

REVIEW

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# Caloric restriction-mimetics for the reduction of heart failure risk in aging heart: with consideration of gender-related differences

Lei Pang<sup>1</sup>, Xi Jiang<sup>2</sup>, Xin Lian<sup>3</sup>, Jie Chen<sup>4</sup>, Er-Fei Song<sup>5,6</sup>, Lei-Gang Jin<sup>6,7</sup>, Zheng-Yuan Xia<sup>7,8</sup>, Hai-Chun Ma<sup>1\*</sup> and Yin Cai<sup>9\*</sup>

## Abstract

The literature is full of claims regarding the consumption of polyphenol or polyamine-rich foods that offer some protection from developing cardiovascular disease (CVD). This is achieved by preventing cardiac hypertrophy and protecting blood vessels through improving the function of endothelium. However, do these interventions work in the aged human hearts? Cardiac aging is accompanied by an increase in left ventricular hypertrophy, along with diastolic and systolic dysfunction. It also confers significant cardiovascular risks for both sexes. The incidence and prevalence of CVD increase sharply at an earlier age in men than women. Furthermore, the patterns of heart failure differ between sexes, as do the lifetime risk factors. Do caloric restriction (CR)-mimetics, rich in polyphenol or polyamine, delay or reverse cardiac aging equally in both men and women? This review will discuss three areas: (1) mechanisms underlying age-related cardiac remodeling; (2) gender-related differences and potential mechanisms underlying diminished cardiac response in older men and women; (3) we select a few polyphenol or polyamine rich compounds as the CR-mimetics, such as resveratrol, quercetin, curcumin, epigallocatechin gallate and spermidine, due to their capability to extend health-span and induce autophagy. We outline their abilities and issues on retarding aging in animal hearts and preventing CVD in humans. We discuss the confounding factors that should be considered for developing therapeutic strategies against cardiac aging in humans.

**Key words** Cardiovascular disease, Cardiac aging, Caloric restriction, Gender difference, Caloric restriction-mimetics, Dietary compounds, Clinical application

## Background

Cardiac aging is a natural process and is accompanied by the progressive development of cardiac hypertrophy and dysfunction[1,2]. As a major contributor to cardiovascular disease (CVD), cardiac aging occurs in both sexes with most of the burden falling on middle-aged and older adults. This is because cardiac aging predisposes the heart to stress, thereby increasing cardiovascular mortality in the elderly[3,4]. Incidence and prevalence of age-related CVD, such as hypertension, atherosclerosis, coronary, and cerebral artery disease increase dramatically in men aged around 45, and 10 years later in women who reach menopause[5]. A sharp increase is also evident in post-menopausal women[6]. Females are usually under-represented in clinical trials, as

the participants in most studies evaluating CVD risk factors are men instead of mixed populations[7,8]. Evidence shows that, besides age, comorbidities and comedications, as well as additional confounding factors such as sex hormones may affect the endogenous cardioprotective aspects. Thus, there is an unmet need to assess whether gender differences in age-related comorbidities associated with heart failure (HF) require specific management strategies.

Since the postulation of free radical theory of aging, mitochondrial theory has been a key focus area for aging research. Mitochondrial theory focuses on mitochondria as the main producer of reactive oxygen species (ROS)[9], while radical theory focuses on ROS as the effector of oxidative stress[10], which is beyond the threshold of an endogenous antioxidant system[11]. ROS is produced along the electron transport chain[12], in which electrons are capable of establishing a proton gradient that is necessary for ATP production and is completely neutralized with oxygen to water (Fig. 1a). Both theories suggest that the cellular deterioration

\*Correspondence: mahc@jlu.edu.cn; david-yin.cai@polyu.edu.hk

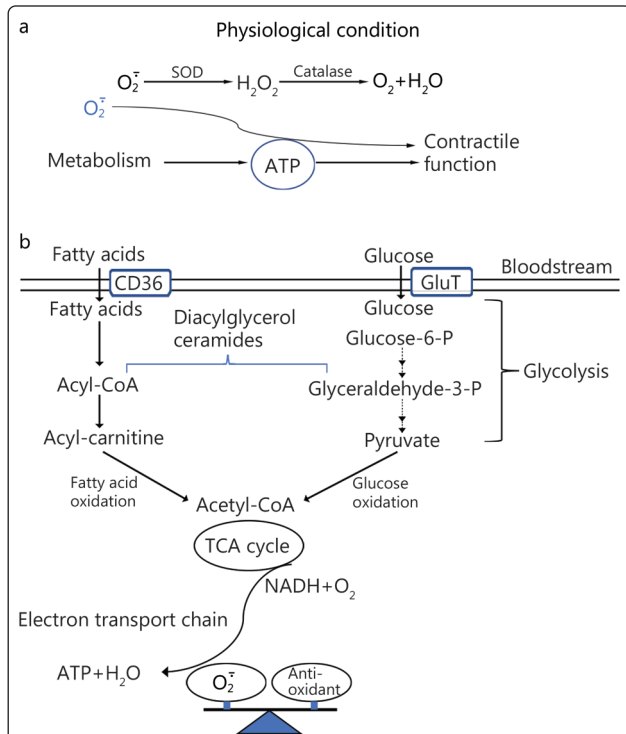
<sup>1</sup>Department of Anesthesiology, the First Hospital of Jilin University, Changchun 130021, China

<sup>3</sup>Department of Health Technology and Informatics, the Hong Kong Polytechnic University, Hong Kong, China

Full list of author information is available at the end of the article

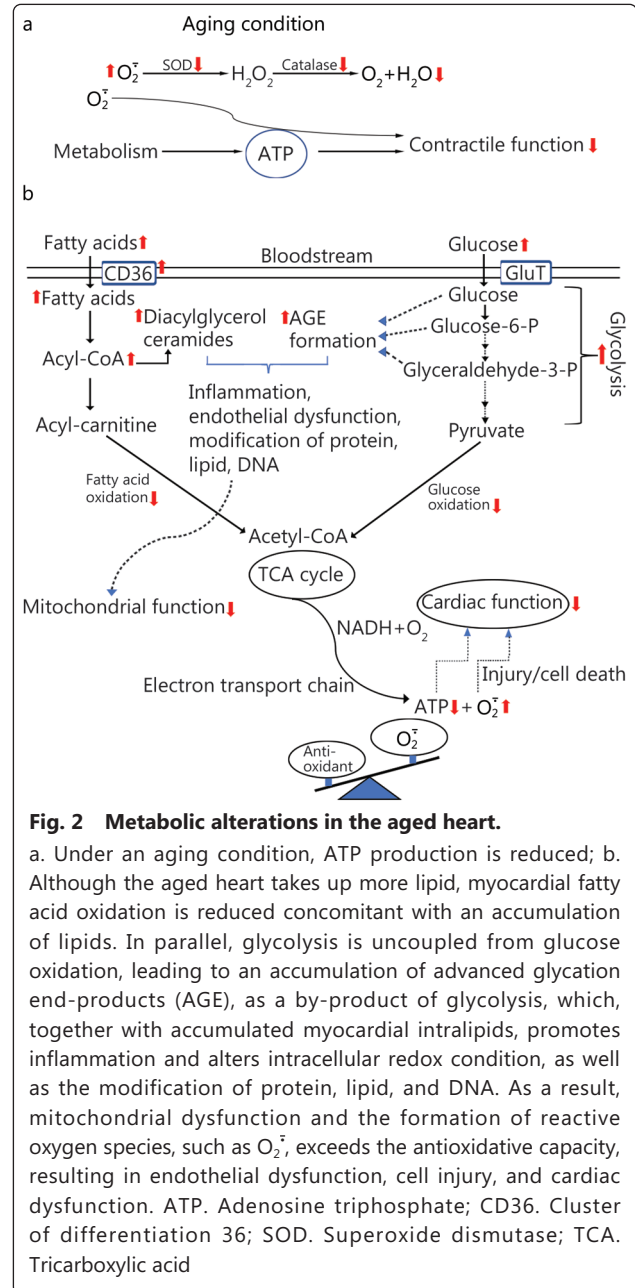
seen with increasing age is related to mitochondrial dysfunction, causing endothelial dysfunction, alteration in the vasculature, and/or vascular injury[11,12]. Given the extraordinary demand for energy, the heart contains the highest density of mitochondria, allowing it to produce cellular adenosine triphosphate (ATP) mainly from fatty acid oxidation (Fig. 1b), with glucose metabolism contributing less[13]. Myocardial ATP production and fatty acid oxidation decline in the aged human heart, concomitant with the accumulation of lipids[14] (Fig. 2a). Meanwhile, increased activity of myocardial aldose reductase and sorbitol dehydrogenase in the aged heart enhances polyol pathway by driving the flux of glucose to sorbitol[15]. This alters not only intracellular redox status by decreasing the synthesis of reduced glutathione and nitric oxide (NO) production, but also the modification of protein, lipid, and DNA with advanced glycation endo-

products (Fig. 2b) to promote ROS production. Thus, alteration in mitochondrial metabolism in an aging heart is the underlying basis for the increased sensitivity to stress.



**Fig. 1 Energy metabolism in the heart under physiological condition.**

a. In a normal heart, the main task of energy metabolism is to produce ATP for the pumping function; b. To maintain a high energy demand, the heart is equipped with an enzymatic machinery orchestrating ATP production that mainly uses fatty acids and glucose under physiological condition. Under physiological condition, the production of reactive species is minor, and mainly produced in the mitochondria with superoxide (O<sub>2</sub><sup>-</sup>) as the primary form in the heart. Of which, the balance is maintained by the action of superoxide dismutase and catalase by converting them to O<sub>2</sub> and H<sub>2</sub>O. ATP. Adenosine triphosphate; CD36. Cluster of differentiation 36; SOD. Superoxide dismutase; TCA. Tricarboxylic acid



**Fig. 2 Metabolic alterations in the aged heart.**

a. Under an aging condition, ATP production is reduced; b. Although the aged heart takes up more lipid, myocardial fatty acid oxidation is reduced concomitant with an accumulation of lipids. In parallel, glycolysis is uncoupled from glucose oxidation, leading to an accumulation of advanced glycation end-products (AGE), as a by-product of glycolysis, which, together with accumulated myocardial intralipids, promotes inflammation and alters intracellular redox condition, as well as the modification of protein, lipid, and DNA. As a result, mitochondrial dysfunction and the formation of reactive oxygen species, such as O<sub>2</sub><sup>-</sup>, exceeds the antioxidative capacity, resulting in endothelial dysfunction, cell injury, and cardiac dysfunction. ATP. Adenosine triphosphate; CD36. Cluster of differentiation 36; SOD. Superoxide dismutase; TCA. Tricarboxylic acid

The interplay between mitochondria function and sex steroid hormone biosynthesis (Fig. 3a) is evident[16]. Age-related decrease in sex hormone and mitochondrial dysfunction has been demonstrated in both men and women[17]. Emerging evidence has revealed that signaling pathways in the aged human hearts differ between males and females—specifically in the context of antioxidative defense, inflammation state, and mitochondrial biogenesis[18]. Additionally, failing human hearts with preserved ejection

fraction (HFpEF) display a distinctive metabolic profile and gene transcriptome from that with reduced ejection fraction (HFrEF)[19]. Currently, there are several therapies for treating HFrEF, including devices, transplants and medications with beta-blockers and sodium-glucose co-transporter 2 inhibitors. Of which, however, none have been shown to be effective for HFpEF in randomized clinical trials[20,21].

In contrast, herbal or dietary compounds, rich in polyphenols or polyamine, have become alternative therapy with several advantages, such as being relatively inexpensive compared to pharmaceutical drugs[22]; relatively easy for most people to receive benefits through dietary modifications or supplementation and starting from an earlier age. More importantly, epidemiological studies have demonstrated that regular consumption of polyphenol-rich foods may reduce the risk of CVD and slow cardiac aging[23]. Hence, we have selected a few dietary compounds, including resveratrol, quercetin, epigallocatechin gallate (EGCG), curcumin, and spermidine, due to their capacity to extend health-span in model organisms, alleviate cardiac aging[24-35] (Table 1), and prevent CVDs in humans[36-61] (Table 2). As most of the studies regarding the beneficial effects of the abovementioned compounds were carried out using genetically homogeneous laboratory strains, which, in contrast to genetic diversity in human populations[62], it remains unclear which of the effects would be beneficial for an aging human heart. Thus, this study will not present the extensive literature on signaling pathways of caloric restriction (CR)-mimetics in animal studies, and instead, will discuss their effect on preventing CVDs in human hearts (Table 2). We will focus on three areas: (1) cardiac remodeling and molecular and cellular mechanisms; (2) gender-related differences and potential

mechanisms underlying diminished cardiovascular response in older men and women; (3) protective effect of the above-mentioned compounds on aged animal hearts and CVD in humans, as well as the confounding factors that should be considered for developing therapeutic approaches against cardiac aging in humans. We believe that understanding the differences of molecular mechanisms underlying the cardiac aging process in both males and females will lay a foundation for new therapeutic strategies that ensure effective gender-specific intervention strategies.

## Mechanisms underlying age-related cardiac remodeling

### Remodeling in aged heart

This refers to a series of changes related to cardiac aging and vascular aging at the cellular and molecular levels[63]. The structural and functional transformation of a human heart occurs in healthy adults aged between 20 to 85 years old[64]. Structurally, it mostly affects blood vessel geometry, valves, and chambers, such as thickening of blood vessels and heart valves, increasing the size and volume of the left atrium, left ventricle (LV) hypertrophy, and interventricular septum, accompanied by increased wall thickness and interstitial fibrosis[63]. Functionally, diastolic function declines with advanced age, in both LV and the right ventricle, which can be assessed by diastolic filling in two phases: passive filling (early) and active filling (late)[65]. The rates of early diastolic filling in LV progressively decline after age 20 and reduce up to 50% by age 80 with increased filling in late diastole[66]. These changes are similar to the filling profile in the right ventricle[67]. Although systolic function with respect to ejection fraction is not affected at rest[4], age-related ventricular dysfunction is

**Table 1 Resveratrol, Quercetin, Curcumin, EGCG and Spermidine alleviates cardiac aging in animal models**

| CR-mimetics | Animal/dose  | Duration  | References |
|-------------|--|-----------|------------|
| Resveratrol | 2 months old mice, 4.9 mg/(kg-d)                                 | 8 months  | [24]       |
|             | 10 months old mice, 20 mg/(kg-d)                                 | 4 d       | [25]       |
|             | 14 months old mice, 50 mg/(kg-d)                                 | 16 months | [26]       |
| Quercetin   | 1 year old diabetic Zucker Diabetic Fatty rats, 20 mg/(kg-d)     | 6 weeks   | [27]       |
|             | 8 weeks old dystrophin-deficient mice, diet with 0.2% quercetin  | 8 months  | [28]       |
| Curcumin    | 26-28 months old rats, 50 mg/(kg-d)                              | 2 months  | [29]       |
| EGCG        | 16 months old mice, 50 mg/(kg-d)                                 | 8 weeks   | [30]       |
|             | 24-26 months old mice, 200 mg/(kg-d)                             | 1 month   | [31]       |
| Spermidine  | 4 months old mice, 3 mmol/L in drinking water                    | 26 months | [32]       |
|             | 18 months old mice, 3 mmol/L in drinking water                   | 6 months  | [33]       |
|             | 27-29 months old mice, 3 mmol/L in drinking water                | 4 weeks   | [34]       |
|             | 7 weeks old Dahl salt-sensitive rats, 3 mmol/L in drinking water | 12 weeks  | [32]       |
|             | 22-24 months old rats, 10 mg/(kg-d)                              | 6 weeks   | [35]       |

**Table 2 Resveratrol, Quercetin, Curcumin, EGCG and Spermidine prevents CVD in randomized clinical trials with patients**

| CR-mimetics | Patients/dose   | Duration       | References |
|-------------|---|----------------|------------|
| Resveratrol | Type 2 diabetic patients, 10 mg/d (n=10) or 250 mg/d (n=28), respectively                     | 1 and 3 months | [36,37]    |
|             | Patients with stable angina pectoris, 20 mg/d (n=29) or 100 mg/d (n=30), respectively         | 2 months       | [38,39]    |
|             | Patients post ischemia infarction, 10 mg/d (n=20), or patients with HFrEF (n=30), 100 mg/d    | 3 months       | [40,41]    |
|             | Patients with high risk of CVD (n=75); 8 mg/d or 16 mg/d for 6 months                         | 12 months      | [42]       |
|             | Hypertensive patients (n=24), 300 mg or obese men and post-menopausal woman (n=19), 30-270 mg | Single dose    | [43,44]    |
|             | Obese individual (n=28), 75 mg/d  | 6 weeks        | [45]       |
|             | Obese men (n=11), 150 mg/d  | 4 weeks        | [46]       |
|             | Patients with metabolic syndrome (n=22); 2 pills FRAMINTROL (contains 100 mg/d resveratrol)   | 3 months       | [47]       |
| Quercetin   | Both gender (n=37), quercetin-3-glucoside (160 mg/d)  | 4 weeks        | [48]       |
|             | Women with type 2 diabetes (n=72), 500 mg/d   | 10 weeks       | [49]       |
|             | Patients with stable coronary heart disease (n=30), 120 mg/d                                  | 2 months       | [50]       |
|             | Overweight patients, 150 mg/d (n=93), or 163 mg/d (n=70) quercetin from onion skin extract    | 5 and 6 weeks  | [51,52]    |
|             | Pre-hypertensive men and women (n=37), 160 mg/d quercetin-3-glucoside                         | 4 weeks        | [48]       |
| Curcumin    | Patients with coronary artery bypass grafting (n=121), curcuminoids                           | 4 g/d, 9 d     | [53]       |
|             | Type 2 diabetes, 1000 mg/d (n=30), or 300 mg/d (n=50), respectively                           | 12 weeks       | [54,55]    |
|             | Postmenopausal women, 150 mg/d (n=32), or 150 mg/d (n=45), respectively                       | 8 weeks        | [56,57]    |
| EGCG        | Patients with coronary artery disease (n=42), 300 mg/d  | 2 weeks        | [58]       |
|             | Patients with early atherosclerosis (n=28), 30 ml of EGCG containing olive oil/day            | 4 months       | [59]       |
|             | Obese postmenopausal women (n=38), 300 mg/d   | 12 weeks       | [60]       |
| Spermidine  | Healthy male volunteers (n=30), aged from 40 to 69 years, with Japanese food (natto)          | 12 months      | [61]       |

evident under exercise[68].

### Intracellular processes in aged heart

Arterial stiffening and endothelial dysfunction are both characteristics of vascular aging. The pathways can be quite diverse, but attributable to a prolonged imbalance between damaging and repairing[69].

On a cellular level, the composition of a mammalian heart is often described in the context of cardiomyocytes and non-cardiomyocytes. Cardiomyocytes are the contractile element, contributing to 35% of the total cells in the myocardium[70,71]. Non-cardiomyocytes include a diverse set of cells, such as fibroblasts and endothelial cells. The first line of evidence regarding an imbalance in damaging and repairing is the reduced regenerative capacity of the heart, which relies not only on proliferation of cardiomyocytes, but also on populations of other cells. In this case, there are two major challenges. One is the demise of cells due to necrosis and apoptosis[72,73]. Apoptosis occurs not only on cardiomyocytes, but also on endothelial cells, in response to age-related alterations in systemic and local environment, as well as cell-cell communication impairment[74]. Another challenge is the low regenerative capacity of the heart because adult cardiomyocytes are terminally differentiated cells, and

the aging heart contains more senescent cardiomyocytes[1]. The regenerative capacity of a murine heart is reduced from day 7 post-birth, while the mitotic activity of cardiomyocytes is lost during adulthood, largely due to age-related increase in the number of fibroblasts[75,76]. Likewise, the regeneration rate of human cardiomyocytes is approximately 1% annually in young adults, which diminishes to 0.45% in the elderly[77], indicative of limited regenerative capacity in an adult human heart. Another line of evidence regarding imbalance theory in an aging heart is the impaired dynamic crosstalk between cardiomyocytes and non-cardiomyocytes, such as endothelial cells[76,78,79]. To this point, one form of direct evidence is demonstrated *via* vascular endothelial growth factor (VEGF), an endothelial cell marker protein, which functions *via* its receptor (VEGF-receptor) on the surface of cardiomyocytes. Adult mice with deletion of VEGF-receptor displayed an increase in the coronary vasculature and induction of cardiomyocytes hypertrophy[80]. Additionally, mice with deletion of apelin, a protein produced by endothelial cells[81], developed a progressive impairment of cardiac contractility associated with systolic dysfunction[82]. Furthermore, miR-217 is identified as the most highly inducible miRNA during human endothelial cell aging[83]. Mice with

overexpression of endothelial-specific miR-217 displayed endothelial dysfunction in conjunction with an altered left ventricular diastolic and systolic dysfunction[83].

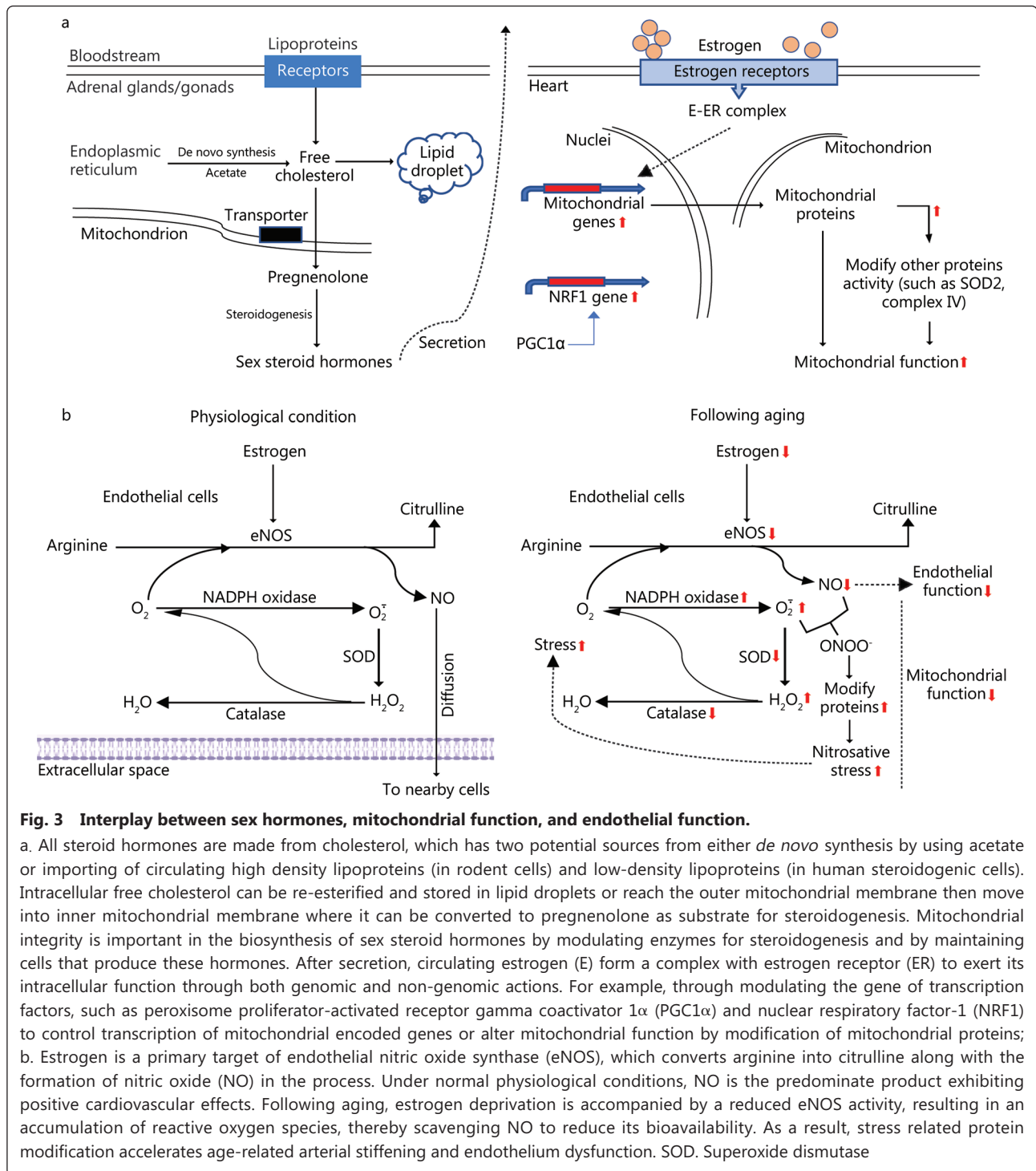
On a molecular level, multiple factors contribute to the damaging mechanism of an aging heart, such as autophagy (an intracellular recycling program targets dysfunctional organelles and proteins to lysosomes for degradation), mitochondrial dysfunction, oxidative stress, inflammation, and genomic instability caused by DNA damage or telomere attrition[84,85]. A significant challenge is to dissect their relative contribution to aging due to interrelation. However, mitochondrion plays a critical role in forming the crossroads for the pathways related to cardiac aging[86]. Mitochondrial function is determined by mitochondrial dynamics, which includes a network process of mitochondrial fusion, fission, and biogenesis, in which mitophagy, a specific form of autophagy to remove dysfunctional mitochondria, is essential for mitochondrial morphology, quality and abundance[87]. Mitophagy activity is downregulated during aging, concomitant with a decline in mitochondrial function[32], and increased ROS generation in aged cardiomyocytes[88]. This is associated with functional impairment at the organ levels, such as diastolic dysfunction, LV hypertrophy, increased risk of atrial fibrillation, and decreased exercise capacity in an aging heart[63]. On a mechanistic level, ROS-induced DNA damage is a key regulator of autophagy in aging heart. In adult cardiomyocytes, more chemical energy is consumed by excitation and contraction than in other non-contractile cells, so the adult heart greatly relies on cellular quality control mechanisms to maintain mitochondrial quality. However, ROS progressively accumulate during aging, which induces mutations in mitochondrial DNA and impedes the tricarboxylic acid cycle and electron transport chain complexes, thereby progressively reducing mitochondrial DNA content and promoting mitochondrial dysfunction[89]. That said, signaling through oxidative stress/DNA damage axis also promotes redox-sensitive mediators, such as nuclear factor  $\kappa$ B, that, in turn, modulates the transcription of several pro-inflammatory cytokines[90]. It is evident that targeting mitochondria-inflammation circuit can mitigate HFpEF[91]. Direct evidence of oxidative stress-linked mitochondrial dysfunction is provided by using mice overexpressing mitochondrial-targeted catalase, which is an antioxidant enzyme[92]. Mitochondrial-targeted catalase prevents ROS-mediated damage on mitochondrial DNA and increases median life span[92]. Furthermore, telomere dysfunction links cardiac dysfunction through telomere-p53/peroxisome proliferator-activated receptor gamma coactivator

1-alpha (PGC1 $\alpha$ )/mitochondrial axis along with the changes, such as decreased ATP generation capacity and increased oxidative stress, seen in aged mouse heart[1,93]. Collectively, mitochondrion is a primary place of ROS production, which in turn leads to a forward-feedback spiral of increasing damage to mitochondrial DNA, as reflected in the aged heart of laboratory animals to humans[94]. Thus, mitochondrial dysfunction is a major contributor to heart senescence, irrespective of the differences between individuals and species[95].

### **Interplay between sex steroid hormones, mitochondrial function and endothelial function**

Evidence suggests that sex hormone deficiency contributes to oxidative stress in the aged heart[96]. Estrogen, progesterone, and testosterone are sex steroid hormones and are classically functional by binding to their receptors[96]. All steroid hormones are made from cholesterol, which has two potential sources, either de novo synthesis by using acetate or importing circulating lipoproteins (Fig. 3a). Intracellular free cholesterol can be stored in lipid droplets or moved into inner mitochondrial membrane where it can be converted to pregnenolone as a substrate for steroidogenesis. Importantly, mitochondria modulate the enzymes for steroidogenesis. 17 $\beta$ -estradiol is the major female sex hormone of circulating estrogen, which is functional through forming a complex with its receptor, followed by translocation into the nucleus for directly binding to DNA sites known as estrogen response elements or indirectly binding to DNA through other transcriptional factors (Fig. 3a)[97].

In particular, estrogen can regulate endothelial function through enzymes related to mitochondrial oxidative stress. One line of evidence is that estrogen up-regulates not only factors associated with mitochondrial biogenesis, electron transport chain, and complex IV activity for enhancing mitochondrial function, but also superoxide dismutase (SOD) activity for reducing cellular levels of ROS[98]. The age-dependent decrease of mitochondrial SOD2 has been observed in female human hearts, but not in male hearts[18], suggesting its favorable expression in younger female hearts. Meanwhile, estrogen also regulates endothelial NO synthase (eNOS) (Fig. 3b), which can be two completely different physiological outcomes depending on eNOS as a source of NO or superoxide [99]. Under normal conditions in younger women, the production of NO in the vasculature is generally considered to have positive cardiovascular effects[100]. As a woman ages, estrogen deprivation is accompanied by a reduced eNOS activity and mitochondrial dysfunction (Fig. 3b), resulting in reduced NO bioavailability and ROS accumulation



**Fig. 3 Interplay between sex hormones, mitochondrial function, and endothelial function.**

a. All steroid hormones are made from cholesterol, which has two potential sources from either *de novo* synthesis by using acetate or importing of circulating high density lipoproteins (in rodent cells) and low-density lipoproteins (in human steroidogenic cells). Intracellular free cholesterol can be re-esterified and stored in lipid droplets or reach the outer mitochondrial membrane then move into inner mitochondrial membrane where it can be converted to pregnenolone as substrate for steroidogenesis. Mitochondrial integrity is important in the biosynthesis of sex steroid hormones by modulating enzymes for steroidogenesis and by maintaining cells that produce these hormones. After secretion, circulating estrogen (E) form a complex with estrogen receptor (ER) to exert its intracellular function through both genomic and non-genomic actions. For example, through modulating the gene of transcription factors, such as peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) and nuclear respiratory factor-1 (NRF1) to control transcription of mitochondrial encoded genes or alter mitochondrial function by modification of mitochondrial proteins;

b. Estrogen is a primary target of endothelial nitric oxide synthase (eNOS), which converts arginine into citrulline along with the formation of nitric oxide (NO) in the process. Under normal physiological conditions, NO is the predominate product exhibiting positive cardiovascular effects. Following aging, estrogen deprivation is accompanied by a reduced eNOS activity, resulting in an accumulation of reactive oxygen species, thereby scavenging NO to reduce its bioavailability. As a result, stress related protein modification accelerates age-related arterial stiffening and endothelium dysfunction. SOD. Superoxide dismutase

along with arterial stiffening and decline of endothelium-dependent vasodilation[101], in postmenopausal women than in young women[102]. Of which, the reduction is more pronounced in late perimenopausal women than early perimenopausal women, despite being similar in age[103]. The flow-mediated vasodilation is increased in estrogen-deficient postmenopausal women with systemic infusion of

ascorbic acid, a nonspecific antioxidant, whereas the effect is not observed with estradiol[104]. Thus, oxidative stress and endothelial dysfunction has a positive association in estrogen-deficient postmenopausal women[105,106].

### Gender-related differences in aged heart

Accumulating evidence has demonstrated that men are at

higher risk of CVD than women, with sex steroids playing a role[107]. Clinical trials have demonstrated that women living with HF, despite being older, have significantly better survival rates than men[108]. This is attributable to gender-related differences with respect to human LV morphology, chamber function, hemodynamics as well as changes of sex hormone and mitochondrial function with aging[109].

#### **Cardiac aging—LV mass and chamber function**

Cardiac aging is accompanied with the development of cardiac hypertrophy. LV mass is lower while LV contractility is stronger in women relative to men[7], which is attributed to a lower apoptotic rate of myocytes in women, thereby preserving LV mass with aging[7]. The maximal cardiac pumping capability is preserved with age in women, but decreases by 20%–25% in men[110]. Likewise, age-related cardiac dysfunction, as reflected by the maximal aerobic capacity or end diastolic volume response to vigorous exercise, is more pronounced in men than women of similar ages. This difference becomes blunted in women across age range[111].

#### **Vascular aging—hemodynamics, arterial function, and endothelial function**

Women have a faster heart rate, lower blood pressure, and a higher index of LV afterload than men at all comparable ages[112]. Age-related abnormalities in systemic arteries occur earlier in men than in women, irrespective of the known risk factors[113]. Likewise, levels of estrogenic hormone affect arterial distensibility, as reflected by stiffer pre-pubertal arteries and distensible post-puberty arteries in women than their male counterparts[112]. Pulse pressure is an accepted predictor of CVD in human populations, and younger women have a lower pulse pressure[112]. Thus, the risk of CVD is much lower in pre-menopausal women.

With respect to endothelial dysfunction: it starts 10 years earlier in healthy men than in women, who reach the time of menopause, indicating that endothelial function is, in part, controlled by sex steroid-dependent pathways[6]. Indeed, a steep decline of endothelial function is more evident in elderly women than in men[6]. Excessive circulating androgen may be related to endothelial dysfunction and arterial stiffness in menopausal women, as reflected by coronary artery calcification[114,115] and carotid intima media thickness[116]. This notion, however, needs further evidence to corroborate. As an important androgen in males, circulating testosterone concentrations decline as men age[117]. Testosterone replacement strategy can mitigate some of the aging characteristics, but it does not significantly improve physical function in aged men[118,119]. The effect of testosterone on the cardiovascular system ranges widely from

being protective to deleterious and even no association at all in men[120,121]. In addition, an increased risk of developing symptomatic coronary heart disease has been reported in postmenopausal women with the lowest and highest quintile of bioavailable testosterone compared with women in the middle quintile[122]. Obviously, we are far from concluding that estrogens are cardioprotective and androgens are detrimental.

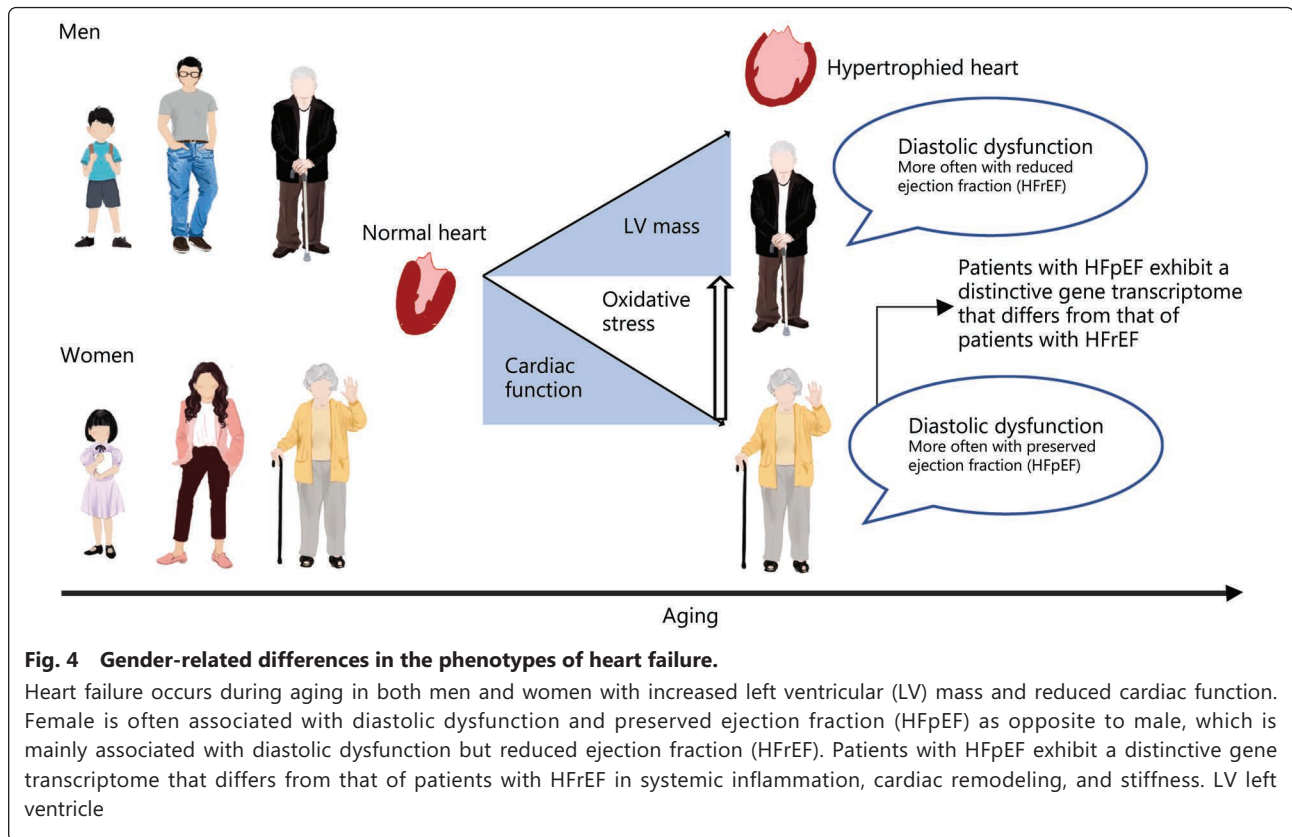
#### **Phenotypes of HF and lifetime risk factors**

Age-related HF can be HFpEF or HFrEF (Fig. 4), in association with gender and races. Most older women have HFpEF in contrast to HFrEF in men[123]. Of interest, the highest proportion of hospitalized patients with HFpEF is white women (59%), in contrast to black males in HFrEF (70%)[124]. Regarding lifetime risk factors: ischemic heart disease is the etiology frequently causing HFrEF in men, whereas HFpEF is a multifactorial disease with obesity, diabetes, valve disease, and hypertension, which is predominant in women[7]. Although lifetime risks of developing HF are equal between men and women by the age of 40[125], the incidence is higher in men, while the prevalence is higher in women with advancing age[126]. However, the rates of HF for women aged between 65–84 triples with each decade, which, only double in men[7,125]. Of interest, the lifetime risks for developing HF are higher in white males and females relative to their black counterparts[127]. Regarding prognosis: both gender-related and gender-unrelated relationships have been described in the literature. Among hospitalized patients with HFpEF, 20% lower mortality rates are found in women relative to men[128]. In contrast, recent studies have shown that age and creatinine are the only variables associated with mortality rate since the probability of survival does not show gender-related difference between patients admitted for decompensated HF[8,129].

#### **CR-mimetics in aged heart**

##### **Health concerns of CR**

The principle of CR is to achieve a weight loss with a lifelong reduction (30%–40%) of caloric intake by using a diet containing adequate amounts of protein, vitamins and minerals[130]. As expected, data regarding the longterm effect of CR in humans is scarce. One of the reasons may be due to the difficulties of adhering to the life-long rigorous intervention, which may explain some failures in the clinical studies[131]. Apart from loss of muscle mass and bone density in older women[132,133], CR-related physiological symptoms also include hypotension, eating disorders, higher risk of hypothermia, loss of strength and stamina, slower wound healing, as well as a decline in sex steroids and infertility or



preterm delivery in females[134-138]. Therefore, CR is not recommended for women prior to or during pregnancy[139]. Furthermore, CR-related psychological conditions include depression, emotional deadening, and irritability, which affect not only the quality of their life but also the family members who care for them[140,141].

**Potential molecular mechanism of CR-mimetics in heart**

As discussed above, mitochondrial dysfunction plays a critical role in cardiac aging. Thus, the efficient removal of defective mitochondria through autophagy is essential for maintaining viability and homeostasis of cardiomyocytes. The efficiency of autophagy declines gradually with age, which contributes to heart senescence and age-related CVD[142-144]. CR is an effective autophagy inducer. Hence, compounds that are considered as CR-mimetics, in addition to extending health-span[145], should have the capability of inducing autophagy[146,147] by regulating intracellular levels of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) through inhibiting acetyltransferases or activating deacetylases[145]. NAD<sup>+</sup> levels decline with age[148,149], and the plasma NAD<sup>+</sup>/NADH ratio is sex-dependent and higher in women than in men although the difference reduces with increasing age[150]. Notably, resveratrol[151] and quercetin[152] act as a deacetylase activator, while curcumin[153], EGCG[154],

and spermidine[155] are well-established acetyltransferase inhibitors. They display cardio-protection in the aged animal hearts (Table 1) through distinct signaling pathways converging on the acetylproteome in association with autophagy.

**What is known about their effect on cardiac aging and CVD?**

**Resveratrol**

**Sources**

The highest content of resveratrol has been demonstrated as 30 mg/kg fresh weight of lingonberry (*Vaccinium vitisidaea L.*)[156], followed by a higher content in dried grape skins or red grapes, relative to grapes themselves or white ones, respectively[157,158].

**Alleviating cardiac aging**

The evidence that resveratrol can alleviate cardiac aging has been demonstrated in mice[24-26]. The mechanisms include restoring the expression of aging related transcription genes, such as Wnt/ $\beta$ -catenin signaling pathway, in the aged heart to levels found in a young heart[26] or protecting aged mice from myocardial toxicity[25] in a sirtuin 1 (SIRT1)-dependent manner[24]. With respect to cardiac aging in humans, the effect is unproven. However, it is evident that resveratrol augments autophagy to reverse remodeling in a post-infarction

mouse heart[159], and shows great ability to reduce red blood cell aggregation in patients with HF[160]. All of these aspects may positively affect cell viability and microcirculation thereby improving oxygen supply in an aging heart.

#### **Alleviating CVD**

The effects of resveratrol on mitigating CVD risk factors have been attributed to its antioxidant[106], antiinflammatory[161], antiplatelet[162], and lipid-lowering properties in preclinical studies[163,164]. Regarding the effect in humans, the first clinical trial of resveratrol with CVD patients was reported by Brasnyó *et al.*[36], in which, type 2 diabetic patients showed improvements in insulin sensitivity and oxidative stress after taking 10 mg of resveratrol daily for one month. Likewise, type 2 diabetic patients showed significant improvement in fasting blood glucose, systolic and diastolic blood pressure, and blood lipid profile with hypoglycemic drugs plus 250 mg daily resveratrol for three months when compared to hypoglycemic drugs alone[37]. In addition, the cardioprotective effect of resveratrol in humans are evident in patients with ischemic heart disease or HF. Resveratrol was used for patients from 2 to 3 months with a dosage of 10–20 mg/d[38,40] to 100 mg/d [39,41]. Longer duration of treatment was one year, with 8 mg/d and 16 mg/d for each 6 months, respectively[42]. Although the patients either had myocardial infarction[40], stable angina pectoris[38,42], coronary artery disease[39], or HFrEF[41], the effect of resveratrol on improving clinical parameters were mainly converged to improved endothelial function[40], cardiac function[39,41], and reduced inflammation[42]. It is noteworthy that resveratrol increases the expression of glucose transporter 4 through activation of endothelial estrogen receptors (ERs) to improve mitochondrial energy metabolism[165]. This could be beneficial for postmenopausal women, as menopause has adverse effects on lipid and glucose metabolism[166,167]. Currently, hormone therapy is not recommended for primary or secondary prevention of CVD at any age[168]. Therefore, resveratrol has been proposed to be a substitute of estradiol in women based on its effect on increasing endothelial function by enhancing the bioavailability of NO[169], as determined by using brachial artery flow-mediated vasodilation in healthy obese adults with or without mild hypertension, or in hypertensive postmenopausal women[43-45]. Importantly, resveratrol displays a beneficial effect on cognitive performance and total well-being in postmenopausal women[170], which can be sustained with ongoing supplementation for over a year[171].

#### **Conundrum**

Long-term studies are required to investigate the efficacy of resveratrol in humans, especially in patients with CVD. The

overall beneficial effects of resveratrol are not proportional to its dosing in humans. As an example, resveratrol supplementation for 30 d reduced insulin resistance[36,46] or plasma triglyceride[46] concentration at both low (10 mg/d) and moderate doses (150 mg/d), but not at high doses (1–2 g/d) [172]. The bioavailability of resveratrol is not reported in these studies but could be a potential reason attributable to the conflicting results. In general, oral resveratrol has low bioavailability but high absorption, due to a rapid hepatic first-pass metabolism[173]. Of note, the bioavailability of resveratrol can be greatly enhanced over 10 times by piperine, which is a type of bioactive alkaloid[174]. The intake of resveratrol appears to be at least 70% in the urinary excretion[175]. It is the sulfate conjugated form, rather than free form, of resveratrol detectable in human plasma samples within 2 h after either intravenous or oral doses, indicating that the formation of sulfation might be a rate-limiting factor to the bioavailability[175].

#### **Quercetin**

##### **Sources**

The highest content of quercetin is in cranberries (1.49 g/kg), followed by yellow sweet savannah onions (650 mg/kg)[176].

##### **Alleviating cardiac aging**

As a potent SIRT1/PGC-1 $\alpha$  activator[177], quercetin provides cardio-protection by reversing the effects of diabetes on SOD inhibition in the aged fatty rats[27], and improving aged-related cardiac dysfunction through activating PGC-1 $\alpha$ , SOD, and mitochondrial function while reducing inflammatory markers in mice[28]. Direct evidence of quercetin on alleviating cardiac aging in humans is lacking, but the number and duration of ischemic episodes reliably decreased by using quercetin in patients with ischemic heart disease[178]. Importantly, the reduced vulnerability is evident in human cardiomyocytes incubated with quercetin under hypoxic condition, which is associated with quercetin-mediated activation of mitophagy in a SIRT1-dependent manner[179]. Thus, the ability of quercetin to restore myocardial cell viability through ameliorating mitophagy may be useful for alleviating cardiac aging in humans.

##### **Alleviating CVD**

Quercetin has the highest antioxidant capacity among plant polyphenols[180] to modulate the levels of different antioxidant enzymes, such as SOD and catalase[181,182]. The protective effect of quercetin on CVD has been demonstrated in human studies[49,183-185]. For example, daily treatment of quercetin (120 mg) for two months significantly improved LV diastolic/systolic function in patients with stable coronary heart disease[50]. Likewise, 150 mg of quercetin[51] improved

blood pressure and reduced concentration of oxidized low density lipoprotein (LDL), a risk factor for CVD, in patients with hypertension or obesity[48,51,52]. Moreover, a 500 mg intake of quercetin for 70 d greatly reduced the blood pressure and plasma concentration of some inflammation markers, in women with type 2 diabetes[49].

#### **Conundrum**

Quercetin has low bioavailability, which is attributed to first-pass metabolism and being modified as methylated or dehydroxylated forms[186]. Quercetin can be administered intraperitoneally or orally. Compared to oral administration, the intraperitoneal method has less effect on systemic blood pressure, which is attributed to a higher content of methylated metabolites of quercetin after taking it orally[187]. A clinical trial has reported that quercetin from rutin is more bioavailable in women than in men[188]. Co-administration with high-fat meals is suggested to improve the bioavailability of quercetin[189], indicating that quercetin requires a specific application form and dose for keeping its activity.

#### **Curcumin**

##### **Sources**

It is an active constituent of turmeric with 31.4 g/kg of pure turmeric powder[190].

##### **Alleviating cardiac aging**

Curcumin promotes heart performance by improving VEGF-related angiogenesis in an old rat heart[29]. Although direct evidence of curcumin on retarding cardiac aging in humans is unavailable, a randomized clinical trial has demonstrated that curcuminoid treatment significantly decreases the incidence of in-hospital myocardial infarction, along with a reduced level of C-reactive protein, plasma malondialdehyde, and N-terminal pro-B-type natriuretic peptide in old patients [age (61±9) years] after coronary artery bypass grafting[53]. Importantly, curcumin activates autophagy in vascular endothelial cells[191], which may be a useful property for alleviating cardiac aging in humans by protecting endothelial cells from oxidative stress.

##### **Alleviating CVD**

The effects of curcumin on preventing CVD in humans have been demonstrated through its antioxidant, antiinflammatory, and lipid lowering properties. Administration of curcumin for 12 weeks caused a significant increase in total antioxidant capacity and a decrease in the expression of inflammatory markers in diabetic patients with coronary heart disease[54]. The lipidlowering effect of curcumin is mainly reflected by reducing serum LDL, triglyceride[192], and free fatty acid in diabetic patients[55]. It is interesting that curcumin attenuates abnormalities of the vascular system[56] and LV afterload[57] preferentially in postmenopausal women. The magnitudes of

the improved endothelial function with curcumin, as reflected by an increase in flow-mediated dilation, are comparable to that obtained with exercise in normotensive postmenopausal women[56], suggesting that curcumin treatment may be a special alternative approach against CVD in normotensive postmenopausal women who are unable to exercise. Regular aerobic exercise improves endothelial function in association with increased NO bioavailability[193]. It is unclear whether curcumin can improve endothelial function in men through a similar mechanism as in postmenopausal women.

#### **Conundrum**

Due to the relatively low absorption of the small intestine and fast metabolism, the oral bioavailability of curcumin is low[194]. However, it can be significantly increased by piperine through slowing the metabolism of curcumin[195]. It is evident that a combination of curcumin with piperine improves the lipid-modifying effect in patients with metabolic syndrome[196]. Studies showing no effect of curcumin on blood lipid profile were conducted with unformulated curcumin[197], which, in contrast to curcumin prepared in amorphous forms[198] or nanoparticles[199], is considered to have low bioavailability.

#### **EGCG**

##### **Sources**

EGCG is exclusively in tea, including green, black and oolong tea. Green tea has the highest levels of EGCG relative to oolong tea and black tea[200,201].

##### **Alleviating cardiac aging**

The anti-cardiac aging effects of EGCG have been demonstrated by improving cardiac function and reducing LV hypertrophy in mice[30] and rats[31]. One of the mechanisms is associated with the antioxidant activity of EGCG, thereby reducing circulating lipids, such as LDL, triglyceride, and inhibiting ROS-related activation of inflammatory factors in the aged rat heart[31]. On the other hand, the mechanism is also attributable to the effect of EGCG on inhibiting histone deacetylase 1 and 3, thereby up-regulating the acetylation of cardiac troponin I in the aged mouse heart[30]. The question remains unclear as to whether EGCG alleviates cardiac aging in humans. However, emerging data have revealed that increased histone acetylation is a hallmark of aging[74,202], and inhibition of which is beneficial in the heart by preventing oxidative stress and inflammation[203]. This may be associated with the role of EGCG in promoting autophagy-dependent survival[204], thereby protecting the heart against myocardial ischemia/reperfusion injury[205].

##### **Alleviating CVD**

EGCG prevents atherosclerosis and cardiac hypertrophy

via anti-oxidant[206], anti-inflammatory[207], and lipid-modulating properties [208]. Regarding the effect in humans, Kuriyama *et al.*[209] have demonstrated that older adults consuming five or more cups of green tea daily can significantly prevent CVD-related mortality. This is further supported by two population-based studies in Greece demonstrating that only green tea displays an association with greater levels of physical activity and reduced likelihood of hypertension[210], of which, the mechanism is attributed to the high levels of EGCG in green tea[210]. This notion is further supported by clinical studies, in which EGCG can ameliorate endothelial dysfunction in patients with coronary artery disease[58] or early atherosclerosis[59], while also reducing LV myocardial mass in patients with wild-type transthyretin amyloid cardiomyopathy[211]. Thus, most of the pharmacological effects are attributed to its antioxidant properties. One hypothesis is that the EGCG molecule is a strong electron donor due to its eight hydroxyl groups, thereby possessing an efficient ability in scavenging ROS[212]. Of interest, EGCG has a sex-dependent effect on reducing total cholesterol in males and LDL-cholesterol in females[213]. However, the efficacy of EGCG in humans is inconsistent, and either positive[60] or not proven[214,215] due to a major problem with low levels of stability and bioavailability.

#### **Conundrum**

The bioavailability of EGCG is rather low (i.e., 0.2%–2% of total ingestion) in humans under healthy conditions[216], but increases linearly with the dose of each intake[217]. However, patients have shown liver toxicity after continuous daily intake of more than 800 mg of EGCG of green tea[218]. Recent study has demonstrated that oxidized phosphatidylcholines can specifically deliver EGCG to intimal macrophages through cluster of differentiation 36 (CD36) receptors, while reducing toxicity due to the accumulation of EGCG in the liver[219]. This molecular approach has suggested a potential clinical usage by using biocompatible and biodegradable ligand-coated-EGCG nanoparticles to atherosclerosis formation.

#### **Spermidine**

##### **Sources**

Spermidine can be derived endogenously from amino acid catabolism, such as arginine, and presented in almost all eukaryotic and prokaryotic cells in millimolar concentration[220]. However, dietary spermidine is the major source of polyamines *in vivo*[221]. Spermidine is present in many foods, with comparable amount (100–200  $\mu\text{mol}/\text{kg}$ ) in vegetables, fermented cheeses, and meats, while less than 50  $\mu\text{mol}/\text{kg}$  in bread, potatoes and fruits[222].

#### **Alleviating cardiac aging**

Oral supplementation of spermidine can alleviate cardiac aging in mice[32,33] and rats[32,35] by enhancing autophagy, mitophagy[32] and mitochondrial respiration[223]. Spermidine also reverses arteria aging in mice by restoring NO-related endothelium-dependent dilation and reducing oxidative stress in an autophagy-dependent manner[34].

#### **Alleviating CVD**

Spermidine has become a leading candidate for treating CVD in humans[224], by promoting autophagy and mitophagy, as well as reducing systemic chronic inflammatory responses[84] and mortality[225]. From a clinical perspective, hypertension occurs in most elderly patients suffering from CVD[32,226]. High levels of dietary spermidine correlate with reduced blood pressure and low incidence of CVD[32] through inhibiting pro-inflammatory status in humans[61]. Spermidine intake has been observed to be greater in women than in men, and declines with age[225]. The regression analysis showed that plasma levels of spermidine tended to change with age[227] and sex[228]. However, due to large individual differences, trends were not statistically significant[228]. In fact, the exact biological mechanisms underlying the individual differences remain unknown. A good tolerability with no safety concerns is reported post supplementation of spermidine-rich plant extracts with older adults[229]. In addition, spermidine has neither adverse effects on glucose and insulin metabolism[32], nor side effects. Thus, keeping an optimal level of the polyamine content in various organs is an important consideration in the elderly because the activity of ornithine decarboxylase, a key polyamine biosynthetic enzyme, decreases with age[230].

#### **Conundrum**

The exact molecular mechanisms responsible for spermidine-induced activation of autophagy in cardiomyocytes remain unknown because the internalization or uptake of exogenous spermidine by cardiomyocytes has not been investigated. Based on the observation that the level of cardiac spermidine is higher in mice post spermidine treatment, it has been proposed that the exogenous spermidine is preferentially taken-up by cardiomyocytes[32]. Thus, it is necessary to establish *in vivo* studies to investigate the underlying mechanisms of spermidine uptake by cardiomyocytes. This may help us to understand whether it is the differences in dosage or routes of administration that have caused inconsistent findings.

#### **Perspective**

##### **What remains unclear?**

On the mechanistic level, the above-mentioned CR-mimetics

protect the heart and blood vessels through reducing mitochondrial damage, apoptosis, inflammation, and oxidative stress, which are relevant to delay cardiac aging and are associated with autophagy activation[147] *via* improving mitochondrial turnover. However, an increased autophagy is evident in a mouse heart with type 1 diabetes, while a decrease of which is seen in type 2 diabetes[231]. Likewise, the numbers of autophagosomes are increased in cardiac tissues of patients with LV-hypertrophy[232], aortic valve stenosis[233], hibernating myocardium[234], and HF[235]. What are the responses of autophagy to cardiac function in these conditions: adaptive or maladaptive? It has been proposed that low levels of autophagy can protect cardiomyocytes and endothelial cells, whereas excessive of which do the opposite *via* damaging mechanisms[236]. To date, there is no available method to assess autophagy flux within the human body or specific organs, which challenges the investigations to identify the optimal autophagic activation windows. Hence, the current clinical evidence is insufficient to discuss if their cardiac effects are systemic or organ specific. Another puzzle is that the beneficial effects on CVD in humans are inconsistent, and inequitable to the dosing of CR-mimetics. Hence, should CR-mimetics be a supplemental molecule that can boost the effectiveness of existing medical drugs for CVD? From a dietary perspective, the main challenge of alleviating cardiac aging is to quantify the degree of prevention achieved in healthy individuals. Thus, what are the most relevant features to be evaluated? Collectively, to understand and quantify the therapeutic efficacy of CR-mimetics in a human heart, we propose that a few factors should be taken into consideration.

#### **What more should be considered?**

First, a dose-dependent response and long-term observation with higher sample size. Most of the interventional studies with the above-mentioned CR-mimetics lack the dose response relationship with long term effects. They have focused on traditional cardiovascular risk factors, such as obesity, hypertension, and hyperlipidemia[32,223,237], without considering the cardiovascular endpoints, such as age-related atrial wall stiffness and flow-mediated dilation. In addition, bioavailability and metabolization are important factors for designing clinical experiments and ensuring therapeutic efficacy. Low oral bioavailability may be a major challenge associated with the ambiguous therapeutic effects in clinical trials, from positive[42,44] to ineffectual[238-240] or large individual variations[228]. Factors causing low bioavailability may include not only their content in the diet and intake in humans, but also their metabolic processes mediated by the liver, intestines and microbiota[241]. As an example, dietary

intake levels of total flavanols are estimated to vary greatly from 386 mg/d in Germany[242], 192 mg/d in the United States[243], and 23 mg/d in the Netherlands[244]. Likewise, daily intake of spermidine is reported to correlate with gross domestic product[245]. These discrepancies cause problems for estimating an efficient intake, which certainly influence dosing schemes and clinical outcomes. With respect to absorption, the forms displaying in circulation are often not the forms seen in food, indicating that absorption is accompanied by certain conjugation and metabolism. As an example, quercetin in a form of glucoside in onions is efficiently absorbed and bioavailable compared to the free forms[246] or other forms containing rutin in apples and tea[247]. In contrast, plasma EGCG is mostly in an unconjugated form, and has proven to have higher activity than its metabolites[248]. Lastly, a combinational therapy should be considered. Biological cardiac aging is a multifactorial process with many systemic contributing mechanisms occurring within the heart and surrounding tissues. As such, it is unlikely that any single pathway or intervention would fully restore age-related cardiac phenotypes. It has been demonstrated that the impact of combinational therapies on boosting the functional abilities of vasculature and endothelial function is greater than those of individual treatments in postmenopausal women[249,250]. Based on the observation that curcumin pharmacokinetics are affected by sex[251], we propose that the dosage of polyphenol or polyamine, personalized as a “one-dose-fits-all” strategy, is unlikely to work. Thus, as an example of combinational therapies, we propose that stimulating glucose oxidation, by pyruvate dehydrogenase kinase inhibitor[252], along with a supplementation of polyphenol or polyamine, may be beneficial to human aging hearts[253]. The concept is that glycolysis is increased in the aged heart along with unaltered glucose oxidation[14,254]. As a result, glycolytic intermediates are diverted to form advanced glycation end-products[255] (Fig. 1b), which can be recognized by CD36[256] causing oxidative stress-related inflammation and endothelial dysfunction[257,258]. Thus, stimulating glucose oxidation will amplify the effect of CR-mimetics by enhancing ATP production in concert with improving systemic glucose tolerance and inflammation. This notion can be further supported by others showing that a combination of spermidine from a natural product with nicotinamide inhibits oxidative stress and improves endothelial cell survival, in a potentiated manner than each compound alone, in platelets isolated from patients with metabolic syndrome[259]. This also holds true for the effect of combinational resveratrol-piperine with  $\alpha$ -tocopherol (has an anti-inflammatory activity[260]),

in a clinical trial[47], in which, the decrease in arterial hypertension and inflammation is evident in older patients [age (68±4.7) years] with metabolic syndrome[47].

## Conclusions

CR-mimetics show promising results in alleviating aspects of CVD in humans. Based on the role of autophagy in the prevention of age-related conditions, CR-mimetics can be considered as a potential therapeutic tool for alleviating cardiac aging in humans, which is especially true for cardiomyocytes due to the heavy reliance on mitochondrial oxidative metabolism to keep contractility. However, the baseline intake of dietary CR-mimetics will influence the outcomes of dosing schemes. Sex-specific differences in absorption, distribution or excretion of the interventional compounds have important clinical consequences and side effects, which may affect the therapeutic efficacy and anti-aging potential in humans. To improve the clinical effectiveness, some important data need to be addressed from CR-mimetics, such as bioactive levels, oral bioavailability, metabolization, organ-specific effects, and interaction with body-endogenous biosynthesis pathways. Larger size of participants and longer follow-up are required to confirm the clinical effect.

## Abbreviations

ATP: Adenosine triphosphate; CD36: Cluster of differentiation 36; CR: Caloric restriction; CVD: Cardiovascular disease; eNOS: Endothelial NO synthase; EGCG: Epigallocatechin gallate; ERs: Estrogen receptors; HF: Heart failure; HFpEF: HF patients with preserved ejection fraction; HFrEF: HF patients with reduced ejection fraction; LDL: Low density lipoprotein; LV: Left ventricle; NAD: Nicotinamide adenine dinucleotide; NO: Nitric oxide; PGC1 $\alpha$ : Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ROS: Reactive oxygen species; SIRT1: Sirtuin 1; SOD: Superoxide dismutase; VEGF: Vascular endothelial growth factor.

## Acknowledgements

We acknowledge Dr. Yun Lan [Centre for Immunology and Infection (C2I), Hong Kong] for the help on figure preparation.

## Author contributions

LP, XJ, XL and JC drafted the manuscript and developed the figures; EFS, LGJ and ZYX edited the manuscript and developed the figures; HCM and YC conceived, supervised the study and edited the manuscript. All authors read and approved the final manuscript.

## Funding

This work was supported by grants from the National Natural Science Foundation of China (81800245, 81970228, 82102306, 81900779), the China Postdoctoral Science Foundation (2020M670030ZX), the Shaoguan Science and Technology Program (2019sn078), and the Start-up Fund for RAPs under the Strategic Hiring Scheme (P0035913).

## Availability of data and materials

Not applicable.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>Department of Anesthesiology, the First Hospital of Jilin University, Changchun 130021, China. <sup>2</sup>Health Promotion Center, the First Hospital of Jilin University, Changchun 130021, China. <sup>3</sup>Department of Urology, the First Hospital of Jilin University, Changchun 130021, China. <sup>4</sup>Henry Fok School of Biology and Agriculture, Shaoguan University, Shaoguan 512000, Guangdong, China. <sup>5</sup>Department of Metabolic and Bariatric Surgery, Jinan University First Affiliated Hospital, Guangzhou 510630, China. <sup>6</sup>Department of Medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong, China. <sup>7</sup>State Key Laboratory of Pharmaceutical Biotechnology, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong, China. <sup>8</sup>Department of Anesthesiology, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, Guangdong, China. <sup>9</sup>Department of Health Technology and Informatics, the Hong Kong Polytechnic University, Hong Kong, China.

## References

1. Cai Y, Liu H, Song E, Wang L, Xu J, He Y, et al. Deficiency of telomere-associated repressor activator protein 1 precipitates cardiac aging in mice via p53/PPAR $\alpha$  signaling. *Theranostics*. 2021;11(10):4710–27.
2. Hu C, Zhang X, Teng T, Ma ZG, Tang QZ. Cellular senescence in cardiovascular diseases: a systematic review. *Aging Dis*. 2022;13(1):103.
3. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation*. 2018;137(12):e67–492.
4. Jakovljevic DG. Physical activity and cardiovascular aging: physiological and molecular insights. *Exp Gerontol*. 2018;109:67–74.
5. Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular risks associated with gender and aging. *J Cardiovasc Dev Dis*. 2019;6(2):19.
6. Stanhewicz AE, Wenner MM, Stachenfeld NS. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. *Am J Physiol Heart Circ Physiol*. 2018;315(6):H1569–88.
7. Bozkurt B, Khalaf S. Heart failure in women. *Methodist Debakey Cardiovasc J*. 2017;13(4):216–23.
8. López-Vilella R, Marqués-Sulé E, Laymito Quispe RDP, Sánchez-Lázaro I, Donoso Trenado V, Martínez Dolz L, et al. The female sex confers different prognosis in heart failure: same mortality but more readmissions. *Front Cardiovasc Med*. 2021;8:618398.
9. Wong KHY, Cai Y, Ying F, Chen X, Vanhoutte PM, Tang EH. Deletion of Rap1 disrupts redox balance and impairs endothelium-dependent relaxations. *J Mol Cell Cardiol*. 2018;115:1–9.

10. Bokov A, Chaudhuri A, Richardson A. The role of oxidative damage and stress in aging. *Mech Ageing Dev.* 2004;125(10–11):811–26.
11. Cadenas S. Mitochondrial uncoupling, ROS generation and cardioprotection. *Biochim Biophys Acta Bioenerg.* 2018;1859(9):940–50.
12. Zhao RZ, Jiang S, Zhang L, Yu ZB. Mitochondrial electron transport chain, ROS generation and uncoupling. *Int J Mol Med.* 2019;44(1):3–15.
13. Wang L, Cai Y, Jian L, Cheung CW, Zhang L, Xia Z. Impact of peroxisome proliferator-activated receptor- $\alpha$  on diabetic cardiomyopathy. *Cardiovasc Diabetol.* 2021;20(1):2.
14. Sithara T, Drosatos K. Metabolic complications in cardiac aging. *Front Physiol.* 2021;12:669497.
15. Pang L, Lian X, Liu H, Zhang Y, Li Q, Cai Y, et al. Understanding diabetic neuropathy: focus on oxidative stress. *Oxid Med Cell Longev.* 2020;2020:9524635.
16. Velarde MC. Mitochondrial and sex steroid hormone crosstalk during aging. *Longev Healthspan.* 2014;3(1):2.
17. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. *Proc Natl Acad Sci U S A.* 1994;91(23):10771–8.
18. Barcena De Arellano ML, Pozdniakova S, Kühl AA, Baczko I, Ladilov Y, Regitz-Zagrosek V. Sex differences in the aging human heart: decreased sirtuins, pro-inflammatory shift and reduced anti-oxidative defense. *Aging (Albany NY).* 2019;11(7):1918–33.
19. Hahn VS, Knutsdottir H, Luo X, Bedi K, Margulies KB, Haldar SM, et al. Myocardial gene expression signatures in human heart failure with preserved ejection fraction. *Circulation.* 2021;143(2):120–34.
20. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res.* 2019;124(11):1598–617.
21. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;21(10):1169–86.
22. Adegbola P, Aderibigbe I, Hamed W, Omotayo T. Antioxidant and antiinflammatory medicinal plants have potential role in the treatment of cardiovascular disease: a review. *Am J Cardiovasc Dis.* 2017;7(2):19–32.
23. Santos CN, Gomes A, Oudot C, Dias-Pedroso D, Rodriguez-Mateos A, Vieira HLA, et al. Pure polyphenols applications for cardiac health and disease. *Curr Pharm Des.* 2018;24(19):2137–56.
24. Sin TK, Yu AP, Yung BY, Yip SP, Chan LW, Wong CS, et al. Modulating effect of SIRT1 activation induced by resveratrol on Foxo1-associated apoptotic signalling in senescent heart. *J Physiol.* 2014;592(12):2535–48.
25. Sin TK, Tam BT, Yung BY, Yip SP, Chan LW, Wong CS, et al. Resveratrol protects against doxorubicin-induced cardiotoxicity in aged hearts through the SIRT1-USP7 axis. *J Physiol.* 2015;593(8):1887–99.
26. Li Q, Hannah SS. Wnt/ $\beta$ -catenin signaling is downregulated but restored by nutrition interventions in the aged heart in mice. *Arch Gerontol Geriatr.* 2012;55(3):749–54.
27. Botanska B, Bartekova M, Ferenczyova K, Fogarassyova M, Kindernay L, Barancik M. Matrix metalloproteinases and their role in mechanisms underlying effects of quercetin on heart function in aged Zucker diabetic fatty rats. *Int J Mol Sci.* 2021;22(9):4457.
28. Ballmann C, Denney TS, Beyers RJ, Quindry T, Romero M, Amin R, et al. Lifelong quercetin enrichment and cardioprotection in Mdx/Utrn $\pm$  mice. *Am J Physiol Heart Circ Physiol.* 2017;312(1):H128–40.
29. Ghorbanzadeh V, Pourheydar B, Dariushnejad H, Ghalibafabbaghi A, Chodari L. Curcumin improves angiogenesis in the heart of aged rats: Involvement of TSP1/NF- $\kappa$ B/VEGF-A signaling. *Microvasc Res.* 2022;139:104258.
30. Pan B, Quan J, Liu L, Xu Z, Zhu J, Huang X, et al. Epigallocatechin gallate reverses cTnI-low expression-induced age-related heart diastolic dysfunction through histone acetylation modification. *J Cell Mol Med.* 2017;21(10):2481–90.
31. Muhammed I, Sankar S, Govindaraj S. Ameliorative effect of epigallocatechin gallate on cardiac hypertrophy and fibrosis in aged rats. *J Cardiovasc Pharmacol.* 2018;71(2):65–75.
32. Eisenberg T, Abdellatif M, Schroeder S, Primessnig U, Stekovic S, Pendl T, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med.* 2016;22(12):1428–38.
33. Wierich MC, Schipke J, Brandenberger C, Abdellatif M, Eisenberg T, Madeo F, et al. Cardioprotection by spermidine does not depend on structural characteristics of the myocardial microcirculation in aged mice. *Exp Gerontol.* 2019;119:82–8.
34. LaRocca TJ, Gioscia-Ryan RA, Hearon CM Jr, Seals DR. The autophagy enhancer spermidine reverses arterial aging. *Mech Ageing Dev.* 2013;134(7–8):314–20.
35. Zhang H, Wang J, Li L, Chai N, Chen Y, Wu F, et al. Spermine and spermidine reversed age-related cardiac deterioration in rats. *Oncotarget.* 2017;8(39):64793–808.
36. Brasnyó P, Molnár GA, Mohás M, Markó L, Laczy B, Cseh J, et al. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. *Br J Nutr.* 2011;106(3):383–9.
37. Bhatt JK, Thomas S, Nanjan MJ. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutr Res.* 2012;32(7):537–41.
38. Militaru C, Donoiu I, Craciun A, Scorei ID, Bulearca AM, Scorei RI. Oral resveratrol and calcium fructoborate supplementation in subjects with stable angina pectoris: effects on lipid profiles, inflammation markers, and quality of life. *Nutrition.* 2013;29(1):178–83.
39. Chekalina NI. Resveratrol has a positive effect on parameters of central hemodynamics and myocardial ischemia in patients with stable coronary heart disease. *Wiad Lek.* 2017;70(2 pt 2):286–91.
40. Magyar K, Halmosi R, Palfi A, Feher G, Czopf L, Fulop A, et al. Cardioprotection by resveratrol: a human clinical trial in patients with stable coronary artery disease. *Clin Hemorheol Microcirc.* 2012;50(3):179–87.
41. Gal R, Deres L, Horvath O, Eros K, Sandor B, Urban P, et al. Resveratrol improves heart function by moderating inflammatory processes in patients with systolic heart failure. *Antioxidants (Basel).* 2020;9(11):1108.
42. Tomé-Carneiro J, González M, Larrosa M, Yáñez-Gascón MJ, García-Almagro FJ, Ruiz-Ros JA, et al. One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. *Am J Cardiol.* 2012;110(3):356–63.
43. Marques BCAA, Trindade M, Aquino JCF, Cunha AR, Gismondini RO, Neves MF, et al. Beneficial effects of acute trans-resveratrol supplementation in treated hypertensive patients with endothelial dysfunction. *Clin Exp Hypertens.* 2018;40(3):218–23.

44. Wong RHX, Howe PRC, Buckley JD, Coates AM, Kunz I, Berry NM. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. *Nutr Metab Cardiovasc Dis.* 2011;21(11):851–6.
45. Wong RHX, Berry NM, Coates AM, Buckley JD, Bryan J, Kunz I, *et al.* Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults. *J Hypertens.* 2013;31(9):1819–27.
46. Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, *et al.* Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab.* 2011;14(5):612–22.
47. Pastor RF, Repetto MG, Lairion F, Lazarowski A, Merelli A, Manfredi Carabetti Z, *et al.* Supplementation with resveratrol, piperine and alphatocopherol decreases chronic inflammation in a cluster of older adults with metabolic syndrome. *Nutrients.* 2020;12(10):3149.
48. Dower JI, Geleijnse JM, Gijsbers L, Schalkwijk C, Kromhout D, Hollman PC. Supplementation of the pure flavonoids epicatechin and quercetin affects some biomarkers of endothelial dysfunction and inflammation in (pre)hypertensive adults: a randomized double-blind, placebocontrolled, crossover trial. *J Nutr.* 2015;145(7):1459–63.
49. Zahedi M, Ghiasvand R, Feizi A, Asgari G, Darvish L. Does quercetin improve cardiovascular risk factors and inflammatory biomarkers in women with type 2 diabetes: a double-blind randomized controlled clinical trial. *Int J Prev Med.* 2013;4(7):777–85.
50. Chekalina NI, Shut SV, Trybrat TA, Burmak YH, Petrov YY, Manusha YI, *et al.* Effect of quercetin on parameters of central hemodynamics and myocardial ischemia in patients with stable coronary heart disease. *Wiad Lek.* 2017;70(4):707–11.
51. Egert S, Bosy-Westphal A, Seiberl J, Kurbitz C, Settler U, Plachta-Danielzik S, *et al.* Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebocontrolled cross-over study. *Br J Nutr.* 2009;102(7):1065–74.
52. Brüll V, Burak C, Stoffel-Wagner B, Wolfram S, Nickenig G, Müller C, *et al.* Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: a randomised double-blinded placebo-controlled cross-over trial. *Br J Nutr.* 2015;114(8):1263–77.
53. Wongcharoen W, Jai-Aue S, Phrommintikul A, Nawarawong W, Woragidpoonpol S, Tepsuwan T, *et al.* Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. *Am J Cardiol.* 2012;110(1):40–4.
54. Shafabakhsh R, Mobini M, Raygan F, Aghadavod E, Ostadmohammadi V, Amirani E, *et al.* Curcumin administration and the effects on psychological status and markers of inflammation and oxidative damage in patients with type 2 diabetes and coronary heart disease. *Clin Nutr ESPEN.* 2020;40:77–82.
55. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M, *et al.* Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. *Mol Nutr Food Res.* 2013;57(9):1569–77.
56. Akazawa N, Choi Y, Miyaki A, Tanabe Y, Sugawara J, Ajisaka R, *et al.* Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women. *Nutr Res.* 2012;32(10):795–9.
57. Sugawara J, Akazawa N, Miyaki A, Choi Y, Tanabe Y, Imai T, *et al.* Effect of endurance exercise training and curcumin intake on central arterial hemodynamics in postmenopausal women: pilot study. *Am J Hypertens.* 2012;25(6):651–6.
58. Widlansky ME, Hamburg NM, Anter E, Holbrook M, Kahn DF, Elliott JG, *et al.* Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease. *J Am Coll Nutr.* 2007;26(2):95–102.
59. Widmer RJ, Freund MA, Flammer AJ, Sexton J, Lennon R, Romani A, *et al.* Beneficial effects of polyphenol-rich olive oil in patients with early atherosclerosis. *Eur J Nutr.* 2013;52(3):1223–31.
60. Hill AM, Coates AM, Buckley JD, Ross R, Thielecke F, Howe PRC. Can EGCG reduce abdominal fat in obese subjects? *J Am Coll Nutr.* 2007;26(4):396S–402S.
61. Soda K, Uemura T, Sanayama H, Igarashi K, Fukui T. Polyamine-rich diet elevates blood spermine levels and inhibits pro-inflammatory status: an interventional study. *Med Sci (Basel).* 2021;9(2):22.
62. De Magalhaes JP. Why genes extending lifespan in model organisms have not been consistently associated with human longevity and what it means to translation research. *Cell Cycle.* 2014;13(17):2671–3.
63. Singam NSV, Fine C, Fleg JL. Cardiac changes associated with vascular aging. *Clin Cardiol.* 2020;43(2):92–8.
64. Fleg JL, O'Connor F, Gerstenblith G, Becker LC, Clulow J, Schulman SP, *et al.* Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. *J Appl Physiol.* 1995;78(3):890–900.
65. Zhang TY, Zhao BJ, Wang T, Wang J. Effect of aging and sex on cardiovascular structure and function in wildtype mice assessed with echocardiography. *Sci Rep.* 2021;11(1):22800.
66. D'Andrea A, Vriz O, Carbone A, Ferrara F, Di Maio M, Cocchia R, *et al.* The impact of age and gender on right ventricular diastolic function among healthy adults. *J Cardiol.* 2017;70(4):387–95.
67. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Taliencio CP, Taylor CL, *et al.* Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. *J Am Soc Echocardiogr.* 1990;3(1):54–63.
68. Feridooni HA, Dibb KM, Howlett SE. How cardiomyocyte excitation, calcium release and contraction become altered with age. *J Mol Cell Cardiol.* 2015;83:62–72.
69. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and age-related diseases: role of inflammation triggers and cytokines. *Front Immunol.* 2018;9:586.
70. Cai Y, Ying F, Liu H, Ge L, Song E, Wang L, *et al.* Deletion of Rap1 protects against myocardial ischemia/reperfusion injury through suppressing cell apoptosis *via* activation of STAT3 signaling. *FASEB J.* 2020;34(3):4482–96.
71. Perbellini F, Watson SA, Scigliano M, Alayoubi S, Tkach S, Bardi I, *et al.* Investigation of cardiac fibroblasts using myocardial slices. *Cardiovasc Res.* 2018;114(1):77–89.
72. Ge L, Cai Y, Ying F, Liu H, Zhang D, He Y, *et al.* miR-181c-5p exacerbates hypoxia/reoxygenation-induced cardiomyocyte apoptosis *via* targeting PTPN4. *Oxid Med Cell Longev.* 2019;2019:1957920.
73. Pang L, Cai Y, Tang EHC, Yan D, Kosuru R, Li H, *et al.* Cox-2 inhibition protects against hypoxia/reoxygenation-induced

- cardiomyocyte apoptosis via Akt-dependent enhancement of iNOS expression. *Oxid Med Cell Longev*. 2016;2016:3453059.
74. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–217.
  75. Porrello ER, Mahmoud AI, Simpson E, Hill JA, Richardson JA, Olson EN, et al. Transient regenerative potential of the neonatal mouse heart. *Science*. 2011;331(6020):1078–80.
  76. Tang X, Li PH, Chen HZ. Cardiomyocyte senescence and cellular communications within myocardial microenvironments. *Front Endocrinol (Lausanne)*. 2020;11:280.
  77. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabé-Heider F, Walsh S, et al. Evidence for cardiomyocyte renewal in humans. *Science*. 2009;324(5923):98–102.
  78. Perbellini F, Watson SA, Bardi I, Terracciano CM. Heterocellularity and cellular cross-talk in the cardiovascular system. *Front Cardiovasc Med*. 2018;5:143.
  79. Wagner JUG, Dimmeler S. Cellular cross-talks in the diseased and aging heart. *J Mol Cell Cardiol*. 2020;138:136–46.
  80. Kivelä R, Hemanthakumar KA, Vaparanta K, Robciuc M, Izumiya Y, Kidoya H, et al. Endothelial cells regulate physiological cardiomyocyte growth via VEGFR2-mediated paracrine signaling. *Circulation*. 2019;139(22):2570–84.
  81. Helker CS, Eberlein J, Wilhelm K, Sugino T, Malchow J, Schuermann A, et al. Apelin signaling drives vascular endothelial cells toward a proangiogenic state. *Elife*. 2020;9:e55589.
  82. Kuba K, Zhang L, Imai Y, Arab S, Chen M, Maekawa Y, et al. Impaired heart contractility in Apelin gene-deficient mice associated with aging and pressure overload. *Circ Res*. 2007;101(4):e32–42.
  83. de Yébenes VG, Briones AM, Martos-Folgado I, Mur SM, Oller J, Bilal F, et al. Aging-associated miR-217 aggravates atherosclerosis and promotes cardiovascular dysfunction. *Arterioscler Thromb Vasc Biol*. 2020;40(10):2408–24.
  84. Yamaguchi O. Autophagy in the heart. *Circ J*. 2019;83(4):697–704.
  85. Li H, Hastings MH, Rhee J, Trager LE, Roh JD, Rosenzweig A. Targeting age-related pathways in heart failure. *Circ Res*. 2020;126(4):533–51.
  86. Wang Y, Li Y, He C, Gou B, Song M. Mitochondrial regulation of cardiac aging. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(7):1853–64.
  87. Vásquez-Trincado C, García-Carvajal I, Pennanen C, Parra V, Hill JA, Rothermel BA, et al. Mitochondrial dynamics, mitophagy and cardiovascular disease. *J Physiol*. 2016;594(3):509–25.
  88. Sciarretta S, Maejima Y, Zablocki D, Sadoshima J. The role of autophagy in the heart. *Annu Rev Physiol*. 2018;80:1–26.
  89. Gatica D, Chiong M, Lavandero S, Klionsky DJ. Molecular mechanisms of autophagy in the cardiovascular system. *Circ Res*. 2015;116(3):456–67.
  90. Fougere B, Boulanger E, Nourhashemi F, Guyonnet S, Cesari M. Chronic inflammation: accelerator of biological aging. *J Gerontol A Biol Sci Med Sci*. 2017;72(9):1218–25.
  91. Deng Y, Xie M, Li Q, Xu X, Ou W, Zhang Y, et al. Targeting mitochondriainflammation circuit by beta-hydroxybutyrate mitigates HFpEF. *Circ Res*. 2021;128(2):232–45.
  92. Dai DF, Santana LF, Vermulst M, Tomazela DM, Emond MJ, Maccoss MJ, et al. Overexpression of catalase targeted to mitochondria attenuates murine cardiac aging. *Circulation*. 2009;119(21):2789–97.
  93. Sahin E, Colla S, Liesa M, Moslehi J, Muller FL, Guo M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature*. 2011;470(7334):359–65.
  94. Moslehi J, Depinho RA, Sahin E. Telomeres and mitochondria in the aging heart. *Circ Res*. 2012;110(9):1226–37.
  95. Tan BL, Norhaizan ME, Liew WPP, Sulaiman RH. Antioxidant and oxidative stress: a mutual interplay in age-related diseases. *Front Pharmacol*. 2018;9:1162.
  96. Cruz-Topete D, Dominic P, Stokes KY. Uncovering sex-specific mechanisms of action of testosterone and redox balance. *Redox Biol*. 2020;31:101490.
  97. Mahmoodzadeh S, Dworatzek E. The role of 17β-estradiol and estrogen receptors in regulation of Ca<sup>2+</sup> channels and mitochondrial function in cardiomyocytes. *Front Endocrinol (Lausanne)*. 2019;10:310.
  98. Xiang D, Liu Y, Zhou S, Zhou E, Wang Y. Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. *Oxid Med Cell Longev*. 2021;2021:5523516.
  99. Förstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. *Circ Res*. 2017;120(4):713–35.
  100. White RE, Gerrity R, Barman SA, Han G. Estrogen and oxidative stress: A novel mechanism that may increase the risk for cardiovascular disease in women. *Steroids*. 2010;75(11):788–93.
  101. Taddei S, Virdis A, Ghiadoni L, Mattei P, Sudano I, Bernini G, et al. Menopause is associated with endothelial dysfunction in women. *Hypertension*. 1996;28(4):576–82.
  102. Gavin KM, Seals DR, Silver AE, Moreau KL. Vascular endothelial estrogen receptor alpha is modulated by estrogen status and related to endothelial function and endothelial nitric oxide synthase in healthy women. *J Clin Endocrinol Metab*. 2009;94(9):3513–20.
  103. Moreau KL. Modulatory influence of sex hormones on vascular aging. *Am J Physiol Heart Circ Physiol*. 2019;316(3):H522–6.
  104. Moreau KL, Stauffer BL, Kohrt WM, Seals DR. Essential role of estrogen for improvements in vascular endothelial function with endurance exercise in postmenopausal women. *J Clin Endocrinol Metab*. 2013;98(11):4507–15.
  105. Virdis A, Ghiadoni L, Pinto S, Lombardo M, Petraglia F, Gennazzani A, et al. Mechanisms responsible for endothelial dysfunction associated with acute estrogen deprivation in normotensive women. *Circulation*. 2000;101(19):2258–63.
  106. Xia N, Daiber A, Förstermann U, Li H. Antioxidant effects of resveratrol in the cardiovascular system. *Br J Pharmacol*. 2017;174(12):1633–46.
  107. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health*. 2017;2(2):e000298.
  108. Ghali JK, Piña IL, Gottlieb SS, Deedwania PC, Wikstrand JC, MERIT-HF Study Group. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation*. 2002;105(13):1585–91.
  109. Hayward CS, Kalnins WV, Kelly RP. Gender-related differences in left ventricular chamber function. *Cardiovasc Res*. 2001;49(2):340–50.
  110. Goldspink DF, George KP, Chantler PD, Clements RE, Sharp L, Hodges G, et al. A study of presbycardia, with gender differences favoring ageing women. *Int J Cardiol*. 2009;137(3):236–45.
  111. Jakovljevic DG, Papakonstantinou L, Blamire AM, Macgowan GA, Taylor R, Hollingsworth KG, et al. Effect of physical activity on age-

- related changes in cardiac function and performance in women. *Circ Cardiovasc Imaging*. 2014;8(1):e002086.
112. Smulyan H, Asmar RG, Rudnicki A, London GM, Safar ME. Comparative effects of aging in men and women on the properties of the arterial tree. *J Am Coll Cardiol*. 2001;37(5):1374–80.
  113. Mitoff PR, Al-Hesayen A, Azevedo E, Newton GE, Mak S. Sex differences in basal hemodynamics and left ventricular function in humans with and without heart failure. *Am Heart J*. 2007;154(3):575–80.
  114. Creatsa M, Armeni E, Stamatelopoulos K, Rizos D, Georgiopoulos G, Kazani M, et al. Circulating androgen levels are associated with subclinical atherosclerosis and arterial stiffness in healthy recently menopausal women. *Metabolism*. 2012;61(2):193–201.
  115. Ouyang P, Vaidya D, Dobs A, Golden SH, Szklo M, Heckbert SR, et al. Sex hormone levels and subclinical atherosclerosis in postmenopausal women: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2009;204(1):255–61.
  116. Bernini GP, Sgro M, Moretti A, Argenio GF, Barlascini CO, Cristofani R, et al. Endogenous androgens and carotid intimal-medial thickness in women. *J Clin Endocrinol Metab*. 1999;84(6):2008–12.
  117. Ishay A, Tzemah S, Nitzan R, Jehassi A, Cohen M. Testosterone management in aging males: surveying clinical practices of urologists and endocrinologists in Israel. *Sexual Med*. 2019;7(4):409–17.
  118. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Am Geriatr Soc*. 2010;58(6):1134–43.
  119. Gonzalez-Campoy JM, St Jeor ST, Castorino K, Ebrahim A, Hurley D, Jovanovic L, et al. Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. *Endocr Pract*. 2013;19(Suppl 3):1–82.
  120. Kaur H, Werstuck GH. The effect of testosterone on cardiovascular disease and cardiovascular risk factors in men: a review of clinical and preclinical data. *CJC Open*. 2021;3(10):1238–48.
  121. Goodale T, Sadhu A, Petak S, Robbins R. Testosterone and the heart. *Methodist Debakey Cardiovasc J*. 2017;13(2):68–72.
  122. Laughlin GA, Goodell V, Barrett-Connor E. Extremes of endogenous testosterone are associated with increased risk of incident coronary events in older women. *J Clin Endocrinol Metab*. 2010;95(2):740–7.
  123. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev*. 2017;3(1):7–11.
  124. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146–603.
  125. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016;133(4):e38–360.
  126. Goldberg RJ, Spencer FA, Farmer C, Meyer TE, Pezzella S. Incidence and hospital death rates associated with heart failure: a community-wide perspective. *Am J Med*. 2005;118(7):728–34.
  127. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, et al. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol*. 2013;61(14):1510–7.
  128. Martínez-Sellés M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. *Eur J Heart Fail*. 2012;14(5):473–9.
  129. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175(6):996–1004.
  130. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. *Ageing Res Rev*. 2017;39:36–45.
  131. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab*. 2018;27(4):805–15.e4.
  132. Bales CW, Buhr G. Is obesity bad for older persons? a systematic review of the pros and cons of weight reduction in later life. *J Am Med Dir Assoc*. 2008;9(5):302–12.
  133. Wherry SJ, Miller RM, Jeong SH, Beavers KM. The ability of exercise to mitigate caloric restriction-induced bone loss in older adults: a structured review of RCTs and narrative review of exercise-induced changes in bone biomarkers. *Nutrients*. 2021;13(4):1250.
  134. Nicoll R, Henein MY. Caloric restriction and its effect on blood pressure, heart rate variability and arterial stiffness and dilatation: a review of the evidence. *Int J Mol Sci*. 2018;19(3):751.
  135. Stewart TM, Martin CK, Williamson DA. The complicated relationship between dieting, dietary restraint, caloric restriction, and eating disorders: is a shift in public health messaging warranted? *Int J Environ Res Public Health*. 2022;19(1):491.
  136. Guijas C, Montenegro-Burke JR, Cintron-Colon R, Domingo-Almenara X, Sanchez-Alavez M, Aguirre CA, et al. Metabolic adaptation to calorie restriction. *Sci Signal*. 2020;13(648):eabb2490.
  137. Wang M, Zhang L, Zhu W, Zhang J, Kim SH, Wang Y, et al. Calorie restriction curbs proinflammation that accompanies arterial aging, preserving a youthful phenotype. *J Am Heart Assoc*. 2018;7(18):e009112.
  138. Sun J, Shen X, Liu H, Lu S, Peng J, Kuang H. Caloric restriction in female reproduction: is it beneficial or detrimental? *Reprod Biol Endocrinol*. 2021;19(1):1.
  139. Dirks AJ, Leeuwenburgh C. Caloric restriction in humans: potential pitfalls and health concerns. *Mech Ageing Dev*. 2006;127(1):1–7.
  140. Stambler I. Recognizing degenerative aging as a treatable medical condition: methodology and policy. *Ageing Dis*. 2017;8(5):583–9.
  141. Manchishi SM, Cui RJ, Zou XH, Cheng ZQ, Li BJ. Effect of caloric restriction on depression. *J Cell Mol Med*. 2018;22(5):2528–35.
  142. Miyamoto S. Autophagy and cardiac aging. *Cell Death Differ*. 2019;26(4):653–64.
  143. Abdellatif M, Sedej S, Carmona-Gutierrez D, Madeo F, Kroemer G. Autophagy in cardiovascular aging. *Circ Res*. 2018;123(7):803–24.
  144. Pulakat L, Chen HH. Pro-senescence and anti-senescence mechanisms of cardiovascular aging: cardiac MicroRNA regulation of longevity drug-induced autophagy. *Front Pharmacol*. 2020;11:774.
  145. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G.

- Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential. *Cell Metab.* 2019;29(3):592–610.
146. Madeo F, Pietrocola F, Eisenberg T, Kroemer G. Caloric restriction mimetics: towards a molecular definition. *Nat Rev Drug Discov.* 2014;13(10):727–40.
147. Yessenkyzy A, Saliev T, Zhanaliyeva M, Masoud AR, Umbayev B, Sergazy S, et al. Polyphenols as caloric-restriction mimetics and autophagy inducers in aging research. *Nutrients.* 2020;12(5):1344.
148. Schultz MB, Sinclair DA. Why NAD<sup>+</sup> declines during aging: it's destroyed. *Cell Metab.* 2016;23(6):965–6.
149. Peluso A, Damgaard MV, Mori MAS, Treebak JT. Age-dependent decline of NAD<sup>+</sup> - Universal truth or confounded consensus? *Nutrients.* 2021;14(1):101.
150. Schwarzmann L, Pliquett RU, Simm A, Bartling B. Sex-related differences in human plasma NAD<sup>+</sup>/NADH levels depend on age. *Biosci Rep.* 2021;41(1):BSR20200340.
151. Deng Z, Li Y, Liu H, Xiao S, Li L, Tian J, et al. The role of sirtuin 1 and its activator, resveratrol in osteoarthritis. *Biosci Rep.* 2019;39(5):BSR20190189.
152. Liu T, Li Z, Tian F. Quercetin inhibited the proliferation and invasion of hepatoblastoma cells through facilitating SIRT6-mediated FZD4 silence. *Hum Exp Toxicol.* 2021;40(12\_suppl):96–107.
153. Rainey NE, Moustapha A, Petit PX. Curcumin, a multifaceted hormetic agent, mediates an intricate crosstalk between mitochondrial turnover, autophagy, and apoptosis. *Oxid Med Cell Longev.* 2020;2020:3656419.
154. Lombó M, Herráez MP. Paternal inheritance of bisphenol A cardiotoxic effects: the implications of sperm epigenome. *Int J Mol Sci.* 2021;22(4):2125.
155. Antonazzi F, Di Felice F, Camilloni G. GCN5 enables HSP12 induction promoting chromatin remodeling, not histone acetylation. *Biochem Cell Biol.* 2021;99(6):700–6.
156. Ehala S, Vaher M, Kaljurand M. Characterization of phenolic profiles of Northern European berries by capillary electrophoresis and determination of their antioxidant activity. *J Agric Food Chem.* 2005;53(16):6484–90.
157. Moore A, Beidler J, Hong MY. Resveratrol and depression in animal models: a systematic review of the biological mechanisms. *Molecules.* 2018;23(9):2197.
158. Singh CK, Liu X, Ahmad N. Resveratrol, in its natural combination in whole grape, for health promotion and disease management. *Ann NY Acad Sci.* 2015;1348(1):150–60.
159. Kanamori H, Takemura G, Goto K, Tsujimoto A, Ogino A, Takeyama T, et al. Resveratrol reverses remodeling in hearts with large, old myocardial infarctions through enhanced autophagy-activating AMP kinase pathway. *Am J Pathol.* 2013;182(3):701–13.
160. Gal R, Praksch D, Kenyeres P, Rabai M, Toth K, Halmosi R, et al. Hemorheological alterations in patients with heart failure with reduced ejection fraction treated by resveratrol. *Cardiovasc Ther.* 2020;2020:7262474.
161. Cheng CK, Luo JY, Lau CW, Chen ZY, Tian XY, Huang Y. Pharmacological basis and new insights of resveratrol action in the cardiovascular system. *Br J Pharmacol.* 2020;177(6):1258–77.
162. Chiang YC, Wu YS, Kang YF, Wang HC, Tsai MC, Wu CC. 3,5,2',4'-Tetramethoxystilbene, a fully methylated resveratrol analog, prevents platelet aggregation and thrombus formation by targeting the protease-activated receptor 4 pathway. *Chem Biol Interact.* 2022;357:109889.
163. Xu L, Wang R, Liu H, Wang J, Mang J, Xu Z. Resveratrol treatment is associated with lipid regulation and inhibition of lipoprotein-associated phospholipase a2 (lp-pla2) in rabbits fed a high-fat diet. *Evid Based Complement Alternat Med.* 2020;2020:9641582.
164. Zhou L, Long J, Sun Y, Chen W, Qiu R, Yuan D. Resveratrol ameliorates atherosclerosis induced by high-fat diet and LPS in ApoE<sup>-/-</sup> mice and inhibits the activation of CD4<sup>+</sup> T cells. *Nutr Metab (Lond).* 2020;17:41.
165. Wong RHX, Howe PRC. Resveratrol counteracts insulin resistance—potential role of the circulation. *Nutrients.* 2018;10(9):1160.
166. Ko SH, Kim HS. Menopause-associated lipid metabolic disorders and foods beneficial for postmenopausal women. *Nutrients.* 2020;12(1):202.
167. Fonseca MIH, da Silva IT, Ferreira SRG. Impact of menopause and diabetes on atherogenic lipid profile: is it worth to analyse lipoprotein subfractions to assess cardiovascular risk in women? *Diabetol Metab Syndr.* 2017;9:22.
168. Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health.* 2013;103(9):1583–8.
169. Dolinsky VW, Jones KE, Sidhu RS, Haykowsky M, Czubyrt MP, Gordon T, et al. Improvements in skeletal muscle strength and cardiac function induced by resveratrol during exercise training contribute to enhanced exercise performance in rats. *J Physiol.* 2012;590(11):2783–99.
170. Evans HM, Howe PRC, Wong RHX. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomised placebo-controlled intervention trial. *Nutrients.* 2017;9(1):27.
171. Thaug Zaw JJ, Howe PRC, Wong RHX. Sustained cerebrovascular and cognitive benefits of resveratrol in postmenopausal women. *Nutrients.* 2020;12(3):828.
172. Crandall JP, Oram V, Trandafirescu G, Reid M, Kishore P, Hawkins M, et al. Pilot study of resveratrol in older adults with impaired glucose tolerance. *J Gerontol A Biol Sci Med Sci.* 2012;67(12):1307–12.
173. Iannitti RG, Floridi A, Lazzarini A, Tantucci A, Russo R, Ragonese F, et al. Resveratrol supported on magnesium DiHydroxide (Resv@MDH) represents an oral formulation of resveratrol with better gastric absorption and bioavailability respect to pure resveratrol. *Front Nutr.* 2020;7:570047.
174. Pannu N, Bhatnagar A. Resveratrol: from enhanced biosynthesis and bioavailability to multitargeting chronic diseases. *Biomed Pharmacother.* 2019;109:2237–51.
175. Walle T, Hsieh F, DeLegge MH, Oatis JE Jr, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos.* 2004;32(12):1377–82.
176. Aherne SA, O'Brien NM. Dietary flavonols: chemistry, food content, and metabolism. *Nutrition.* 2002;18(1):75–81.
177. Shen P, Lin W, Ba X, Huang Y, Chen Z, Han L, et al. Quercetin-mediated SIRT1 activation attenuates collagen-induced mice arthritis. *J Ethnopharmacol.* 2021;279:114213.
178. Malishevskaja IV, Ilashchuk TA, Okipniak IV [Therapeutic efficacy of quercetin in patients with is ischemic heart disease with underlying metabolic syndrome]. *Georgian Med News.* 2013;225:67–71.
179. Chang X, Zhang T, Meng Q, Wang S, Yan P, Wang X, et al. Quercetin improves cardiomyocyte vulnerability to hypoxia by regulating

- SIRT1/TMBIM6-related mitophagy and endoplasmic reticulum stress. *Oxid Med Cell Longev*. 2021;2021:5529913.
180. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev*. 2009;2(5):270–8.
181. Xu D, Hu M, Wang YQ, Cui YL. Antioxidant activities of quercetin and its complexes for medicinal application. *Molecules*. 2019;24(6):1123.
182. Demkovych A, Bondarenko Y, Hasiuk P. Effects of quercetin on antioxidant potential in the experimental periodontitis development. *Interv Med Appl Sci*. 2019;11(1):60–4.
183. Kondratiuk VE, Synytsia YP. Effect of quercetin on the echocardiographic parameters of left ventricular diastolic function in patients with gout and essential hypertension. *Wiad Lek*. 2018;71(8):1554–9.
184. Serban MC, Sahebkar A, Zanchetti A, Mikhailidis DP, Howard G, Antal D, et al. Effects of quercetin on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2016;5(7):e002713.
185. Leyva-Soto A, Chavez-Santoscoy RA, Porras O, Hidalgo-Ledesma M, Serrano-Medina A, Ramírez-Rodríguez AA, et al. Epicatechin and quercetin exhibit *in vitro* antioxidant effect, improve biochemical parameters related to metabolic syndrome, and decrease cellular genotoxicity in humans. *Food Res Int*. 2021;142:110101.
186. Riva A, Ronchi M, Petrangolini G, Bosisio S, Allegrini P. Improved oral absorption of quercetin from quercetin phytosome®, a new delivery system based on food grade lecithin. *Eur J Drug Metab Pharmacokinet*. 2019;44(2):169–77.
187. Galindo P, González-Manzano S, Zarzuelo MJ, Gómez-Guzmán M, Quintela AM, González-Paramás A, et al. Different cardiovascular protective effects of quercetin administered orally or intraperitoneally in spontaneously hypertensive rats. *Food Funct*. 2012;3(6):643–50.
188. Erlund I, Alftan G, Mäenpää J, Aro A. Tea and coronary heart disease: the flavonoid quercetin is more bioavailable from rutin in women than in men. *Arch Intern Med*. 2001;161(15):1919–20.
189. Guo Y, Mah E, Davis CG, Jalili T, Ferruzzi MG, Chun OK, et al. Dietary fat increases quercetin bioavailability in overweight adults. *Mol Nutr Food Res*. 2013;57(5):896–905.
190. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as “Curecumin”: from kitchen to clinic. *Biochem Pharmacol*. 2008;75(4):787–809.
191. Guo S, Long M, Li X, Zhu S, Zhang M, Yang Z. Curcumin activates autophagy and attenuates oxidative damage in EA. hy926 cells *via* the Akt/mTOR pathway. *Mol Med Rep*. 2016;13(3):2187–93.
192. Qin S, Huang L, Gong J, Shen S, Huang J, Ren H, et al. Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Nutr J*. 2017;16(1):68.
193. Gao J, Pan X, Li G, Chatterjee E, Xiao J. Physical exercise protects against endothelial dysfunction in cardiovascular and metabolic diseases. *J Cardiovasc Transl Res*. 2021;1–17.
194. Dei Cas M, Ghidoni R. Dietary curcumin: correlation between bioavailability and health potential. *Nutrients*. 2019;11(9):2147.
195. Wang P, Li H, Lin Z, Luo H, Luo W. Comparing the effect of piperine and ilepicimide on the pharmacokinetics of curcumin in SD rats. *Front Pharmacol*. 2021;12:725362.
196. Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A. Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. *Complement Ther Med*. 2014;22(5):851–7.
197. Sahebkar A. A systematic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels. *Clin Nutr*. 2014;33(3):406–14.
198. Rahmani S, Asgary S, Askari G, Keshvari M, Hatampour M, Feizi A, et al. Treatment of non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial. *Phytother Res*. 2016;30(9):1540–8.
199. Rahimi HR, Mohammadpour AH, Dastani M, Jaafari MR, Abnous K, Ghayour Mobarhan M, et al. The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. *Avicenna J Phytomed*. 2016;6(5):567–77.
200. Zhang H, Bian Z, Lin Z. Are acupoints specific for diseases? A systematic review of the randomized controlled trials with sham acupuncture controls. *Chin Med*. 2010;5:1.
201. Chu C, Deng J, Man Y, Qu Y. Green tea extracts epigallocatechin-3-gallate for different treatments. *Biomed Res Int*. 2017;2017:5615647.
202. Yi SJ, Kim K. New insights into the role of histone changes in aging. *Int J Mol Sci*. 2020;21(21):8241.
203. Ferguson BS, Mckinsey TA. Non-sirtuin histone deacetylases in the control of cardiac aging. *J Mol Cell Cardiol*. 2015;83:14–20.
204. Holczer M, Besze B, Zámbo V, Csala M, Bánhegyi G, Kapuy O. Epigallocatechin-3-gallate (EGCG) promotes autophagy-dependent survival *via* influencing the balance of mTOR-AMPK pathways upon endoplasmic reticulum stress. *Oxid Med Cell Longev*. 2018;2018:6721530.
205. Xuan F, Jian J. Epigallocatechin gallate exerts protective effects against myocardial ischemia/reperfusion injury through the PI3K/Akt pathway-mediated inhibition of apoptosis and the restoration of the autophagic flux. *Int J Mol Med*. 2016;38(1):328–36.
206. Yan X, Li Y, Yu H, Wang W, Wu C, Yang Y, et al. Epigallocatechin-3-gallate inhibits H<sub>2</sub>O<sub>2</sub>-induced apoptosis in mouse vascular smooth muscle cells *via* 67 kD laminin receptor. *Sci Rep*. 2017;7(1):7774.
207. Yamagata K, Xie Y, Suzuki S, Tagami M. Epigallocatechin-3-gallate inhibits VCAM-1 expression and apoptosis induction associated with LC3 expressions in TNF $\alpha$ -stimulated human endothelial cells. *Phytomedicine*. 2015;22(4):431–7.
208. Chen SJ, Kao YH, Jing L, Chuang YP, Wu WL, Liu ST, et al. Epigallocatechin-3-gallate reduces scavenger receptor A expression and foam cell formation in human macrophages. *J Agric Food Chem*. 2017;65(15):3141–50.
209. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *JAMA*. 2006;296(10):1255–65.
210. Naumovski N, Foscolou A, D’Cunha NM, Tyrovolas S, Chrysohoou C, Sidossis LS, et al. The association between green and black tea consumption on successful aging: a combined analysis of the ATTICA and MEDiterranean ISlands (MEDIS) Epidemiological Studies. *Molecules*. 2019;24(10):1862.
211. AusdemSiepen F, Bauer R, Aurich M, Buss SJ, Steen H, Altland K, et al. Green tea extract as a treatment for patients with wild-type transthyretin amyloidosis: an observational study. *Drug Des Dev Ther*. 2015;9:6319–25.
212. Chotphruethipong L, Sukketsiri W, Battino M, Benjakul S.

- Conjugate between hydrolyzed collagen from defatted seabass skin and epigallocatechin gallate (EGCG): characteristics, antioxidant activity and *in vitro* cellular bioactivity. *RSC Adv*. 2021;11(4):2175–84.
213. Onakpoya I, Spencer E, Heneghan C, Thompson M. The effect of green tea on blood pressure and lipid profile: a systematic review and meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis*. 2014;24(8):823–36.
214. Mielgo-Ayuso J, Barrenechea L, Alcorta P, Larrarte E, Margareto J, Labayen I. Effects of dietary supplementation with epigallocatechin-3-gallate on weight loss, energy homeostasis, cardiometabolic risk factors and liver function in obese women: randomised, double-blind, placebo-controlled clinical trial. *Br J Nutr*. 2014;111(7):1263–71.
215. Song Y, Manson JE, Buring JE, Sesso HD, Liu S. Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: a prospective study and cross-sectional analysis. *J Am Coll Nutr*. 2005;24(5):376–84.
216. Mereles D, Hunstein W. Epigallocatechin-3-gallate (EGCG) for clinical trials: more pitfalls than promises? *Int J Mol Sci*. 2011;12(9):5592–603.
217. Ullmann U, Haller J, Decourt JP, Girault N, Girault J, Richard-Caudron AS, et al. A single ascending dose study of epigallocatechin gallate in healthy volunteers. *J Int Med Res*. 2003;31(2):88–101.
218. Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults - Results of a systematic review. *Regul Toxicol Pharmacol*. 2018;95:412–33.
219. Zhang J, Nie S, Zu Y, Abbasi M, Cao J, Li C, et al. Anti-atherogenic effects of CD36-targeted epigallocatechin gallate-loaded nanoparticles. *J Control Release*. 2019;303:263–73.
220. Bekebrede AF, Keijer J, Gerrits WJJ, De Boer VCJ. The molecular and physiological effects of protein-derived polyamines in the intestine. *Nutrients*. 2020;12(1):197.
221. Bardócz S, Duguid TJ, Brown DS, Grant G, Pusztai A, White A, et al. The importance of dietary polyamines in cell regeneration and growth. *Br J Nutr*. 1995;73(6):819–28.
222. Hofer SJ, Davinelli S, Bergmann M, Scapagnini G, Madeo F. Caloric restriction mimetics in nutrition and clinical trials. *Front Nutr*. 2021;8:717343.
223. Wang J, Li S, Wang J, Wu F, Chen Y, Zhang H, et al. Spermidine alleviates cardiac aging by improving mitochondrial biogenesis and function. *Aging (Albany NY)*. 2020;12(1):650–71.
224. Minois N. Molecular basis of the “anti-aging” effect of spermidine and other natural polyamines - a mini-review. *Gerontology*. 2014;60(4):319–26.
225. Kiechl S, Pechlaner R, Willeit P, Notdurfter M, Paulweber B, Willeit K, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
226. Benetos A, Petrovic M, Strandberg T. Hypertension management in older and frail older patients. *Circ Res*. 2019;124(7):1045–60.
227. Pucciarelli S, Moreschini B, Micozzi D, De Fronzo GS, Carpi FM, Polzonetti V, et al. Spermidine and spermine are enriched in whole blood of nona/centenarians. *Rejuvenation Res*. 2012;15(6):590–5.
228. Elworthy P, Hitchcock E. Polyamine levels in red blood cells from patient groups of different sex and age. *Biochim Biophys Acta*. 1989;993(2–3):212–6.
229. Schwarz C, Stekovic S, Wirth M, Benson G, Royer P, Sigrist SJ, et al. Safety and tolerability of spermidine supplementation in mice and older adults with subjective cognitive decline. *Aging (Albany NY)*. 2018;10(1):19–33.
230. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
231. Kanamori H, Takemura G, Goto K, Tsujimoto A, Mikami A, Ogino A, et al. Autophagic adaptations in diabetic cardiomyopathy differ between type 1 and type 2 diabetes. *Autophagy*. 2015;11(7):1146–60.
232. Yamamoto S, Sawada K, Shimomura H, Kawamura K, James TN. On the nature of cell death during remodeling of hypertrophied human myocardium. *J Mol Cell Cardiol*. 2000;32(1):161–75.
233. Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation*. 2003;107(7):984–91.
234. Elsässer A, Vogt AM, Nef H, Kostin S, Möllmann H, Skwara W, et al. Human hibernating myocardium is jeopardized by apoptotic and autophagic cell death. *J Am Coll Cardiol*. 2004;43(12):2191–9.
235. Kostin S, Pool L, Elsässer A, Hein S, Drexler HC, Arnon E, et al. Myocytes die by multiple mechanisms in failing human hearts. *Circ Res*. 2003;92(7):715–24.
236. Delbridge LMD, Mellor KM, Taylor DJ, Gottlieb RA. Myocardial stress and autophagy: mechanisms and potential therapies. *Nat Rev Cardiol*. 2017;14(7):412–25.
237. Yamagata K. Polyphenols regulate endothelial functions and reduce the risk of cardiovascular disease. *Curr Pharm Des*. 2019;25(22):2443–58.
238. Auclair S, Chironi G, Milenkovic D, Hollman PCH, Renard CMGC, Mégnien JL, et al. The regular consumption of a polyphenol-rich apple does not influence endothelial function: a randomised double-blind trial in hypercholesterolemic adults. *Eur J Clin Nutr*. 2010;64(10):1158–65.
239. Basu A, Du M, Sanchez K, Leyva MJ, Betts NM, Blevins S, et al. Green tea minimally affects biomarkers of inflammation in obese subjects with metabolic syndrome. *Nutrition*. 2011;27(2):206–13.
240. Schwarzmuller F, Eisenhauer N, Brose U. “Trophic whales” as biotic buffers: weak interactions stabilize ecosystems against nutrient enrichment. *J Anim Ecol*. 2015;84(3):680–91.
241. Kibe R, Kurihara S, Sakai Y, Suzuki H, Ooga T, Sawaki E, et al. Upregulation of colonic luminal polyamines produced by intestinal microbiota delays senescence in mice. *Sci Rep*. 2014;4:4548.
242. Vogiatzoglou A, Heuer T, Mulligan AA, Lentjes MAH, Luben RN, Kuhnle GG. Estimated dietary intakes and sources of flavanols in the German population (German National Nutrition Survey II). *Eur J Nutr*. 2014;53(2):635–43.
243. Bai W, Wang C, Ren C. Intakes of total and individual flavonoids by US adults. *Int J Food Sci Nutr*. 2014;65(1):9–20.
244. Hollman PC, Katan MB. Dietary flavonoids: intake, health effects and bioavailability. *Food Chem Toxicol*. 1999;37(9–10):937–42.
245. Madeo F, Hofer SJ, Pendl T, Bauer MA, Eisenberg T, Carmona-Gutierrez D, et al. Nutritional aspects of spermidine. *Annu Rev Nutr*. 2020;40:135–59.
246. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr*. 2004;79(5):727–47.
247. Manach C, Williamson G, Morand C, Scalbert A, Remesy C.

- Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr.* 2005;81(1 Suppl):230S-S242.
248. James KD, Forester SC, Lambert JD. Dietary pretreatment with green tea polyphenol, (–)-epigallocatechin-3-gallate reduces the bioavailability and hepatotoxicity of subsequent oral bolus doses of (–)-epigallocatechin-3-gallate. *Food Chem Toxicol.* 2015;76:103–8.
249. Yoshizawa M, Maeda S, Miyaki A, Misono M, Choi Y, Shimojo N, et al. Additive beneficial effects of lactotripeptides and aerobic exercise on arterial compliance in postmenopausal women. *Am J Physiol Heart Circ Physiol.* 2009;297(5):H1899–903.
250. Yoshizawa M, Maeda S, Miyaki A, Misono M, Choi Y, Shimojo N, et al. Additive beneficial effects of lactotripeptides intake with regular exercise on endothelium-dependent dilatation in postmenopausal women. *Am J Hypertens.* 2010;23(4):368–72.
251. Mahale J, Singh R, Howells LM, Britton RG, Khan SM, Brown K. Detection of plasma curcuminoids from dietary intake of turmeric-containing food in human volunteers. *Mol Nutr Food Res.* 2018;62(16):e1800267.
252. Michelakis ED, Gurtu V, Webster L, Barnes G, Watson G, Howard L, et al. Inhibition of pyruvate dehydrogenase kinase improves pulmonary arterial hypertension in genetically susceptible patients. *Sci Transl Med.* 2017;9(413):eaao4583.
253. Cardoso AC, Lam NT, Savla JJ, Nakada Y, Pereira AHM, Elnwasany A, et al. Mitochondrial substrate utilization regulates cardiomyocyte cell cycle progression. *Nat Metab.* 2020;2(2):167–78.
254. Kates AM, Herrero P, Dence C, Soto P, Srinivasan M, Delano DG, et al. Impact of aging on substrate metabolism by the human heart. *J Am Coll Cardiol.* 2003;41(2):293–9.
255. Rowan S, Bejarano E, Taylor A. Mechanistic targeting of advanced glycation end-products in age-related diseases. *Biochim Biophys Acta Mol Basis Dis.* 2018;1864(12):3631–43.
256. Strieder-Barboza C, Baker NA, Flesher CG, Karmakar M, Neeley CK, Polsinelli D, et al. Advanced glycation end-products regulate extracellular matrix-adipocyte metabolic crosstalk in diabetes. *Sci Rep.* 2019;9(1):19748.
257. Deng X, Huang W, Peng J, Zhu TT, Sun XL, Zhou XY, et al. Irisin alleviates advanced glycation end products-induced inflammation and endothelial dysfunction via inhibiting ROS-NLRP3 inflammasome signaling. *Inflammation.* 2018;41(1):260–75.
258. Yang P, Feng J, Peng Q, Liu X, Fan Z. Advanced glycation end products: potential mechanism and therapeutic target in cardiovascular complications under diabetes. *Oxid Med Cell Longev.* 2019;2019:9570616.
259. Carnevale R, Nocella C, Schiavon S, Cammisotto V, Cotugno M, Forte M, et al. Beneficial effects of a combination of natural product activators of autophagy on endothelial cells and platelets. *Br J Pharmacol.* 2021;178(10):2146–59.
260. Skalicky J, Muzakova V, Kandar R, Meloun M, Rousar T, Palicka V. Evaluation of oxidative stress and inflammation in obese adults with metabolic syndrome. *Clin Chem Lab Med.* 2008;46(4):499–505.

<https://doi.org/10.1186/s40779-022-00389-w>

**Cite this article as:** Pang L, Jiang X, Lian X, Chen J, Song EF, Jin LG, et al. Caloric restriction-mimetics for the reduction of heart failure risk in aging heart: with consideration of gender-related differences. *Mil Med Res.* 2022;9(1):33.