doi.org/10.3390/nu17030583.

Puri, V., M. Nagpal, I. Singh, et al. 2022. "A Comprehensive Review on Nutraceuticals: Therapy Support and Formulation Challenges." *Nutrients* 14: 4637. https://doi.org/10.3390/nu14214637.

Qu, X., Z. Zhang, W. Hu, et al. 2020. "Attenuation of the Na/K-ATPase/Src/ROS Amplification Signaling Pathway by Astaxanthin Ameliorates Myocardial Cell Oxidative Stress Injury." *Molecular Medicine Reports* 22: 5125–5134. https://doi.org/10.3892/mmr.2020.11613.

Radhiga, T., S. Senthil, A. Sundaresan, and K. V. Pugalendi. 2019. "Ursolic Acid Modulates MMPs, Collagen-I, α-SMA, and TGF-β Expression in Isoproterenol-Induced Myocardial Infarction in Rats." *Human & Experimental Toxicology* 38: 785–793. https://doi.org/10.1177/0960327119842620.

Rafiee, S., M. Bagherniya, G. Askari, T. Sathyapalan, T. Jamialahmadi, and A. Sahebkar. 2021. "The Effect of Curcumin in Improving Lipid Profile in Patients With Cardiovascular Risk Factors: A Systematic Review of Clinical Trials." *Advances in Experimental Medicine and Biology* 1291: 165–177. https://doi.org/10.1007/978-3-030-56153-6_10.

Raj, P., B. M. Aloud, X. L. Louis, L. Yu, S. Zieroth, and T. Netticadan. 2016. "Resveratrol Is Equipotent to Perindopril in Attenuating Post-Infarct Cardiac Remodeling and Contractile Dysfunction in Rats." *Journal of Nutritional Biochemistry* 28: 155–163. https://doi.org/10.1016/j.jnutbio.2015.09.025.

Raj, P., S. J. Thandapilly, J. Wigle, S. Zieroth, and T. Netticadan. 2021. "A Comprehensive Analysis of the Efficacy of Resveratrol in Atherosclerotic Cardiovascular Disease, Myocardial Infarction and Heart Failure." *Molecules* 26: 6600. https://doi.org/10.3390/molecules26216600.

Restini, C. B. A., A. F. E. Garcia, H. M. Natalin, et al. 2022. "Resveratrol Supplants Captopril's Protective Effect on Cardiac Remodeling in a Hypertension Model Elicited by Renal Artery Stenosis." *Yale Journal of Biology and Medicine* 95: 57–69.

Roudi, H. S., R. Safaei, M. M. Dabbaghi, et al. 2025. "Mechanistic Insights on Cardioprotective Properties of Ursolic Acid: Regulation of Mitochondrial and Non-Mitochondrial Pathways." *Current Pharmaceutical Design* 31: 1037–1056. https://doi.org/10.2174/0113816128344497241120025757.

Salehi, B., A. P. Mishra, M. Nigam, et al. 2018. "Resveratrol: A Double-Edged Sword in Health Benefits." *Biomedicine* 6: 91. https://doi.org/10.3390/biomedicines6030091.

Salem, M. A., S. M. Ezzat, K. A. Ahmed, S. Alseekh, A. R. Fernie, and R. M. Essam. 2022. "A Comparative Study of the Antihypertensive and Cardioprotective Potentials of Hot and Cold Aqueous Extracts of *Hibiscus sabdariffa* L. in Relation to Their Metabolic Profiles." *Frontiers in Pharmacology* 13: 840478. https://doi.org/10.3389/fphar.2022.840478.

Sanou, A., K. Konaté, L. Belemnaba, et al. 2024. "In Vivo Diuretic Activity and Anti-Hypertensive Potential of *Hibiscus sabdariffa* Extract by Inhibition of Angiotensin-Converting Enzyme and Hypertension Precursor Enzymes." *Foods* 13: 534. https://doi.org/10.3390/foods13040534.

Santhanakrishnan, R., N. Wang, M. G. Larson, et al. 2016. "Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction." *Circulation* 133: 484–492. https://doi.org/10.1161/CIRCULATIONAHA.115.018614.

Sarapis, K., E. S. George, W. Marx, et al. 2022. "Extra Virgin Olive Oil High in Polyphenols Improves Antioxidant Status in Adults: A Double-Blind, Randomized, Controlled, Cross-Over Study (OLIVAUS)." *European Journal of Nutrition* 61: 1073–1086. https://doi.org/10.1007/s00394-021-02712-y.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Sarapis, K., C. J. Thomas, J. Hoskin, et al. 2020. "The Effect of High Polyphenol Extra Virgin Olive Oil on Blood Pressure and Arterial Stiffness in Healthy Australian Adults: A Randomized, Controlled, Cross-Over Study." *Nutrients* 12: 2272. https://doi.org/10.3390/nu12082272.

Satoh, N., A. Shimatsu, K. Kotani, et al. 2009. "Highly Purified Eicosapentaenoic Acid Reduces Cardio-Ankle Vascular Index in Association With Decreased Serum Amyloid A-LDL in Metabolic Syndrome." *Hypertension Research* 32: 1004–1008. https://doi.org/10.1038/hr.2009.145.

Schurtz, G., N. Mewton, G. Lemesle, et al. 2023. "Beta-Blocker Management in Patients Admitted for Acute Heart Failure and Reduced Ejection Fraction: A Review and Expert Consensus Opinion." *Frontiers in Cardiovascular Medicine* 10: 1263482. https://doi.org/10.3389/fcvm.2023.1263482.

Sherratt, S. C. R., P. Libby, H. Dawoud, D. L. Bhatt, and R. P. Mason. 2024. "Eicosapentaenoic Acid Improves Endothelial Nitric Oxide Bioavailability via Changes in Protein Expression During Inflammation." *Journal of the American Heart Association* 13: e034076. https://doi.org/10.1161/JAHA.123.034076.

Smith, S. J., A. L. Lopresti, and T. J. Fairchild. 2023. "Exploring the Efficacy and Safety of a Novel Standardized Ashwagandha (*Withania somnifera*) Root Extract (Witholytin) in Adults Experiencing High Stress and Fatigue in a Randomized, Double-Blind, Placebo-Controlled Trial." *Journal of Psychopharmacology* 37: 1091–1104. https://doi.org/10.1177/02698811231200023.

Soltan, F., M. Esmaili Dahej, M. Yadegari, A. Moradi, Z. Hafizi Barjin, and F. Safari. 2021. "Resveratrol Confers Protection Against Ischemia/Reperfusion Injury by Increase of Angiotensin (1-7) Expression in a Rat Model of Myocardial Hypertrophy." *Journal of Cardiovascular Pharmacology* 78: e55–e64. https://doi.org/10.1097/FJC.0000000000001035.

Soltani, D., B. Azizi, R. Rahimi, A. H. Talasaz, H. Rezaeizadeh, and A. Vasheghani-Farahani. 2022. "Mechanism-Based Targeting of Cardiac Arrhythmias by Phytochemicals and Medicinal Herbs: A Comprehensive Review of Preclinical and Clinical Evidence." *Frontiers in Cardiovascular Medicine* 9: 990063. https://doi.org/10.3389/fcvm.2022.990063.

Sosnowska, B., P. Penson, and M. Banach. 2017. "The Role of Nutraceuticals in the Prevention of Cardiovascular Disease." *Cardiovascular Diagnosis and Therapy* 7: S21–S31. https://doi.org/10.21037/cdt.2017.03.20.

Speers, A. B., K. A. Cabey, A. Soumyanath, and K. M. Wright. 2021. "Effects of *Withania somnifera* (Ashwagandha) on Stress and the Stress- Related Neuropsychiatric Disorders Anxiety, Depression, and Insomnia." *Current Neuropharmacology* 19: 1468–1495. https://doi.org/10.2174/1570159X19666210712151556.

Stange, D., L. Kriston, A. von Wolff, M. Baehr, and D. C. Dartsch. 2013. "Reducing Cardiovascular Medication Complexity in a German University Hospital: Effects of a Structured Pharmaceutical Management Intervention on Adherence." *Journal of Managed Care Pharmacy* 19: 396–407. https://doi.org/10.18553/jmcp.2013.19.5.396.

Suri, S. S., and S. V. Pamboukian. 2021. "Optimal Diuretic Strategies in Heart Failure." *Annals of Translational Medicine* 9: 517. https://doi.org/10.21037/atm-20-4600.

Szikora, Z., R. O. Mátyus, B. V. Szabó, D. Csupor, and B. Tóth. 2025. "Hawthorn (Crataegus spp.) Clinically Significantly Reduces Blood Pressure in Hypertension: A Meta-Analysis of Randomized Placebo-Controlled Clinical Trials." *Pharmaceuticals (Basel)* 18: 1027. https://doi.org/10.3390/ph18071027.

Sztretye, M., B. Dienes, M. Gönczi, et al. 2019. "Astaxanthin: A Potential Mitochondrial-Targeted Antioxidant Treatment in Diseases and With Aging." *Oxidative Medicine and Cellular Longevity* 2019: 3849692. https://doi.org/10.1155/2019/3849692.

Takagaki, A., and F. Nanjo. 2015. "Effects of Metabolites Produced From (−)-Epigallocatechin Gallate by Rat Intestinal Bacteria on Angiotensin I-Converting Enzyme Activity and Blood Pressure in Spontaneously Hypertensive Rats." *Journal of Agricultural and Food Chemistry* 63: 8262–8266. https://doi.org/10.1021/acs.jafc.5b03676.

Takaki, A., S. Umemoto, K. Ono, et al. 2011. "Add-On Therapy of EPA Reduces Oxidative Stress and Inhibits the Progression of Aortic Stiffness in Patients With Coronary Artery Disease and Statin Therapy: A Randomized Controlled Study." *Journal of Atherosclerosis and Thrombosis* 18: 857–866. https://doi.org/10.5551/jat.7260.

Tang, M.-M., S.-T. Zhao, R.-Q. Li, and W. Hou. 2023. "Therapeutic Mechanisms of Ginseng in Coronary Heart Disease." *Frontiers in Pharmacology* 14: 1271029. https://doi.org/10.3389/fphar.2023.1271029.

Tassell, M. C., R. Kingston, D. Gilroy, M. Lehane, and A. Furey. 2010. "Hawthorn (Crataegus Spp.) in the Treatment of Cardiovascular Disease." *Pharmacognosy Reviews* 4: 32–41. https://doi.org/10.4103/0973-7847.65324.

Tisdale, J. E., M. K. Chung, K. B. Campbell, et al. 2020. "Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association." *Circulation* 142: e214–e233. https://doi.org/10.1161/CIR.0000000000000905.

Tiwari, S., S. K. Gupta, and A. K. Pathak. 2021. "A Double-Blind, Randomized, Placebo-Controlled Trial on the Effect of Ashwagandha (*Withania somnifera* Dunal.) Root Extract in Improving Cardiorespiratory Endurance and Recovery in Healthy Athletic Adults." *Journal of Ethnopharmacology* 272: 113929. https://doi.org/10.1016/j.jep.2021.113929.

Tomasoni, D., G. C. Fonarow, M. Adamo, et al. 2022. "Sodium–Glucose co-Transporter 2 Inhibitors as an Early, First-Line Therapy in Patients With Heart Failure and Reduced Ejection Fraction." *European Journal of Heart Failure* 24: 431–441. https://doi.org/10.1002/ejhf.2397.

Tousoulis, D., A. Plastiras, G. Siasos, et al. 2014. "Omega-3 PUFAs Improved Endothelial Function and Arterial Stiffness With a Parallel Antiinflammatory Effect in Adults With Metabolic Syndrome." *Atherosclerosis* 232: 10–16. https://doi.org/10.1016/j.atherosclerosis.2013.10.014.

Vazquez, A., E. Sanchez-Rodriguez, F. Vargas, et al. 2019. "Cardioprotective Effect of a Virgin Olive Oil Enriched With Bioactive Compounds in Spontaneously Hypertensive Rats." *Nutrients* 11: 1728. https://doi.org/10.3390/nu11081728.

Velayutham, P., A. Babu, and D. Liu. 2008. "Green Tea Catechins and Cardiovascular Health: An Update." *Current Medicinal Chemistry* 15: 1840–1850.

Venskutonis, P. R. 2018. "Phytochemical Composition and Bioactivities of Hawthorn (*Crataegus* spp.): Review of Recent Research Advances." *Journal of Food Bioactives* 4: 69–87. https://doi.org/10.31665/JFB.2018.4163.

Vettorazzi, A., A. López de Cerain, J. Sanz-Serrano, A. G. Gil, and A. Azqueta. 2020. "European Regulatory Framework and Safety Assessment of Food-Related Bioactive Compounds." *Nutrients* 12: 613. https://doi.org/10.3390/nu12030613.

Vizzardi, E., V. Regazzoni, G. Caretta, et al. 2014. "Mineralocorticoid Receptor Antagonist in Heart Failure: Past, Present and Future Perspectives." *International Journal of Cardiology-Heart & Vessels* 3: 6–14. https://doi.org/10.1016/j.ijchv.2014.03.005.

von Schacky, C. 2012. "Omega-3 Fatty Acids: Anti-Arrhythmic, Pro-Arrhythmic, or Both?" *Frontiers in Physiology* 3: 88. https://doi.org/10.3389/fphys.2012.00088.

Walker, A. F., G. Marakis, A. P. Morris, and P. A. Robinson. 2002. "Promising Hypotensive Effect of Hawthorn Extract: A Randomized Double-Blind Pilot Study of Mild, Essential Hypertension." *Phytotherapy Research* 16: 48–54. https://doi.org/10.1002/ptr.947.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Wan, L. F., Z. J. Yuan, and H. Chen. 2022. "Tea Polyphenols Regulate Renin-Angiotensin-Aldosterone System and Transforming Growth Factor-β1/Smads Signaling Pathway in Heart Failure Rats." *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 44: 384–391. https://doi.org/10.3881/j.issn.1000-503X.14385.

Wang, L. F., W. J. Li, X. Y. Zhang, et al. 2024. "Resveratrol Prevents Age-Related Heart Impairment Through Inhibiting the Notch/NF-κB Pathway." *Food Science & Nutrition* 12: 1035–1045. https://doi.org/10.1002/fsn3.3817.

Wang, X.-T., Y. Gong, B. Zhou, et al. 2018. "Ursolic Acid Ameliorates Oxidative Stress, Inflammation and Fibrosis in Diabetic Cardiomyopathy Rats." *Biomedicine & Pharmacotherapy* 97: 1461–1467. https://doi.org/10.1016/j.biopha.2017.11.032.

WHO's Team. 2025. "Cardiovascular Diseases (CVDs)," Accessed September 19, 2025. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

Wiciński, M., A. Fajkiel-Madajczyk, Z. Kurant, et al. 2024. "Ashwagandha's Multifaceted Effects on Human Health: Impact on Vascular Endothelium, Inflammation, Lipid Metabolism, and Cardiovascular Outcomes-A Review." *Nutrients* 16: 2481. https://doi.org/10.3390/nu16152481.

Wróbel-Nowicka, K., C. Wojciechowska, W. Jacheć, M. Zalewska, and E. Romuk. 2024. "The Role of Oxidative Stress and Inflammatory Parameters in Heart Failure." *Medicina (Kaunas, Lithuania)* 60: 760. https://doi.org/10.3390/medicina60050760.

Wu, M., L. Liu, Y. Xing, S. Yang, H. Li, and Y. Cao. 2020. "Roles and Mechanisms of Hawthorn and Its Extracts on Atherosclerosis: A Review." *Frontiers in Pharmacology* 11: 118. https://doi.org/10.3389/fphar.2020.00118.

Wyss, C., P. W. Gündling, and K. Kostev. 2024. "Real World Effectiveness of Hawthorn Special Extract WS 1442 in a Retrospective Cohort Study From Germany." *Scientific Reports* 14: 22986. https://doi.org/10.1038/s41598-024-74325-4.

Xie, C., Y. Zhang, B. Zhu, L. Yang, J. Ren, and N. Lang. 2024. "Exploring the Pathways of Drug Repurposing and *Panax ginseng* Treatment Mechanisms in Chronic Heart Failure: A Disease Module Analysis Perspective." *Scientific Reports* 14: 12109. https://doi.org/10.1038/s41598-024-61926-2.

Xu, L.-L., H.-X. Su, P.-B. Li, and H.-H. Li. 2023. "Ursolic Acid Ameliorates Myocardial Ischaemia/Reperfusion Injury by Improving Mitochondrial Function via Immunoproteasome-PP2A-AMPK Signalling." *Nutrients* 15: 1049. https://doi.org/10.3390/nu15041049.

Yamagata, K. 2020. "Chapter 7—Effects of Dietary n-3 Polyunsaturated Fatty Acids on Cardiovascular Disease." In *Studies in Natural Products Chemistry*, edited by Atta-Ur-Rahman, vol. 64, 217–240. Bioactive Natural Products, Elsevier.

Yin, J., H. Xing, and J. Ye. 2008. "Efficacy of Berberine in Patients With Type 2 Diabetes." *Metabolism* 57: 712–717. https://doi.org/10.1016/j.metabol.2008.01.013.

Youssef, F. M., H. Ateyya, A. E. Hanna Samy, and E. M. Elmokadem. 2025. "The Anti-Inflammatory and Antioxidant Effects of Astaxanthin as an Adjunctive Therapy in Community-Acquired Pneumonia: A Randomized Controlled Trial." *Frontiers in Pharmacology* 16: 1621308. https://doi.org/10.3389/fphar.2025.1621308.

Yu, D., Z. Tang, B. Li, et al. 2021. "Resveratrol Against Cardiac Fibrosis: Research Progress in Experimental Animal Models." *Molecules* 26: 6860. https://doi.org/10.3390/molecules26226860.

Zamanian, M. Y., H. O. Alsaab, M. Golmohammadi, et al. 2024. "NF-κB Pathway as a Molecular Target for Curcumin in Diabetes Mellitus Treatment: Focusing on Oxidative Stress and Inflammation." *Cell Biochemistry and Function* 42: e4030. https://doi.org/10.1002/cbf.4030.

Zhang, K., H. Zhuo, J. Guo, W. Wang, and R. Dai. 2024. "Astaxanthin Alleviates the Process of Cardiac Hypertrophy by Targeting the METTL3/Circ_0078450/MiR-338-3p/GATA4 Pathway." *International Heart Journal* 65: 119–127. https://doi.org/10.1536/ihj.23-423.

Zhang, Q., L. Hu, L. Chen, et al. 2018. "(−)-Epigallocatechin-3-Gallate, the Major Green Tea Catechin, Regulates the Desensitization of B1 Adrenoceptor via GRK2 in Experimental Heart Failure." *Inflammopharmacol* 26: 1081–1091. https://doi.org/10.1007/s10787-017-0429-x.

Zhang, X., M. Xu, S. Cai, B. Chen, H. Lin, and Z. Liu. 2023. "Effects of Astaxanthin on microRNA Expression in a Rat Cardiomyocyte Anoxia-Reoxygenation Model." *Frontiers in Pharmacology* 14: 1103971. https://doi.org/10.3389/fphar.2023.1103971.

Zhao, X., K.-P. Zhang, T. Huang, et al. 2014. "The Rescuable Function and Mechanism of Resveratrol on As_2O_3-Induced hERG K^+ Channel Deficiency." *Naunyn-Schmiedeberg's Archives of Pharmacology* 387: 1079–1089. https://doi.org/10.1007/s00210-014-1019-8.

Zhou, Z., M. Li, Z. Zhang, et al. 2024. "Overview of Panax Ginseng and Its Active Ingredients Protective Mechanism on Cardiovascular Diseases." *Journal of Ethnopharmacology* 334: 118506. https://doi.org/10.1016/j.jep.2024.118506.

Zhu, Y., M. Chen, L. Xie, Y. Pan, Y. Yang, and G. Wan. 2024. "Mechanism Exploration of Astaxanthin in the Treatment of Adriamycin-Induced Cardiotoxicity Based on Network Pharmacology and Experimental Validation." *Current Medicinal Chemistry* 31: 3652–3670. https://doi.org/10.2174/0109298673329567241014071914.

Zi-chang, N., H. Xiao-ling, J. Qi, L. Ting, O. Ming-hui, and M. Hao-ping. 2024. "Ginseng Radix et Rhizoma Enhanced the Effect of Metoprolol in Chronic Heart Failure by Inhibiting Autophagy in Male C57BL/6J Mice." *PLoS One* 19: e0301875. https://doi.org/10.1371/journal.pone.0301875.

10991573, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.70433 by Area Sistemi Dipart & Doc, Wiley Online Library on [01/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License