

Review

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Review

Exploring the Impact of Plant-Derived Antioxidants on Heart Aging: A Mechanistic outlook

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Abstract: Heart aging involves a complex interplay of genetic and environmental influences, leading to a gradual deterioration of cardiovascular integrity and function. Age-related physiological changes, including ventricular hypertrophy, diastolic dysfunction, myocardial fibrosis, increased arterial stiffness, and endothelial dysfunction, are influenced by key mechanisms like autophagy, inflammation, and oxidative stress. This review aims to explore the therapeutic potential of plant-derived bioactive antioxidants in mitigating heart aging. These compounds, often rich in polyphenols, flavonoids, and other phytochemicals, exhibit notable antioxidant, anti-inflammatory, and cardioprotective properties. Through a comprehensive analysis of preclinical and clinical studies, this work highlights the mechanisms associated with heart aging and the promising effects of plant-derived antioxidants. The findings may be helpful for researchers in identifying specific molecules with therapeutic and preventive potential for cardiovascular aging.

Keywords: cardiac aging; cardiac alterations; antioxidants; mechanism; reactive oxygen species

1. Introduction

There is a growing interest in the field of medicine and aging research about the effects of plant-derived antioxidants on heart aging. The aging global population underscores the need of understanding cardiac aging mechanisms and exploring novel treatment techniques. Recent studies have concentrated on the potential of plant-based antioxidants to enhance cardiovascular health and mitigate the effects of heart aging [1,2]. The risk of CVDs, including heart failure, peripheral vascular disease, coronary heart disease, and stroke, is well recognized to increase with age [3]. Heart aging leads to alterations in cardiac structure and function, lowering the threshold for CVDs. With the projected increase in the aged population, nearly 50% of adult Americans are expected to have CVDs by 2030, causing a greater burden of CVDs [4]. The foremost cause of mortality in United States CVDs, are considerably increased by the aging process. A significant proportion of cardiovascular disease-related fatalities and cases (485.6 million) were attributed to adults aged 75 years and above on a global scale [5,6]. Over 40% of all fatalities in China are ascribed to CVD, becoming it the principal cause of mortality; also, China has largest elderly population (aged 65 and above) in the world [7,8]. The exponential and steady growth of this demographic has presented formidable obstacles in the realm of CVD prevention and management [9,10]. In the past, the main focus of efforts to reduce the risk of CVDs has been on controlling the known risk factors, which include hypertension, hyperglycemia, hyperlipidemia, and elevated circulating triglycerides.

Novel approaches to the problem of CVDs have been developed in recent preclinical studies. Restricting calories has been shown to reliably increase longevity in experimental model animals [11]. Calories restriction mimetic and other pharmaceutical interventions have been developed to delay the onset of age-related diseases, which are leading causes of mortality and morbidity due to their impact on the heart and blood circulation [12]. Notable advancements in the field of aging studies have contributed to a better comprehension of the fundamental processes involved in aging and have shown that biological aging is adaptive [13]. When it comes to the majority of persistent diseases that cause functional decline and loss of independence, like dementia, type 2 diabetes, CVDs, and cancer, age is a key risk factor (Figure 1). Due to the substantial increase in the older adult population, projected to reach 12.6% in North America and 12% globally by 2030, it is expected that this percentage will continue to increase [14,15].

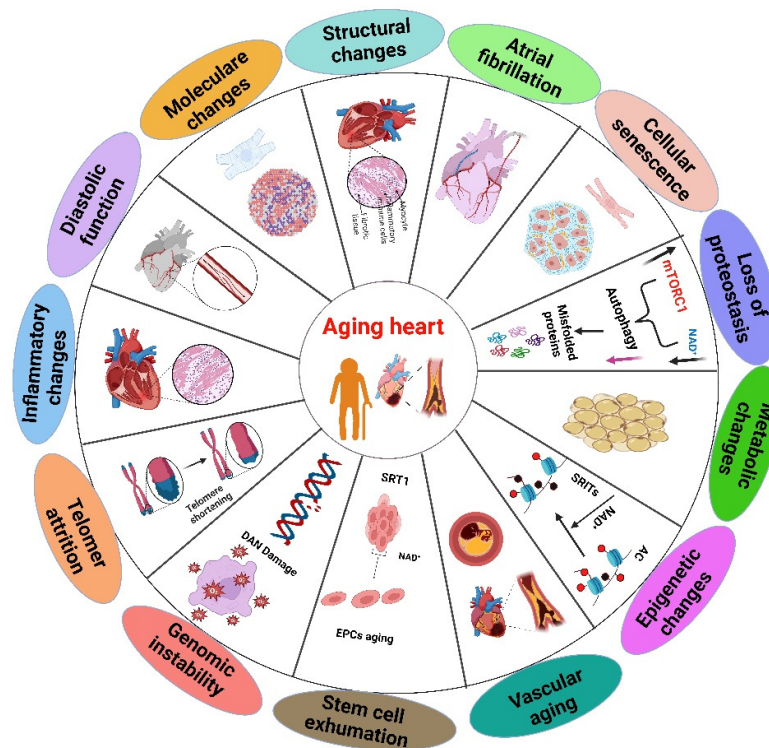


Figure 1. Multiple aspects of the aging heart. Displaying distinct sections and thorough summary of the biochemical and physiological alterations that occur in the heart aging.

2. Cardiac Alterations Related to Heart Aging

The process of aging encompasses alterations in the intricate regulatory interactions between cells, organs, and systems [16]. Cardiac and smooth muscle cells are involved in the involuntary regulation of heart and vascular activities [17]. The cardiovascular regulation relies on the integrity, excitability, conductivity, contractility, and flexibility of these cells. Cellular aging has been linked to the gradual decline in the physiological activity of cardiomyocytes and vascular smooth muscle cells [18]. Aging leads to structural changes in the cardiovascular system, which can impair the function and flexibility of the heart and blood vessels [19]. In humans, cardiac aging is associated with an enlargement of left ventricle, development of fibrosis, and impaired ability of the heart to relax during diastole, leading to reduced filling of the heart and decreased ejection fraction [19,20]. The precise mechanisms remain poorly understood, studies suggest that demise of cardiac myocytes is a crucial factor, (cardiomyocyte apoptosis) and increased stiffness of blood vessels are associated with the structural and functional changes that occur with aging [21,22]. Age significantly increases the susceptibility to numerous diseases. The heart is predisposed to numerous detrimental structural and

functional alterations as a result of aging (Figure 2), this is the main CVD risk factor. In general, the elderly population surpasses 65 years of age at which HF is most prevalent [23].

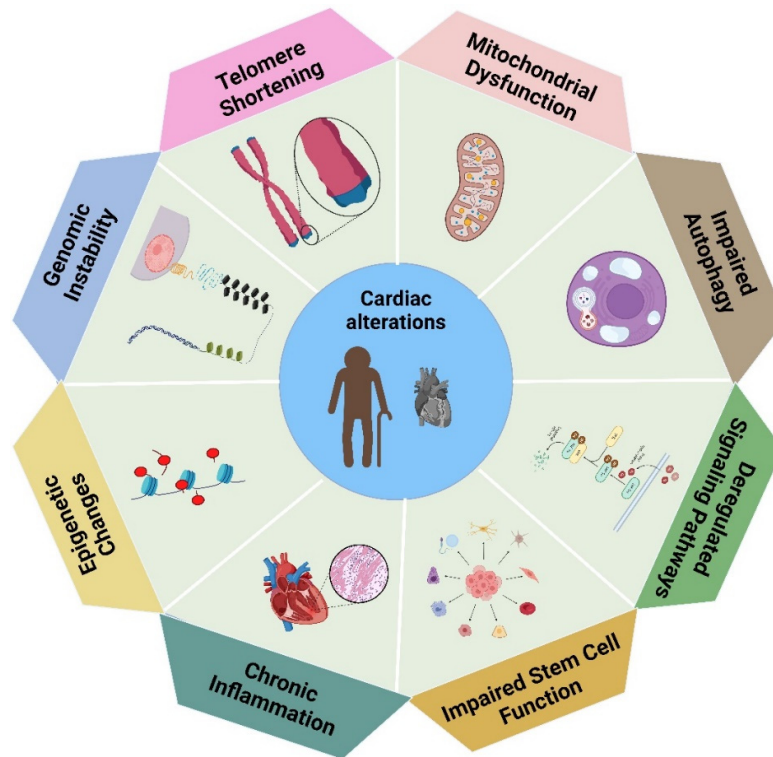


Figure 2. The biological variables associated with cardiac modifications. Each element indicating a distinct contributor to changes in heart function.

Additionally, the functional anomalies of the aged myocardium arise from both structural modifications and cellular and molecular changes. Cardiac aging is influenced by various molecular processes such as cardiac hypertrophy is a characteristic feature of the aging process in the heart [24]. The heart undergoes hypertrophy as it ages, leading to changes in nutrient and growth signaling [25]. The *Rapamycin's mechanistic target (mTOR)* [26], and *insulin-like growth factor-1 (IGF-1)* are two significant signaling pathways that have an involvement in heart hypertrophy and aging [27]. The *mTOR* governs cellular development and has been demonstrated to be a significant regulator of the aging process and diseases associated with aging [28]. Enhanced *mTOR* signaling hinders whereas diminished *mTOR* signaling enhances resilience to cardiac aging in mice models [29]. In animal models, the *insulin/IGF-1* signaling pathway is essential for controlling longevity deficiency in this signaling pathway in mice leads to a decrease in age-related dysfunction of cardiomyocytes [30]. The decline in *IGF-1* levels associated with aging increases the heart failure risk in individuals [31]. The functional damage caused by dysfunctional mitochondria can shorten life expectancy by impairing cellular and organ function [32]. Age-related diseases increase in mitochondrial ROS production result in enlarged, bloated, and damaged mitochondria [33,34]. In the heart, mitochondrial function is regulated by *PGC-1 α* , also known as peroxisome proliferator-activated receptor coactivator [35].

Cardiac dysfunction results from the repression of its expression in failing hearts [36]. By directly harming cellular macromolecules and interfering with regular signaling and energetics, mitochondrial malfunction and aberrant ROS generation accelerate the aging process [37]. The ECM, a conglomeration of proteins located outside cells, offers structural and metabolic support to neighboring cells [38]. Cardiac fibroblasts are the main producers of ECM proteins, such as collagen, elastin, fibronectin, laminin, and fibrinogen [39]. Heart stiffness increases when there is an abundance of ECM deposited on the heart and is responsible for diastolic dysfunction [40]. MMPs, TIMPs, and

other proteases regulate the production and breakdown of ECM proteins [41]. Aging hearts exhibit myocardial fibrosis and dysregulation of ECM protein production and breakdown. Profibrotic factors, such as transforming growth factor- β , stimulate the production of ECM proteins and hinder the breakdown of the matrix by MMPs [40,42]. The regulation of MMPs and TIMPs varies depending on aging, however, their precise roles in cardiac aging are inadequately understood [43].

The process of heart aging causes microscopic alterations, such as rise in the thickness of inner layer of blood vessels (intima) and the buildup of collagen. The symptoms are defined by increased systolic blood pressure and pulse wave velocity, along with an augmentation of pulse pressure. These symptoms are characterized by elevated systolic blood pressure and pulse wave velocity, together with an expansion of the pulse pressure [44,45]. Left ventricular hypertrophy (LVH) may arise as a consequence of increased afterload and wall stress brought on by arterial stiffness. The volume of the myocardium remains constant with age in the heart [46]. Within the age range of 30 to 70 years, research indicates that around 35% of the total myocytes in the ventricle are lost [47]. In order to counteract the loss of cells, the surviving myocytes experience hypertrophy, which is accompanied by an increase in the nonmyocyte compartment. While the exact cause of cell death remains uncertain, it is seen that a decrease in capillary density occurs as a result of aging, which leads to ischemia injury [48]. Mouse models are typically employed for studying cardiac aging because they accurately reproduce the characteristics of human cardiac aging [49]. Another benefit of utilizing mouse models to research the molecular underpinnings of heart aging is their relatively short lifespan and the accessibility of genetically engineered animals [50]. Laboratory mice do not exhibit elevated blood pressure or adverse cholesterol and blood glucose levels, allowing researchers to study the natural heart aging process without additional cardiac complications [51]. The echocardiogram conducted on a mouse model revealed phenotypic alterations such as elevated left ventricular mass, impaired diastolic function, and deteriorated myocardial performance index (MPI), resembling the aging process of the human heart [52].

3. Oxidative Stress

Oxidative stress significantly contributes to aging and the development of degenerative and chronic diseases by binding to transition metal ions, including autoimmune disorders, inflammation, cancer, arthritis, neurodegenerative diseases, and cardiovascular issues [53]. It causes various health problems by triggering abnormalities [54]. When the ability of antioxidants to counteract pro-oxidant compounds is exceeded, oxidative stress occurs, leading to disruptions in biological signaling and pathological events, particularly in older adults [55]. Antioxidants are vital for the body's defense against oxidation, as they help prevent the formation of free radicals and minimize cellular damage [56,57]. Non-enzymatic substances found in blood plasma, such as transferrin, ferritin, ceruloplasmin, and albumin, act as preventive antioxidants through attaching itself to ions of transition metals, thereby inhibiting the formation of new reactive species [58]. These non-enzymatic antioxidants provide an intermediate defense, neutralizing oxidants and radicals [59]. The third line of defense focuses on repairing damage and removing harmful substances, facilitating the regeneration of bio-molecules affected by oxidative stress [60]. ROS and the body's antioxidant defenses are out of balance, which leads to oxidative stress, resulting from both external and internal sources. Exogenous sources of pollution include environmental pollution, tobacco smoke, ionizing radiation, household chemicals, and agricultural chemicals like herbicides as well as insecticides [61]. Within the body, ROS are generated by mitochondria, cytochrome P450 enzymes linked to the endoplasmic reticulum, membrane-bound NADPH oxidases (NOX 1-5), and peroxisomes [62]. ROS, including both free and non-free radicals, are mostly produced in regions of elevated oxygen consumption such as mitochondria, peroxisomes, and the endoplasmic reticulum [63,64]. This imbalance linked to a number of diseases, such as heart conditions, since oxidative stress may harm DNA, lipids, and proteins [65].

The mechanism for producing ROS is oxidative phosphorylation, which entails the transfer of electrons from NADH and FADH via four mitochondrial enzymes, culminating in the synthesis of ATP from ADP [66]. Electrons lost during this process generate superoxide radicals, resulting in

functional degradation of tissues and damage to macromolecules. Superoxide and nitric oxide may react to form *peroxynitrite*, a strong oxidant that penetrates membranes and nitrates numerous enzymes. It may also be converted into hydrogen peroxide via superoxide dismutase, generating a highly reactive radical known as hydroxyl radical [67,68]. ROS derived from mitochondria contribute significantly to vascular dysfunction by downregulating *Nrf2*, decreasing NO bioavailability, and increasing the production of vasoconstrictor molecules [69]. This sequence of occurrences results in the disruption of the mitochondrial membrane, releasing pro-apoptotic factors, resulting in the apoptosis of plaque cells and inflammation [70]. Furthermore, ROS generated by NADPH oxidases during inflammatory reactions are essential for the endogenous production of free radicals [71]. Individuals with a genetic deficit in *NOX2* suffer chronic granulomatous disease, rendering them vulnerable to common infections [72]. A baseline level of ROS is necessary for maintaining cellular homeostasis; however, excessive ROS can damage cellular macromolecules and are linked to aging and cardiovascular diseases [73]. Improved endothelial vasodilation following the inhibition of NADPH oxidase with apocynin suggests that endothelial dysfunction is mediated by NADPH oxidation [74].

3.1. Mitochondrial Dysfunction

Mitochondria are double-membraned organelles featuring a circular genome known as mitochondrial DNA (mtDNA) [75]. Among the many important tasks they perform is the synthesis of ATP, regulation of nutrient metabolism, calcium homeostasis, and programmed cell death [76]. Mitochondria, located in the cytoplasm of eukaryotic cells, function as dynamic networks that perpetually engage in synthesis, fusion, fission, and destruction (mitophagy). Their proper functioning is vital in high energy tissues like the heart, where cardiomyocytes depend on ATP for their activity [77]. In mature cardiomyocytes, mitochondria produce 95% of the ATP the heart needs and make up over one-third of the intracellular volume [70]. Dysfunctional cardiac mitochondria have been identified as a major factor in cardiovascular diseases, leading to decreased ATP production, increased production of ROS, increased cell apoptosis, and disrupted mitochondrial dynamics [78]. An essential part of the whole cellular ROS generation process is the activity of mitochondria, originating from the reduction of oxygen [79,80]. These ROS can subsequently be converted into H_2O_2 , which influences the redox state of proteins [81]. The generation of mtROS is specific to certain sites and varies depending on the stimuli [82]. Electrons derived from substrates can reduce O_2 to $O_2^{\bullet-}$ at eight distinct mitochondrial sites, with complex I (CI) and complex III (CIII) being the most significant [83]. Rotenone, an inhibitor of CI, increases $O_2^{\bullet-}$ production at CI, potentially increasing in mitochondria with lower energy production, elevated ΔpH , higher CoQ ratio, or high NADH-to-NAD⁺ ratio, causing $O_2^{\bullet-}$ to leak into the mitochondrial matrix [84,85].

Mitochondria possess a complex network of ROS scavenging systems that help regulate oxidative stress resulting from mitochondrial ROS [86]. These systems include SODs, which convert superoxide radicals into hydrogen peroxide, which is then detoxified by catalase, *GSH-PX*, and the peroxiredoxin/thioredoxin (PRX/Trx) system [87,88]. SODs serve as the primary defense against mitochondrial ROS, with three isoforms (SOD1, SOD2, and SOD3) managing ROS levels in specific compartments [89]. Whereas SOD2 is found in the mitochondrial matrix, SOD1 is mostly present in the cytosol and has also been identified in the mitochondrial intermembrane gap [90]. Proper regulation of the localization and activity of SOD1 and SOD2 is essential for effective mitochondrial ROS scavenging [91].

Mitochondrial ROS are essential for cardiac tissue, comprising 45% of the heart's cellular volume [92]. ROS may activate TFs for instance *NF- κ B* as well as *AP-1*, hence facilitating an inflammatory process in tissues [93,94]. Pinpointing the underlying cause of this dysfunction is difficult because of the interconnected nature of various processes [95]. Aging-related mitochondrial dysfunction impacts cells through several simultaneous factors, including elevated mitochondrial ROS production, irregular assembly and recycling of mitochondria, alterations in the quality and quantity of mitochondrial DNA, and changes in the substrates related to mitochondrial respiration [96]. These molecular indicators are particularly evident in aged cardiovascular cells.

3.2. Inflammation

The cardiac aging process is defined by key features such as progressive hypertrophy of cardiomyocytes, cardiac fibrosis, and inflammation [24]. Hypertrophied cardiomyocytes contribute to a hypoxic environment, which produces an abundance of free radicals that may damage cellular constituents [97]. In response to this stress, cardiomyocytes release pro-inflammatory cytokines and chemokines, initiating an immunological response and augmenting the population of macrophages in the left ventricle [98,99]. Due to the poor rate of proliferation of mature cardiomyocytes, damaged areas are replaced with fibrotic scar tissue, ultimately leading to organ failure [100]. The production of ROS increases with age due to various factors, including physical, chemical, and biological agents, resulting in endothelial dysfunction and cellular damage [101,102]. When free radicals are produced excessively or uncontrollably, they can trigger an inflammatory response, this is integral to the aging process [82]. Atherosclerosis, heart problems, diabetes, and other age-related diseases are linked to persistent low-grade inflammation [103,104]. The causes of this syndrome include stress and continuous antigen exposure, leading to a diminished ability to manage stressors and a gradual rise in pro-inflammatory activity [105]. The term “inflammaging” refers to the increased inflammatory response that accompanies aging, resulting in a persistent low-grade systemic pro-inflammatory condition [106].

Aging is marked by alterations in the immune, hormonal, and adipose systems, which result in a chronic inflammatory state [107]. This can lead to issues such as frailty, cognitive decline, and various cardiovascular, neurological, and vascular events [108]. Despite its negative associations, inflammation is crucial for sustaining life and maintaining individual integrity [109,110]. An inflammatory state arises when pro-inflammatory compounds exceed anti-inflammatory controls [111]. The origins of this low-grade inflammatory process are still under discussion, but one theory posits that ongoing stimulation of the immune system drives a pro-inflammatory shift [112]. Typically, aging brings about a gradual dysregulation of the immune response, particularly affecting cellular and adaptive immunity, especially T cell function [113]. The persistent inflammatory condition that elderly people experience is largely caused by this imbalance [114]. The causes are likely multifactorial, involving chronic stimulation from viruses, bacteria, and endogenous cellular factors, along with ongoing activation of the immune system's defenses [115].

4. Mechanism of Plant-Derived Antioxidants on Heart Aging

The potential therapeutic benefits of plant-derived antioxidants on aging heart and other areas of health have received increasing attention in recent years. This interest stems from the extensive pharmacological properties of several plant chemicals, which have been investigated for their ability to slow down aging and its impact on the cardiovascular system. Naturally occurring plant-based products are essential for treating and preventing diseases linked to cardiac aging [116]. For many years, natural plant-based products have been employed as active ingredients in conventional medicine [117]. Various natural compounds obtained from plants provide a diverse array of biological and pharmacological attributes that are crucial in modern pharmacotherapy [118]. Among these goods is the anticancer medication *paclitaxel*, which is made from *Taxus brevifolia* [119]; the anticancer drugs *vincristine* and *vinblastine*, which are derived from *catharanthus roseus* [120]; the anticancer drug *camptothecin*, which is de-rived from *camptotheca acuminata* [121]; and the anticancer drug quercetin, a polyphenol present in a variety of vegetables and fruits [122].

Plants are thought to not need some nutrients, such as phytochemicals or secondary plant components like polyphenols [123]. They belong to a large family of compounds found in plants and algae, and their primary function is to shield the organism from UV rays, diseases, and herbivore consumption [124]. Polyphenols possess a variety of structural forms, ranging from simple monomers to intricate polymerized structures [125]. Seaweed polyphenols able to reduce chronic inflammation [126], oxidative stress [127], hyperglycemia, hyperlipidemia, metabolic abnormalities associated with CVDs, and the aftereffects of diabetes [128]. Recent research on marine macroalgae has shown that plant-derived polyphenols can improve health outcomes, including reducing the risk of obesity, diabetes, and cardiovascular disease [129]. Polyphenols are notable secondary metabolites

generated from plants that have notable benefits against cancer, cardiovascular diseases, diabetes, and neurological disorders [130]. Various plant species, such as *dipteryx odorata*, *hierochloe odorata*, *galium odoratum*, *dichanthelium clandestinum*, *verbascum spp.*, and *anthoxanthum odoratum*, comprise a range of substances, including as tannins, lignins, coumarins, flavonoids, and phenicic acid [131]. Resveratrol, with its antioxidant properties, has been shown to improve inflammation, cancer, aging, obesity, diabetes, and provide cardio-protective and neurological benefits [132,133]. The benefits of antioxidative therapy are increasingly acknowledged as a means of lowering ROS in the vascular and, consequently, decreasing their deleterious consequences [134]. In addition to their antihypertensive effects, ACE blockers decrease circulation Ang II also have detoxifying properties [135]. In this sense, statins, or cholesterol-lowering medications, are used to control HMG CoA reductase in addition to their cholesterol-lowering effects [136]. In order to reduce oxidative damage, vitamins E and C are often used as dietary supplements in addition to other medications [137]. Conversely, polyphenols are drawing interest as potential therapeutic agents to lower oxidative stress and shield individuals from heart disease [138]. Polyphenols are the most common antioxidant in the diet, consumed ten times more frequently than water-soluble vitamin C and one hundred times more frequently than lipid-soluble vitamin E and carotenoids [139]. This review study describes the most extensively studied plant-based antioxidants that have been identified.

4.1. Resveratrol

It has been shown that the naturally occurring polyphenol molecule resveratrol, which is present in a variety of plants, may help maintain cardiovascular health and delay the aging process (Figure 3). A wide variety of plant species, including groundnuts and grapes, contain resveratrol, a naturally occurring stilbene [140]. Future studies suggest that resveratrol may be a potential chemopreventive drug due to its ability to inhibit polyphenolic cyclooxygenase. It may be isolated from red wine, grape skins and seeds, and *Polygonum cuspidatum* roots [140]. The cardioprotective effects caused by resveratrol were shown to be associated with a notable augmentation in antioxidant activity and mitochondrial transmembrane potential, with a decrease in oxidative damage [141]. Mechanistically, resveratrol primarily inhibits NADPH oxidase, decreases the production of ROS, and preserves activity of crucial antioxidant enzymes, including SOD, CAT, as well as glutathione peroxidase [142]. The modifications induced by resveratrol decrease lipid peroxidation, enhance cardiomyocyte viability, and decrease cardiac hypertrophy [143]. Resveratrol markedly mitigates cardiac metabolic diseases by the process involves reestablishing glucose homeostasis, regulating free fatty acid oxidation (FFAO), and increasing glucose consumption [144]. These processes enhance the metabolism of cardiac energy, especially in cardiomyocytes when glucose levels are elevated [145].

Currently, numerous studies suggest that resveratrol protects mitochondrial oxidation in endothelial cells, supports endothelial function, and it improves blood circulation and cardiac function by promoting vasodilation and vascular angiogenesis [146]. administration mitigated increased ROS production, MDA levels, the percentage of apoptotic cells, and *Bax* expression, while also enhancing SOD activity in rat CMEC. The substance also demonstrated antioxidative and anti-apoptotic properties by activating *AMPK/Sirt1* [147]. The antioxidant properties of resveratrol through *SIRT1* are illustrated by its activation of AMPK [148], which inhibits NADPH oxidase an enzyme that generates ROS and increases SOD levels, leading to reduced OS [149]. The resveratrol action is attributed to an increase in antioxidant enzyme activity, which varies with age, particularly through modulating crucial pathways [150]. *SIRT1* analysis revealed a silencing of the pathway in leukocytes treated with resveratrol during aging [151]. *SIRT1* impacts the acetylation of *FOXO* family TFs, crucial for lipid and glucose metabolism and cellular response to oxidative stress [152]. The interaction between *SIRT1* and AMPK enhances *FOXO3* transcriptional activity, thereby increasing *MnSOD* production in cells with higher *FOXO3* levels [153]. Resveratrol activated *SIRT3/FOXO3a*-dependent antioxidant enzymes, leading to a reduction in oxidative and DNA damage. Through the activation of the *SIRT3/FOXO3a* signaling pathway, obese mice that were given extended resveratrol demonstrated a decrease in the damage caused by myocardial ischemia [154]. By inhibiting NADPH oxidase, ROS production is diminished, thus decreasing OS [155]. Furthermore, the complex,

including *SIRT1* [156], *FOXO3* [157], and *PGC-1 α* [158], activates *Nrf2* [159], a transcriptional regulator, enhancing antioxidant response gene expression and promoting *MnSOD* production to protect mitochondria from oxidative damage [150]. resveratrol in aged mice reduced *TLR4*, *NF- κ B*, *p65*, and *Notch 1* proteins expression, lowering pro-inflammatory cytokine levels, suggesting heart protection depends on suppressing the *Notch/NF- κ B* pathway [160]. Middle-aged individuals showed improved anti-inflammatory profile in response to resveratrol compared to elderly individuals, particularly in the middle group, resulting in a reduction of key biomarkers associated with oxidation and inflammation [161].

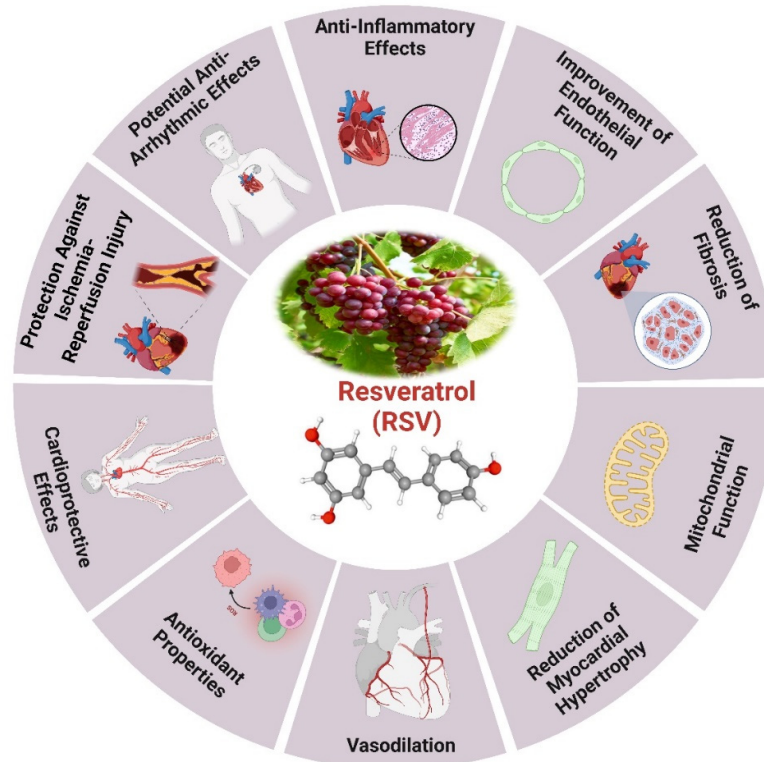


Figure 3. The image illustrates health benefits of resveratrol and the cardioprotective effects induced by RSV.

Furthermore, resveratrol decreased the pH levels in these mice's feces and increased short-chain fatty acids in the intestinal contents. Pro-inflammatory cytokine production, namely *IL-1 β* and *TNF- κ* , was suppressed by injecting resveratrol [162]. Resveratrol, melatonin, and their combined use may reverse the reduced antioxidant activity and enhance the expression of *GLUT4*, *SIRT1*, and *PGC-1 α* genes in the heart tissue of elderly female diabetic rats. Supplementation with resveratrol and melatonin may help preserve cardiac function in this model of aging female diabetes [163]. Resveratrol has shown the ability to mitigate age-related ventricular dysfunction by suppressing oxidative stress and inflammation in heart tissue via the *Notch/NF- κ B* pathway [160]. It has been investigated that resveratrol activates the NAD^+ dependent protein deacetylase *SIRT1*, reduces the hypertrophy of cardiomyocytes and age-related sarcopenia in mice [123]. Resveratrol therapy resulted in the restoration of autophagic activity in the TA muscle and a reduction in acetylated protein levels [164]. Resveratrol may impede autophagy in the context of cardiac ischemia-reperfusion damage via *DJ-1* regulation of the *MEKK1/JNK* pathway [165]. In addition resveratrol significantly mitigated the loss of *SLC7A11*, inhibited ferroptosis, and improved cardiac function via activating the *Sirt1/p53* pathway in heart failure [166].

Furthermore, Resveratrol has been shown to improve lifespan and physical activity in mice with LV pressure, overload-induced hypertension. The investigation elucidates the physiological and molecular processes behind this impact. By decreasing cardiac fibrosis, increasing heart remodeling, and boosting diastolic, vascular, and energy metabolic processes, resveratrol therapy reduces the severity of heart failure in mice [167]. In addition to maintaining endothelium-dependent coronary artery function and improving myocardial perfusion and angiogenesis indicators associated with the VEGF signaling pathway, resveratrol also reduces anomalies in wall motion [168]. In the setting of cardiac ischemia/reperfusion damage, the investigation evaluated the impact of resveratrol on *STIM1*-mediated intracellular Ca^{2+} buildup and cell death. Resveratrol dramatically enhanced heart function, lowered infarct size, and decreased apoptosis in mice. Resveratrol reduced intracellular Ca^{2+} buildup and downregulated *STIM1* expression in rat ventricular cardiomyocytes. In vitro, *STIM1* over-expression enhanced the effects of resveratrol on *STIM1*-mediated intracellular Ca^{2+} buildup, while the *SOCE* inhibitor *SKF96365* partially eliminated these effects [169].

In another study it has investigated that resveratrol play a key role in modulating ferroptosis and cardiac damage in MI. Resveratrol reduced myocardial damage and fibrosis associated with MI in rats, inhibited *IL-6*, *IL-1 β* levels, decreased *GPX4* and *SLC7A11* expression. Resveratrol alleviated cardiomyocyte damage generated by oxygen-glucose deprivation and inhibited ferroptosis in cardiomyocytes under OGD conditions in vitro. Resveratrol mitigated myocardial damage by suppressing ferroptosis via the activation of *KAT5/GPX4* in MI, offering additional evidence for its potential therapeutic efficacy [170]. Administration of resveratrol protected cells from *LPS*-induced apoptotic cell death by reducing proinflammatory cytokine generation, increasing *Nrf2* activation in human heart cells, and mitigating *LPS*-induced heart damage in rats [171]. Extended resveratrol consumption may protect obese mice from myocardial ischemia damage by restoring intracellular redox equilibrium through the activation of the *SIRT3/FOXO3a* signaling pathway [154]. Resveratrol cardioprotective effects in old mice include increased antioxidant activity, mitochondrial transmembrane potential, and decreased oxidative damage. It inhibits pro-inflammatory cytokines and suppresses the *Notch/NF- κ B* pathway, enhancing its cardioprotective properties [172,173].

It has been established that resveratrol activates *Sirt1*, which in turn mediates the deacetylation of *Smad3* and suppresses the fibrotic response generated by *TGF- β 1* [174]. The amount of acetylation of *Smad3* (*Ac-Smad3*) was elevated in rats with cardiac fibrosis, and renal fibrosis but it was reduced in the normal myocardium and nephridial tissue of rats. The *Ac-Smad3* has the ability to control the DNA binding activity and transcriptional activity of certain profibrotic genes. Elevating the level of *Ac-Smad3* through the action of *TGF- β 1* facilitates the progression and advancement of tissue fibrosis [174,175]. Resveratrol has demonstrated not only its ability to slow down the aging process, as well as its ability to provide protection against CVD by eliminating ROS and improving the functioning of several antioxidant enzymes.

4.2. Curcumin

Curcumin, a naturally occurring substance obtained from the desiccated rhizomes of *Curcuma longa* L., often known as turmeric, is extensively used in medical practice to address an extensive range of ailments (Figure 4). Curcumin has been shown in several studies to have positive effects on cardiac conditions and endothelial system dysfunction [176,177]. Studies on a rat model of hypertension and ischemia have shown that curcumin may improve cardiac hemodynamic function and attenuate heart failure [178]. Additionally, by decreasing oxidative stress and inflammation, it increases myocardial infarction size and boosts cardiac function after ischemia events [179]. Curcumin has garnered interest in the realm of CVDs for its capacity to have a variety of beneficial effects on the heart. Owing to its antioxidant qualities, curcumin has been proposed to mitigate heart disease risk factors, such as cardiac angiogenesis, and delay the development of age-related disorders [178,180]. For instance, curcumin contributes to cardiac aging by promoting autophagy and restoring it through the *SIRT1/AMPK/mTOR* pathway. The antioxidant capacity of *SIRT1* was reduced by siRNA-mediated knockdown, anti-aging, and autophagy-enhancing effects, indicating its potential as an effective treatment for cardiac aging [181]. The study explores the involvement of the *Nrf2/HO-*

1 signaling pathway in DCM by employing curcumin and *shRNA-Nrf2* as activators. A Type 2 diabetes animal model induced by streptozotocin and a high-fat diet was used to assess the impact of curcumin on *H9C2* cells. The results indicated that excessive production of ROS impaired *Nrf2*-related signaling, leading to reduced cellular energy metabolism and increased apoptosis. In contrast, activating the *Nrf2* signaling pathway improved cardiomyocyte viability, decreased ROS generation, and inhibited apoptosis [182].

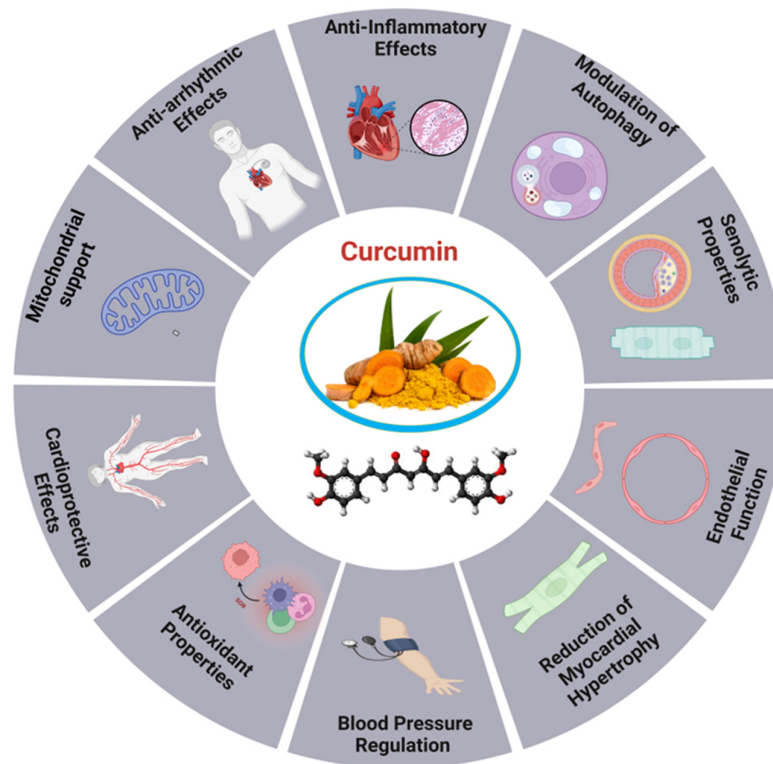


Figure 4. The functional role of curcumin and the cardioprotective effects of curcumin.

Moreover, Curcumin enhances mitochondrial integrity, mitigates oxidative stress, and fosters mitochondrial biogenesis by activating *SIRT1* and *PGC-1 α* . It also prevents the translocation of *DRP1* in sepsis models, indicating potential therapeutic advantages for sepsis-related cardiac muscle (SCM). The *SIRT1-DRP1/PGC-1 α* pathway involved in regulating mitochondrial mass may constitute a prospective target for the advancement of organ-protective pharmacotherapies in critical care environments [183]. Curcumin, a natural remedy, has been shown to increase postmitotic cells' longevity when they lack mitochondria, even though it does not exhibit hormetic effects. Its mechanism includes the inhibition of *TORC1* activity, elevated ATP levels and the onset of oxidative damage, indicating potential therapeutic uses in age-related diseases [184]. Curcumin supplementation can reduce vascular oxidative stress and restore arterial function in aging, positioning it as a promising antioxidant therapy for addressing age-related arterial dysfunction [185]. The treatment of curcumin increased *VEGF-A*, *TSP-1*, and *NF- κ B* levels and boosted age-related decreases in angiogenesis. By upregulating the production of *VEGF* and *NF- κ B* proteins and downregulating *TSP-1* protein levels, it mitigates heart tissue damage and supports cardiac angiogenesis in diabetic rats. Curcumin also induced molecular changes lead to a reduced apoptosis index in cardiac tissue [176]. The study revealed a substantial drop in autophagy and *SIRT-1* levels, while the levels of *MDA*, *NOX4*, *p-NF- κ b*, and *P62* were considerably elevated in the heart of the old group compared to the young group [178,186].

Besides, it turned out that the heart of old rats had notably elevated levels of apoptosis and fibrosis in comparison to young rats. However, the administration of exercise and curcumin shown

a positive effect in ameliorating these negative alterations. The combined administration of curcumin and exercise in elderly rats had a more pronounced impact on molecular mediators and histological alterations in the heart as compared to the use of curcumin isolated [187]. Through its capacity to activate and repair autophagy Curcumin has an impact on heart aging through the *SIRT1/AMPK/mTOR* mechanism. In aged cardiomyocytes subjected to D-galactose treatment, there was a significant increase in the number of cells that tested positive for intracellular ROS, *P53*, *P16*, and senescence-associated β -galactosidase. Curcumin-induced autophagy elevated *SIRT1* and *AMPK* levels, while reducing *mTOR*. *SIRT1-siRNA* stimulated the *SIRT1/AMPK/mTOR* pathway, limiting the antioxidative, antiaging, and autophagy-enhancing effects of curcumin in a dose-dependent manner [181]. Thymoquinone and curcumin synergistically reduced *D-gal*-induced necrosis in the brain and heart, leading to a reduction in *caspase-3*, *calbindin*, *IBA1*, cardiac *caspase-3*, and *BCL2* levels. The combination reduced mRNA expression of *TP53*, *p21*, *Bax*, and *CASP-3* in the brain and heart, while enhancing *BCL2* expression relative to the *D-gal* group. This indicates that TQ and curcumin provide a viable approach for mitigating aging [187].

4.3. Quercetin

One of the most well-known dietary antioxidants is quercetin, a phenolic member of the flavonoid family that is crucial to the process of heart aging (Figure. 5). It is found in vegetables, fruits, tea, wine, and many other healthy goods [188]. The antioxidant effects of quercetin include scavenging free radicals such superoxide, hydrogen peroxide, peroxy, and hydroxyl [189]. Quercetin improves mice's left ventricle function [190], myofibrillar tissue, and mitochondrial structure by lowering oxidative stress brought on by aging, restoring myocardial microcirculation, and decreasing the size of infarcts [191]. The study reveals that in rats with myocardial infarction, quercetin increases the activity of enzymes related to the respiratory chain and the tricarboxylic acid cycle [192]. The production of biomarkers linked to oxidative stress generated by myocardial infarction in rats has been observed to decrease [193]. Moreover, quercetin has been shown to defend *AC16* cells against oxidative stress caused by hyperlipidemia in elevating *p-SIRT1* levels, enhancing endothelial *NOS*, and diminishing *iNOS* [192]. This defensive action is facilitated by the signaling pathway *PI3K/Akt/Nrf2* [194], by obstructing the *HMGB1-TLR4-NF- κ B* signaling pathway, quercetin efficiently reduces inflammatory responses [195].

Studies indicated that quercetin markedly moderates cardiac hypertrophy and fibrosis in spontaneously hypertensive rats, this material preserves mitochondrial integrity, lowers levels of mitochondrial superoxide, and enhances heart performance. In vitro studies demonstrated quercetin alleviated hypertrophic response in rats by maintaining mitochondrial function, while partially weakened mitochondrial protection and *PARP-1* inhibition after *SIRT3* knockdown. Quercetin reduces cardiac hypertrophy by increasing mitochondrial activity by regulating the *SIRT3/PARP-1* pathway, according to study [196]. Prolonged treatment with quercetin in older spontaneously hypertensive rats (SHRs) markedly inhibited *MYC* expression, reduced *CYP2E1* levels, and decreased lipid peroxidation. Quercetin amplifies antioxidant activity, improving the equilibrium between prooxidants and antioxidants in the heart, which may result in reduced blood pressure and relative heart weight in older spontaneously hypertensive rats administered quercetin [197]. Quercetin decreased *MMP* activity, *TGF- β* levels, and oxidative stress in the coronary arteries and left ventricles of *2K1C* rats, but it had no effect on hypertrophic remodeling or functioning in the coronary arteries damaged by hypertension [198]. Quercetin pretreatment activates the *PI3K/AKT* signaling pathway, alleviates CDDP-induced oxidative stress, protects mitochondrial function, and lowers mitochondrial apoptosis in PCs. In vitro BLB models show quercetin diminishes CDDP-induced apoptosis and improves endothelial barrier permeability [199].

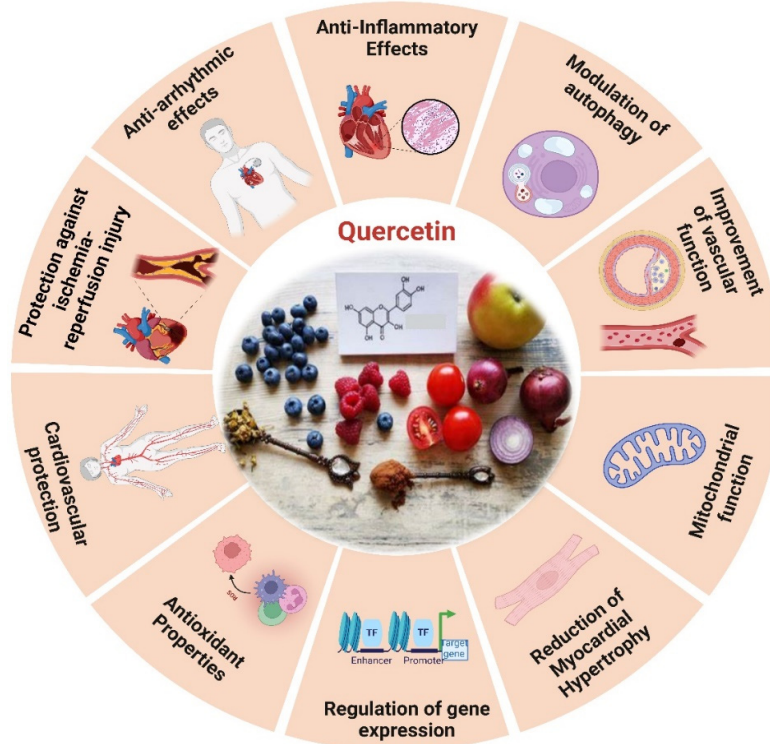


Figure 5. The diverse functional role of quercetin and the cardioprotective effects induced by quercetin.

Quercetin reduces apoptosis in vivo by phosphorylating *JNK* and *p38*, upregulating *Bcl-2* expression, and inhibiting *Bax* and *caspase-3* activation [200], and via *SIRT1/PGC-1 α* signaling, quercetin inhibits MI/R-induced apoptosis [192]. Atherosclerosis is primarily caused by endothelial dysfunction, which occurs during the solute exchange between blood and nerve tissues, the peripheral nerve substructures are defended by the blood-nerve barrier (BNB), which is made up of endothelium. Atherosclerosis is brought about by oxidative injury to endothelial cells induced by oxidized low-density lipo-protein. Therefore, oxLDL promotes the development of foam cells derived from RAW264.7 macrophages, which worsen cellular lipid accumulation and increase ROS levels that result in the oxidation of LDL particles into ox-LDL. Quercetin could inhibit the production of foam cells generated by ox-LDL and prevent cellular senescence [201]. In contrast, quercetin hinders the apoptosis of macrophages induced by cholesterol accumulation, thus resulting in a reduction in atherosclerosis. Quercetin additionally enhances the antioxidant function of cells via the Nrf2 pathway [202].

Chronic atherosclerosis throughout aging stimulates the formation and buildup of ROS, leading to mitochondrial damage caused by damage to mitochondrial DNA (mtDNA) [203]. OxLDL molecules are connected to *NF- κ B*, *TLR*, and scavenger receptors, among other pattern recognition receptors, and have the capacity to activate the immune system [204]. Quercetin, on the other hand, successfully stops ox-LDL-containing macrophages from activating *NLRP3* inflammatory vesicles. This leads to a reduction in cell lipotrophy and the secretion of *IL-1 β* [192,205]. Quercetin markedly decreased *VCAM-1* and *ICAM-1* expression in *HUVECs*, downregulated *MCP-1* mRNA levels, and mitigated nuclear translocation of the *NF- κ B*, *p65* subunit in oxLDL-stimulated *HUVECs*. It reduced *TLR2* and *TLR4* expression, diminished inflammatory mediators, and mitigated the inflammatory process in atherosclerotic rats subjected to a hypercholesterolemic diet. Quercetin functions as an anti-inflammatory and anti-atherogenic compound [204]. The primary mechanism by which quercetin inhibits the development of atherosclerotic plaque is by controlling *caspase-3* and *NF- κ B* activation through the *PI3K/AKT* pathway [202].

4.4. Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG) is the predominant and physiologically active polyphenol found in green tea [206]. As a strong redox agent, EGCG has a strong antioxidant effect and plays a significant role in heart aging (Figure 6). Its structural phenolic hydroxyl group oxidizes to produce a relatively stable molecule and serves as a hydrogen source for redox reactions. This procedure successfully rids the body of a significant amount of harmful free radicals [207]. Mechanistic investigations through its modification of MAPK, PKC, and PI3K activity, EGCG protects cells against oxidative damage, according to mechanistic studies [208]. EGCG possesses anti-oxidant properties and has the ability to mitigate the inflammatory response through its impact on inflammation linked pathways, resulting in suppression of inflammatory factor expression [209]. In vitro studies show that EGCG decreases inflammatory factors caused by LPS via phosphorylating signaling molecules linked to the *NF- κ B/p65*, *MAPK/p38*, Akt, and ERK pathways, as well as by reducing the production of *iNOS* and *COX-2* [210,211]. EGCG has the potential to decelerate the aging process through its modulation of the AMPK pathway, mitochondrial function restoration, and induction of autophagy [212].

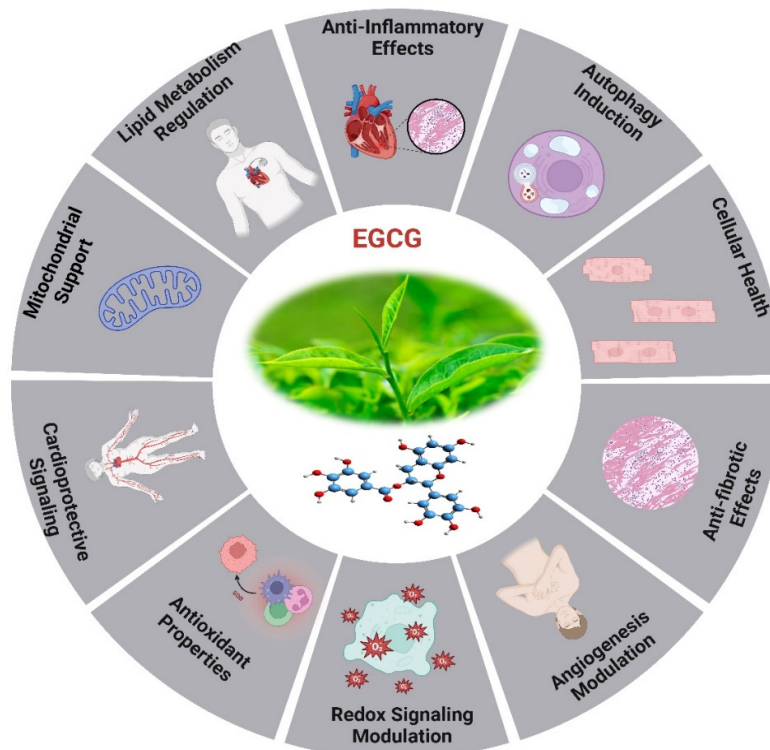


Figure 5. The diverse efficient roles of EGCG and the cardio-protective effects induced by EGCG.

Oxidative stress caused by pressure overload-induced cardiac hypertrophy shortens telomeres in the hypertrophic myocardium and depletes *TRF2*. EGCG, a powerful antioxidant, may impede cardiac myocyte death by averting telomere shortening and the loss of *TRF2* [206,213]. An investigation has revealed that aged rodents treated for 8 weeks with EGCG exhibited enhanced cardiac diastolic function [214]. The aged myocardium reduced expression of *cTnI* was restored by EGCG therapy, which also lowered *HDAC1* and *HDAC3* expression and *HDAC1* binding in the proximal promoter of *cTnI*. The *Ach3K9* was found in greater concentrations when EGCG was applied to the *cTnI* promoter. In reaction to EGCG, transcription factors *GATA4* and *Mef2c* bound to the *cTnI* promoter at higher amounts [215]. The *cTnI* gene plays a crucial role in the regulation of heart function, particularly in relation to diastolic function [216], and deficiencies and mutations in *cTnI* have been associated with diastolic dysfunction and HEpEF [217]. The examination of limited

samples of human heart tissues reveals a reduction in *cTnI* concentration in left ventricular myocardial cells in elderly adults, irrespective of cardiac disease status [218]. It has revealed that a decrease in cTnI in aging hearts may be a contributing factor to the diastolic dysfunction observed in elderly mice.

The EGCG not only affects the sensitivity of myofilament Ca^{2+} , but it also controls gene expression through epigenetic alterations. The study demonstrated that the administration of EGCG reversed the decrease in *cTnI* expression, which is linked to age-related cardiac diastolic dysfunction. This was achieved by increasing the expression of acetylated lysine-9 on histone H3 in aging hearts. The additional it has suggested that the administration of EGCG may have the potential to prevent heart failure through the modulation of histone acetylation [219]. EGCG exhibits antioxidant activity in *HepG2* cells and offers protection against oxidative stress caused by ABAP. In a dose-dependent way, the procedure was accomplished by lowering ROS and increasing the activity of cellular antioxidant enzymes such as SOD, CAT, and *GSH-Px*. Theoretical foundations for the creation of functional food components can be derived from the antioxidant effects exhibited by combinations of EGCG [220].

The therapeutic impacts of EGCG on CVD are associated with its capability to reduce LDL cholesterol, *NF- κ B*, plasma glucose, glycated hemoglobin levels, myeloperoxidase activity, inflammatory indicators, and ROS formation. For example, the combination of EGCG consumption and regular exercise in postmenopausal women who are over-weight or obese resulted in a decrease in their resting heart rate [206]. A study involving randomized controlled trials found that green tea consumption or low polyphenol dosage significantly reduced systolic and diastolic blood pressure in humans by 1.98 and 1.92 mmHg, respectively. The findings of a randomized double-blind placebo-controlled cross-over study demonstrated that the administration of a single dose of 300 mg EGCG resulted in the amelioration of endothelial function and enhancement of arterial-mediated dilation in individuals diagnosed with coronary arterial diseases. However, the administration of 150 mg of EGCG twice daily for a duration of two weeks did not yield any statistically significant effects [221].

Recently investigated study on the impact of *HDAC1*-mediated deacetylation of *NRF1* on cardiac hypertrophy and mitochondrial stability. An *HDAC1* inhibitor called EGCG was reported to enhance *LysoTracker+cardiomyocytes* in hypertrophic circumstances, decrease heart-to-body weight ratios, and improve cardiac function. In hypertrophic *H9C2* cells treated with PE, EGCG decreases cell hypertrophy and increases the presence of *LC3B II+MitoTracker+puncta*. It also inhibits *HDAC1*-mediated histone deacetylation, which aids in maintaining *NRF1* levels [222]. Eight weeks of EGCG treatment significantly reduced systolic, diastolic, and mean arterial pressure while increasing the liasodilator-hypertensive ratio. This suggests a shift towards sympathetic nervous system dominance or reduced parasympathetic nervous system activity. The results may be attributed to EGCG acting as a sympathetic potentiator or compensatory response. SBP was linked to obesity and insulin resistance, while DBP showed a positive association with HF nu and a negative correlation with LF ms2, this highlighted EGCG's potential protective effects against hypertension [223]. A study on adipose-derived stem cells (ADSC) pretreated with EGCG enhanced cell functions in diabetic cardiomyopathy while inhibiting the effects of small interfering C-X-C motif chemokine receptor 4 (siCXCR4) administration. These results were validated in a diabetic animal model, indicating that EGCG-pretreated ADSC may have promising clinical applications to diabetic patients suffering from cardiomyopathy [224]. EGCG is crucial for epigenetic regulation and can reduce DNA hypomethylation in genes like *Sod2*, *Gpx1*, *Cat*, and *TrxR*. The antioxidant properties and epigenetic modifications in CpG methylation can aid in the administration of antioxidant substances and DNA methylation-modifying medicines for chronic disease prevention and treatment [225].

5. Other Plant-Derived Antioxidants

The impact of plant-derived antioxidants on heart aging has garnered significant attention in scientific research. This interest is a result of mounting data showing the potential benefits of several plant-based components, including flavonoids, polyphenols, and other phytochemicals, in relation to the changes in the heart caused by aging. These substances exhibit a variety of mechanisms that

are essential for maintaining cardiovascular function. For instance, many plant-derived compounds demonstrate antioxidant properties that can effectively counteract oxidative stress, an essential determinant in the senescence of the cardiovascular system [226,227].

5.1. Anthocyanins

Anthocyanins, which are found in vibrant fruits and vegetables, have been the subject of recent study that looks at their potential, and their mechanisms in human vascular endothelial cells and rat thoracic aortas subjected to aging models [228]. It has examined that the ability of specific anthocyanins, such as cyanidin-3-rutinoside (C-3-R) and cyanidin-3-glucoside (C-3-G), to inhibit senescence induced by d-galactose in human endothelial cells [229]. The findings demonstrated a reduction in the activity of certain markers of cellular senescence, as well as a suppression of ROS production and NADPH oxidase activity in the presence of D-galactose [230]. Anthocyanins were shown to counteract the inhibition of endothelial *eNOS* activity, leading to the recovery of NO levels in endothelial cells [231]. It was observed that anthocyanins induced *eNOS* deacetylation via *SIRT1*, resulting in increased *eNOS* activity. In an in vivo study involving aged rats, administration of anthocyanin-rich mulberry extract over eight weeks led to a reduction in oxidative stress and endothelial senescence in the aorta, as well as an increase in serum NO levels, *eNOS* phosphorylation, *SIRT1* expression, and a decrease in nitro-tyrosine levels in the aorta [229]. Additionally consuming anthocyanins has been shown to enhance antioxidant defense enzymes, total antioxidant capacity, and the antioxidant properties of HDL in both preclinical and clinical populations [232]. Anthocyanins exhibit direct antioxidant capabilities and indirectly stimulate *Nrf2* and antioxidant gene expression, mitigating oxidative stress and inflammatory signaling in atherosclerotic plaque cells, such as macrophages and endothelial cells, thereby potentially protecting against atherosclerosis and cardiovascular disease [233].

5.2. Allicin

Scientifically known as s-allyl-2-ene-1-thiosulfite, allicin is a physiologically active chemical that is obtained from garlic. It demonstrates a broad spectrum of pharmacological characteristics, such as immunoregulatory, antioxidant, anti-inflammatory, renal, nerve, and cardiac protective, as well as anti-tumor effects. It has been shown that allicin and its derivatives operate biologically by modifying gene expression and interacting with a variety of signaling pathways [234,235]. Allicin, a medication for myocardial infarction, reduces infarction area and fibrosis, increases *SHP2* protein levels, and inhibits ROS in infarction tissue. However, specific knockdown of *SHP2* negates ROS changes. Allicin also modulates *p-PERK* activation, mitigate oxidative stress in rodents [234]. The study revealed that allicin exerted effects on cardiac function, myocardial fibrosis, and the modulation of *NF-κB* signaling pathways in the myocardial tissue of rats afflicted with diabetic cardiomyopathy. The study provided evidence that allicin exhibited positive effects on cardiac dysfunction and reduced myocardial fibrosis in the rats, possibly via facilitating the deactivation of the *NF-κB* signaling cascade [236].

5.3. Ginkgolides Biloba

The longevity of *G. biloba* L. has led to its widespread recognition as a living fossil tree. Throughout its lifespan, *G. biloba* L. is presumed to have acquired or evolved resistance to many diseases as a mechanism of adjusting to its surroundings. Many different phytochemicals, such as flavonoids, terpenoids, alkylphenols, and carboxylic acids, are present in the leaves of *G. biloba* [237,238]. Only *G. biloba* trees contain ginkgolides A, B, C, and J. Ginkgo contains mono-, di-, and triglycosides as its main flavonoids [239]. Ginkgo leaf contains several chemical compounds that have different functions, such as removing oxygen free radicals and decreasing oxidation, regulating superoxide dismutase and catalases, and removing NO. Engaging in these activities has the potential to enhance protection against heart injury and potentially reduce the likelihood of MI [240]. *G. biloba* has the ability to stimulate the *AKT* signaling pathway, the activation of *AKT* initiates cell-specific processes, such as *GSK3β* phosphorylation, which protect cells from acute AMI damage and reduces

the *AKT* signaling pathway due to cardiac ischemia-reperfusion damage [241,242]. The GBE50 is an orally given GBE formulation that corresponds to the German product, EGb761, which has been used in the treatment of AMI [243]. While GBE80 activates the *AKT/GSK3 β / β -catenin* signaling pathway, successfully preventing myocardial damage from AMI and H₂O₂-generated cardiomyocyte cytotoxicity [244].

Additionally, the effects of GBE administration on autophagy and cardiac hypertrophy may be mitigated by the *SIRT1* inhibitor EX-527, which also lowers Ang II oxidative stress and the production of *SIRT1* and *FoxO1*. This implies that GBE may be useful as a medication to treat pathological heart hypertrophy [245]. GBE has demonstrated cardioprotective properties in individuals with diabetes, namely in the context of DCM. Investigation demonstrates that giving diabetic rats GBE treatment successfully lowers metabolic irregularities, enhances cardiac function, and lessens degenerative changes to the heart. GBE treatment, however, may be able to address defective autophagy and dysregulation of the *AMPK/mTOR* signaling pathway. GBE demonstrated a reduction in apoptosis produced by *HG* in *H9C2* cells in vitro [246]. The study establishes a correlation between heightened cardiac oxidative stress, inflammation, apoptosis, and histomorphological alterations in cardiotoxicity generated by *Cs-A*. Additionally GBE administration has been shown to reduce the cardiotoxic effects of *Cs-A* by activating the *mTOR/ERK1/2* signaling pathways. The aforementioned pathways are linked to the suppression of oxidative stress and inflammatory mechanisms, thereby serving as a preventive measure against heart injury. Immunohistochemistry and bio-chemical assays were employed in the study to demonstrate that the supplementation of GBE leads to a reduction in cardiotoxicity through the enhancement of the *mTOR/ERK1/2* signaling pathways [247]. The extract of GBE shown significant efficacy in mitigating myocardial infarction through the enhancement of the body's inherent antioxidant defense mechanism and the reduction of inflammatory cytokine release and heart injury marker enzymes. The leaves of GBE, specifically *EGb761*, are commonly used to treat cerebrovascular diseases due to their neuroprotective properties. Studies have demonstrated the protective effect of *EGb761* on rats' cognitive performance, involves preventing apoptosis and autophagy in models of VD, as well as improving cognitive performance in rats with VD through the activation of *AMPK-mTOR* signaling [248].

5.4. Berberine (BBR)

Berberine (BBR), a fundamental constituent of the Chinese herb *Rhizoma coptidis*, is an isoquinoline alkaloid derived from *Berberidaceae* [249]. BBR has been shown in recent research to possess strong anti-dysenteric qualities in addition to a variety of cardiovascular pharmacological actions, such as controlling dyslipidemia, preventing arrhythmias, inhibiting heart failure, myocardial remodeling, and lowering blood pressure. BBR prevents cardiac senescence by boosting cardiac myocytes' production of *KL* mRNA and protein and controlling the *KL/SIRT1* signaling pathway, thereby enhancing its protective effects [250]. BBR has the ability to improve diabetic cardiomyopathy by increasing the expression of myocardial *methionine sulfoxide reductase A (MsrA)* and simultaneously inhibiting cardiac *CaMKII* oxidation [251]. It has been investigated by Wang et al., 2023, It has been discovered that BBR and its derivative *tetrahydroberberubine (THBru)* improve cardiac remodeling and reduce cardiac aging. Compared to BBR, *THBru* has a greater anti-heart aging effect because it prevents heart aging via *PHB2*-mediated mitophagy [252].

Moreover, researchers are progressively focused on investigating the impact of plant-derived antioxidant on heart aging. This has led to an exploration of various chemical compounds produced from plants, with the aim of promoting cardiovascular health and mitigating the adverse effects of aging on the heart. An excellent proof is seen in several naturally occurring compounds present in plants. These drugs have garnered considerable interest owing to their potential advantages for cardiovascular health, such as enhancing endothelial function, reducing inflammation, and demonstrating antioxidant qualities (Table 1). The effects outlined above are particularly relevant to the phenomenon of cardiac aging, as they have the potential to mitigate the oxidative stress and inflammation associated with the aging of the cardiovascular system. The research findings indicate

that these antioxidants may aid in preserving optimal heart function and vascular health, perhaps decelerating the heart aging process.

Table 1. Examples of recently investigated plant-derived antioxidants associated with heart aging.

Compound	Dosage	Pathway	Impact	References
Astragalus polysaccharides	200 mg/kg/d	<i>SIRT-1/p53</i>	Improved <i>SIRT-1</i> protein expression in rat aortic tissue, decreased aging marker proteins, reduced hydrogen peroxide-induced cell senescence, and restored <i>MMP</i> and <i>T-AOC</i> impairment in <i>RAECs</i> .	[253]
Olive leaves	100 mg/kg/d	<i>COX-2/ IL-6/ GPx/NOX-1/ & IL-10</i>	Significantly reduces inflammation and oxidative stress, potentially enhancing cardiometabolic health in older patients by alleviating the metabolic and vascular changes associated with aging.	[254]
Garlic (<i>A. sativum</i>)	100 mg/kg ⁻¹ /d	<i>Na⁺/K⁺ ATPase and Ca²⁺</i>	The experimental CRF model revealed that GE administration effectively protected the heart by lowering oxidative stress, modulating cardiac <i>Na⁺/K⁺ ATPase</i> activity, and regulating <i>Ca²⁺</i> levels.	[255]
EGCG	100 or 200 mg/kg/d	<i>cTnI</i>	Combat the aging-related decrease in CDD and <i>cTnI</i> expression.	[219]
Lycopene	0.5, 1, or 2 μm/d	<i>SIRT1/Nrf2/HO-1</i>	Reduces intracellular ROS levels, the synthesis of inflammatory factors, cell adhesiveness, and the rate of apoptosis under oxidative stress conditions, therefore mitigating oxidative damage in human VECs.	[256]
β-carotene	40 μM/d	<i>PI3K/Akt/mTOR</i>	Significantly reduced AGE-induced cell death, apoptosis, ROS production, antioxidative enzyme reduction, ER stress, autophagy, and cardioprotection in <i>H9c2</i> cells, thereby reducing ER stress and autophagy.	[257]
Chlorogenic acid	20 or 40 mg/kg/d	<i>Nrf2/HO-1</i>	Positive impact on vascular senescence.	[258]
Chlorogenic acid	90 mg/kg/d	<i>AMPK/SIRT1</i>	<i>AMPK/SIRT1</i> pathway activation by <i>S1pr1</i> regulation decreased ISO-induced ERS and cardiac hypertrophy.	[259]

Chlorogenic acid	15 mg/kg i.p./h	<i>Nrf2/HO-1</i>	Inhibit DT expression, activate the <i>Nrf2/HO-1</i> signaling pathway, decrease oxidative stress, and decrease apoptotic markers to lessen DOX-induced cardiotoxicity in vivo.	[260]
Alpha-lipoic acid	100 mg/kg/d	Upregulated <i>Mfn1</i> , <i>Mfn2</i> & Foxo1 downregulated <i>Drp1</i> and <i>Fis1</i>	Preventing the aging heart against ischemia-reperfusion injury by enhancing oxidative stress, mitochondrial function, and dynamics in elderly rats.	[261]
Bromelain	20 mg/kg/d	<i>AMPK/TFEB</i>	Facilitated anti-hyperlipidemic, antioxidant, & anti-inflammatory actions, contributing to the mitigation of atherosclerosis.	[262]
8-Gingerol	10 or 20 mg/kg/d	<i>PI3K/Akt/mTOR</i>	The findings imply that via inhibiting ROS production, apoptosis, and autophagy, ISO-induced MF may have cardioprotective benefits.	[263]
Apigenin	20 µg/h	NADPH oxidase	Reduce inflammation in the PVN and down-regulating NADPH oxidase-dependent ROS generation in SHRs can improve hypertension and cardiac hypertrophy.	[264]
Astaxanthin	75 mg/kg/d	<i>SIRT1</i>	Improves cardiac function and diminishes fibrosis by decreasing the phosphorylation and deacetylation of R-SMADs.	[265]
Astaxanthin	10 µg/ml/48h	<i>PTP1B/JNK</i>	Reduce LPS-induced mitochondrial apoptosis in H9C2 cells by regulating JNK signaling.	[266]
Ferulic acid	30 mg/kg/d	<i>miR-499-5p/p21</i>	Protect cardiomyocytes from oxidative stress-induced injury, suggesting potential use in treating cardiovascular diseases.	[267]
Naringenin	100 mg/kg/d	<i>SIRT1</i>	A nutraceutical strategy utilizing NAR may ameliorate myocardial senescence by targeting essential characteristics, potentially enhancing heart function in elderly individuals.	[268]
Vanillin	150 mg kg ⁻¹ /d ⁻¹	<i>Akt/HIF-1α/VEGF</i>	Potential of Van and PTX in lowering MI through improving cardiac angiogenesis and controlling apoptosis,	[269]

			inflammation, and oxidative stress.	
Chrysin	100 mg/kg/d	<i>eNOS & Nrf2</i>	Prevents myocardial complications from hypercholesterolemia-induced oxidative stress by activating <i>eNOS</i> and <i>Nrf2</i> signaling.	[270]
Cinnamaldehyde	45 and 90 mg/kg/d	<i>NLRP3</i>	Exhibits cardioprotective characteristics by suppressing <i>NLRP3</i> inflammasome activation and GSDMD-mediated pyroptosis in cardiomyocytes, presenting potential uses for myocardial ischemia/reperfusion damage.	[271]
Pterostilbene	20 mg kg ⁻¹ day ⁻¹	<i>AMPK/Nrf2/HO-1</i>	In diabetic rats, it decreases inflammation and heart oxidative stress.	[272]
Caffeic Acid Phenethyl Ester	10 mg/kg i.p./d	<i>Sirt6/Nrf2</i>	Effectively suppresses oxidative stress and promotes protective polarization in microglia.	[273]
Caffeic acid derivative	3 mg/kg/ i.p./d	<i>TGF-β/SMAD/NOX4</i>	Potential to prevent the progression of Ang II-induced cardiac remodeling.	[274]
Caffeic acid phenethyl ester	1 mg/kg/d	<i>SIRT1/eNOS/NF-κB</i>	The treatment improved MIRI by reducing oxidative stress, inflammatory response, fibrosis, and necrocytosis.	[275]
Fisetin	20 mg/kg/d	<i>SIRT1/Nrf2</i>	Effectively treats DOX-induced cardiomyopathy by inhibiting ferroptosis.	[276]
Hesperidin	25 to 50 mg/kg/d	<i>Sirt1/Nrf2</i>	Protects against ISO-induced myocardial ischemia by regulating oxidative stress, inflammation, and apoptosis.	[277]
Jin-Xin-Kang	4.38 - 13.14g/kg/d	<i>CaN/Drp1</i>	Plays a crucial role in cardioprotection, particularly in regulating mitochondrial function.	[278]
Genistein	100 mg/kg/d	<i>miR-451/TIMP2</i>	Promoted the expression of <i>miR-451</i> and inhibited cardiac hypertrophy.	[279]
Saponins	10-30 mg/kg	<i>AMPK/mTOR/ULK1</i>	Reduce in basal autophagy in cardiomyocytes and enhance the prevention of aging-related cardiac dysfunction.	[280]
<i>Salvia haenkei</i>	0.5 mg/ kg ⁻¹ /d	<i>p16–CDK6</i>	Increases the lifespan of mice via controlling cellular senescence and interfering with the <i>p16-CDK6</i> association.	[281]
Baicalin	5 mg/kg/d	<i>AMPK/mTOR</i>	Cardiomyocytes apoptosis and autophagy in response to Ang II	[282]

were reduced by the inhibition
of the *AMPK/mTOR* pathway.

6. Future Prospective and Conclusions

The rising prevalence of age-related heart aging underscores the urgent need for effective treatment strategies. In this context, investigating plant-derived antioxidants shows considerable potential in addressing this challenge. The results provided in this review confirm that some plant-based antioxidants such as polyphenols, terpenoids and alkaloids might reduce heart aging effects and moderate expression of genes involved in the same process. Plant-derived antioxidants provide protection to the heart by acting on several molecular pathways and signaling cascades. It will need further study to fully comprehend the complex interplay between antioxidant chemicals produced from plants and the aging process in the cardiovascular system, with a particular emphasis on the examination of pathways and signaling cascades. To enhance the effectiveness of antioxidant treatments, it is crucial to evaluate gene expression patterns, epigenetic modifications, and cellular signaling networks. With the use of innovative techniques and formulations, such as targeted-tissue delivery and controlled-release formulations, it is possible to overcome obstacles like poor stability and enhance the absorption and distribution of these antioxidants. The increasing prevalence of aging-related cardiovascular disorders necessitates the development of effective treatment approaches.

This review highlights the potential of plant-derived antioxidants, including polyphenols, terpenoids, and alkaloids, to mitigate the negative effects of heart aging and alter gene expression. These compounds offer cardioprotective benefits through various molecular pathways and signaling cascades, highlighting the need for efficient treatment approaches in this rapidly aging-related issue. The development of innovative delivery methods and formulations can significantly improve the therapeutic effectiveness of plant-based antioxidants. These methods can overcome challenges like poor solubility, low stability, and restricted tissue targeting associated with some plant-based agents, such as transdermal patches, controlled release formulation, and nanoparticle-based drug delivery. Effective collaboration among researchers in the fields of plant biochemistry, pharmacology, molecular biology, and cardiovascular medicine is essential for converting promising preclinical research findings into viable therapeutic interventions. For plant-base antioxidants to be used in comprehensive heart aging care management, rigorous clinical trials assessing their safety, effectiveness, and long-term effects on cardiac aging and related biomarkers are necessary to determine their therapeutic potential.

In conclusion, exploring plant-derived associated marker genes regulator of heart aging holds significate promise for the advancement of novel treatment approaches that are substantial by evidence, aiming to combat the rising incidence of age-related cardiovascular disorders. Researchers may discover novel approaches to prevent and manage cardiac aging by using the wide range of plant-based antioxidants and their complex mechanisms of action. This might eventually result in improved quality of life and health outcomes for the aging population.

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