Role of sirtuin 1 in depression-induced coronary heart disease: Molecular pathways and therapeutic potential (Review)

SHIJIE ZHENG[1,2], LINLIN YANG[3], QIUTING DAI[1], XIANGYAN LI[1], TAKAYOSHI MASUOKA[2] and JIANFENG LV[1]

[1]Department of Cardiology, Affiliated Renhe Hospital of China Three Gorges University, Yichang, Hubei 443001, P.R. China;
[2]Department of Pharmacology, School of Medicine, Kanazawa Medical University, Uchinada, Ishikawa 920-0293, Japan;
[3]Department of Orthopedics, Affiliated Renhe Hospital of China Three Gorges University, Yichang, Hubei 443001, P.R. China

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Abstract. Depression and coronary heart disease (CHD) are two interconnected diseases that profoundly impact global health. Depression is both a complex psychiatric disorder and an established risk factor for CHD. Sirtuin 1 (SIRT1) is an enzyme that requires the cofactor nicotinamide adenine dinucleotide (NAD^+) to perform its deacetylation function, and its involvement is crucial in reducing cardiovascular risks that are associated with depression. SIRT1 exerts its cardioprotective effects via modulating oxidative stress, inflammation and metabolic processes, all of which are central to the pathogenesis of CHD in individuals with depression. Through influencing these pathways, SIRT1 helps to reduce endothelial dysfunction, prevent the formation of atherosclerotic plaques and stabilize existing plaques, thereby decreasing the overall risk of CHD. The present review underscores the important role of SIRT1 in serving as a therapeutic intervention molecule for tackling cardiovascular complications stemming from depression. Furthermore, it highlights the need for further studies to clarify how SIRT1 influences both depression and CHD at the molecular level. The ultimate goal of this research will be to translate these findings into practical clinical intervention strategies.

Contents

Correspondence to: Professor Jianfeng Lv, Department of Cardiology, Affiliated Renhe Hospital of China Three Gorges University, 410 Yiling Avenue, Wujiagang, Yichang, Hubei 443001, P.R. China
E-mail: ljfzxm@yahoo.com

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1. Introduction

Currently, both depression and coronary heart disease (CHD) are among the most prevalent and serious global health issues (1). Depression is a common mental illness that has a profound impact on physical health, and often causes considerable suffering to patients (2). The World Health Organization estimates that ~3.8% of the global population suffers from this disease (3). A lifetime prevalence of depression was retrospectively reported through community epidemiological surveys of adults aged between 18 and 74 years in 28 countries, and an average incidence rate of 10.6% was also reported, comparing across various countries (4). In a prospective epidemiological study, the findings revealed that the lifetime prevalence of major depression ranges from 30-40% (5). The COVID-19 pandemic that broke out around the world in 2020 led to a surge in the incidence of mental health disorders worldwide, with reported cases of major depression increasing by 28%, and anxiety disorders increasing by 26% (6). In addition, the number of individuals with depression surged by 53 million, reflecting a 27.6% increase.

CHD, caused by an accumulation of atherosclerotic plaques in the coronary arteries, is one of the leading causes of mortality and disability in humans (7). In 2019, cardiovascular diseases were responsible for ~17.9 million deaths globally, also accounting for ~32% of all cases of mortality (8). CHD alone was responsible for ~8.5 million deaths, accounting for almost half of all cardiovascular-associated fatalities (8). The global incidence of CHD was ~172 million in 2015, with projections estimating a rise to 234 million cases by 2030 (6). In the United States, CHD results in an estimated 610,000 deaths annually, accounting for ~25% of all deaths (9). Furthermore, CHD imposes a considerable financial burden through both direct medical expenses and indirect costs; for example, in 2010, the expenses directly associated with CHD

treatment in the United States amounted to approximately US $108 billion, and projections suggest this figure will rise to US $137 billion by 2030 (10).

Depression serves as a risk factor leading to the increased prevalence of various diseases (11). A systematic review of global qualitative research on depression has revealed a significant link between the condition and a broad spectrum of physical illnesses, encompassing cardiovascular diseases, diabetes, obesity, hypertension, chronic respiratory disorders and persistent pain syndromes (12). Meta-analyses of longitudinal studies have shown that depression consistently forecasts the initial onset of conditions such as coronary artery disease, stroke, diabetes and obesity (13). From a biological perspective, various mechanisms, including the inflammation hypothesis (14), telomere theory (15), mitochondrial dysfunction (16), gut-brain axis theory (17), and epigenetic mechanisms, which also encompass neuroendocrine-immune interactions (18), have been proposed to explain the potential association between depression and these diseases. Extensive evidence from cohort studies and meta-analyses points to a robust association between depression and CHD, highlighting the significant interrelationship between these conditions (19-21). Depression is acknowledged not only as a standalone risk factor for CHD, but also as a major contributor towards an increased risk of adverse cardiovascular events in affected individuals (22). An analysis involving 22 cohort studies found that depression increases the risk of CHD onset by approximately 1.5 to 2 times, with prevalence rates of depression among CHD patients estimated at 20-30% (22).

In the interaction between depression and CHD, sirtuin 1 (SIRT1), as an NAD^+ deacetylase, has attracted widespread attention. SIRT1 fulfills a crucial role in orchestrating a spectrum of biological activities, including cellular growth, programmed cell death, aging, and glucose and lipid handling, in addition to controlling oxidative stress and inflammation. These functions of SIRT1 have been shown via animal experiments to exert significant protective effects on both the nervous and cardiovascular systems (23). Moreover, studies involving animal models of depression and clinical patients with CHD have suggested that SIRT1 may have an important role in the pathophysiology of these two common diseases through regulation of inflammation, oxidative stress and metabolic activity (24-26). The present review describes the impact of SIRT1 on the progression of CHD caused by depression. Through reviewing and compiling the findings reported in the research literature, the objective of this review is to enhance the understanding of the role of SIRT1 in both diseases, thereby offering a theoretical basis for future clinical investigations and therapeutic developments.

2. Overview of SIRT1

Role of SIRT1 in cell proliferation and apoptosis regulation. As an NAD^+-dependent deacetylase, SIRT1 is a member of the sirtuin family within the broader category of serine/threonine kinases (27). SIRT1 is present in both the cytoplasm and the nucleus, and is crucially involved in a variety of cellular processes, including gene regulation, DNA repair and maintaining metabolic functions (28). A key mechanism through which SIRT1 regulates cell proliferation involves its interaction with the tumor suppressor protein p53 (29). p53 has a critical role in regulating the cell cycle and apoptosis, especially in response to DNA damage and cellular stress (30). Upon activation, SIRT1 deacetylates p53, leading either to cell cycle arrest to facilitate DNA repair, or the initiation of apoptosis when damage has become irreparable (31). This process reduces the ability of p53 to initiate cell cycle arrest and apoptosis, thereby promoting cell survival and proliferation (32). A previously published study on human tumor cells *in vitro* revealed that SIRT1 deacetylates p53, which may lead to a reduction in pro-apoptotic factors such as B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) and the p53-upregulated modulator of apoptosis (PUMA), thereby promoting tumor cell growth and limiting stress-induced apoptosis (33). The operation of this mechanism is especially important in situations such as tissue injury, where cell survival and proliferation are critical for tissue repair and regeneration (33). However, an experiment on pregnant rats using the SIRT1 inhibitor EX-527 showed that blocking SIRT1 activity led to an increase in PUMA expression, with a concomitant decrease in the levels of Bcl-2 and Bcl-extra large (Bcl-XL) proteins through the p53 pathway, thereby promoting apoptosis (34).

Beyond its influence on p53, SIRT1 also regulates the activity of the forkhead box O (FOXO) transcription factor family, the members of which are critical in the cellular response to oxidative stress, senescence and apoptosis (35). SIRT1-mediated deacetylation activates the FOXO3a transcription factor, thereby increasing the expression of protective genes, such as manganese superoxide dismutase (MnSOD) and catalase (CAT), which guard cells against oxidative stress (36). This action not only supports cell survival, but also leads to the inhibition of apoptosis through the reduction of oxidative damage. In a study wherein a mouse model of myocardial infarction was established, through upregulation of SIRT1 expression, the deacetylation of FOXO3a in cardiomyocytes was found to be increased, thereby strengthening the cell defense mechanism and reducing cardiomyocyte apoptosis during myocardial infarction. On the other hand, under certain conditions, the upregulation of SIRT1 expression may also inhibit the pro-apoptotic effects of FOXO (37). Through the balance of signals for survival and apoptosis, SIRT1 ensures that cells can manage oxidative stress without undergoing excessive apoptosis, a process that is particularly relevant in aging and neurodegenerative diseases (38).

The regulation of apoptosis by SIRT1, however, is highly context-dependent, as it can also promote cell death under specific conditions, especially in cancerous or damaged cells (39). A previously published study using a rat model of diabetic retinopathy revealed that SIRT1 is able to downregulate anti-apoptotic proteins such as Bcl-2, and increase the expression of pro-apoptotic factors such as Bax, thereby promoting irreversible damage caused to, or the apoptosis of, retinal cells (40). This dual functionality of SIRT1 is critical for maintaining cellular homeostasis, ensuring that healthy cells are preserved while they are damaged, or that potentially cancerous cells are eliminated. The complexity of the role of SIRT1 has been highlighted in a number of reviews, showing that its involvement in apoptosis is tightly regulated by the cellular environment and specific signaling pathways, allowing for a balance between cell proliferation and death (41).

SIRT1 fulfills another important role in influencing the cell cycle, which is crucial for regulating cell proliferation. In this regard, it interacts with various cyclins to promote the progression of the cell cycle (42). The transcription factor E2F transcription factor 1 (E2F1) is an important transcription factor that has been shown to regulate the cell cycle, cell proliferation and apoptosis. SIRT1 activates E2F1 through deacetylation, which helps to promote the transition of cells from the G_1 to S phase, facilitating cell proliferation, especially in tumor cells (43). This pathway is particularly relevant in stem cells and cancer cells, where rapid cell division is vital. However, a study on mouse macrophages showed that excessive activation of SIRT1 may lead to carcinogenesis, as unregulated cell proliferation led to tumor growth (44). This finding highlighted the importance of carefully regulating SIRT1 activity in diverse cellular environments.

SIRT1 also exerts a regulatory role in autophagy, influencing the clearance of damaged organelles and proteins via the deacetylation of key proteins, which is crucial for maintaining cellular stress responses and the balance of energy metabolism (45). Autophagy supports cell survival under stress by removing damaged components and providing essential nutrients (46). SIRT1 stimulates autophagy by deacetylating key autophagy-associated proteins, including microtubule-associated protein 1A/1B-light chain 3 (LC3) and autophagy protein 5 (Atg5), which leads to enhanced autophagic activity (47). In turn, autophagy is able to prevent apoptosis by eliminating dysfunctional mitochondria, which are major sources of pro-apoptotic signals (48). However, when the autophagic process is insufficient to restore cellular homeostasis, SIRT1 may shift its role towards promoting apoptosis, especially in cells that are beyond repair (49). This dynamic interplay between autophagy and apoptosis is fundamental to the function of SIRT1 in regulating the cell fate, ensuring the survival of healthy cells, while eliminating damaged ones (50).

Role of SIRT1 in the regulation of inflammation. SIRT1 has a multifaceted role in the regulation of inflammation, which is mediated through its interactions with several key molecular pathways to maintain cellular homeostasis and prevent chronic inflammation, serving as a contributing factor in numerous diseases (51). In these molecular pathways, SIRT1 inhibits chronic inflammation by regulating the transcription factors nuclear factor-κB (NF-κB) and FOXO3a, as well as through the reduction of oxidative stress (27). These regulatory processes are crucial in preventing chronic inflammatory states. A key function of SIRT1 in inflammation control is the suppression of pro-inflammatory cytokine transcription via the deacetylation of NF-κB; specifically, its p65 subunit (52). The transcription factor NF-κB fulfills a crucial role in regulating inflammation through the regulation of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) (53). Research on diabetic nephropathy in mice has shown that SIRT1 deacetylates the p65 subunit of NF-κB, leading to a reduction in its transcriptional activity and a mitigation of diabetic renal pathology (54). These functions have been validated in various disease models, including metabolic and neurodegenerative disorders, where inflammation is a key driver of disease pathology (55,56). Through the inhibition of NF-κB, SIRT1 effectively attenuates inflammatory responses, demonstrating its critical role in inflammation regulation (57).

Apart from modulating NF-κB, SIRT1 helps to decrease inflammation by minimizing oxidative stress (27). Via the deacetylation of FOXO3a, SIRT1 enhances the expression of antioxidant enzymes, including MnSOD and CAT, thereby reducing oxidative damage and, in turn, inflammation (58). In a macrophage-specific mouse model, the absence of SIRT1 was found to promote the polarization of pro-inflammatory macrophages and to regulate the tissue inhibitor of metalloproteinase 3 (TIMP3)/ADAM17 pathway, thereby facilitating the development of atherosclerosis, demonstrating that SIRT1 activation through FOXO3a may both enhance the proportion of anti-inflammatory macrophages and reduce inflammatory responses (59). Moreover, SIRT1 has been shown to regulate inflammasome activity, notably influencing the nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, which is critically involved in inflammatory responses (60).

Overactivation of NLRP3 inflammasomes results in chronic low-grade inflammation, thereby promoting the production of the cytokines IL-1β and IL-18 (60). In the airways of these mice, SIRT1 mitigates inflammation via deacetylating components of the NLRP3 inflammasome, which restricts the release of pro-inflammatory cytokines (61). This mechanism is crucial in preventing chronic inflammation, which is a common factor in diseases such as atherosclerosis and type 2 diabetes, further highlighting the pivotal role of SIRT1 in controlling inflammatory responses (62).

Additionally, the activation of SIRT1 has been shown to lead to an improvement in insulin sensitivity in obesity models through inhibiting inflammation via NF-κB signaling pathways (63). In cardiovascular diseases, the anti-inflammatory properties of SIRT1 have been shown to contribute towards improving vascular function through the reduction of the expression of adhesion molecules in endothelial cells (64). In a study involving the overexpression of SIRT1 in mice, it was found that activation of SIRT1 in endothelial cells could mitigate vascular inflammation, affording protection against vascular aging and atherosclerosis (65). Consequently, SIRT1 is a crucial factor both in terms of regulating apoptosis, and offering resistance to oxidative stress, autophagy and inflammation (Fig. 1).

3. Association between depression and CHD

Depression, a common mood disorder, is marked by prolonged sadness, diminished interest in activities, fatigue, poor concentration and low self-esteem (66). Analyzing data from 22 cohort studies involving over 500,000 individuals, researchers found that depression has a substantial effect on both mental and physical well-being, notably increasing the risk for CHD (67-69). CHD is a disease caused by myocardial ischemia and hypoxia due to coronary atherosclerosis, which, in turn, causes adverse cardiovascular events, including angina pectoris and myocardial infarction (70). A previous study suggested that both acute and chronic stress disrupt the production or activity of key neurotransmitters and hormones, including noradrenaline, dopamine, serotonin, cortisol, aldosterone and angiotensin II (71). These disruptions may

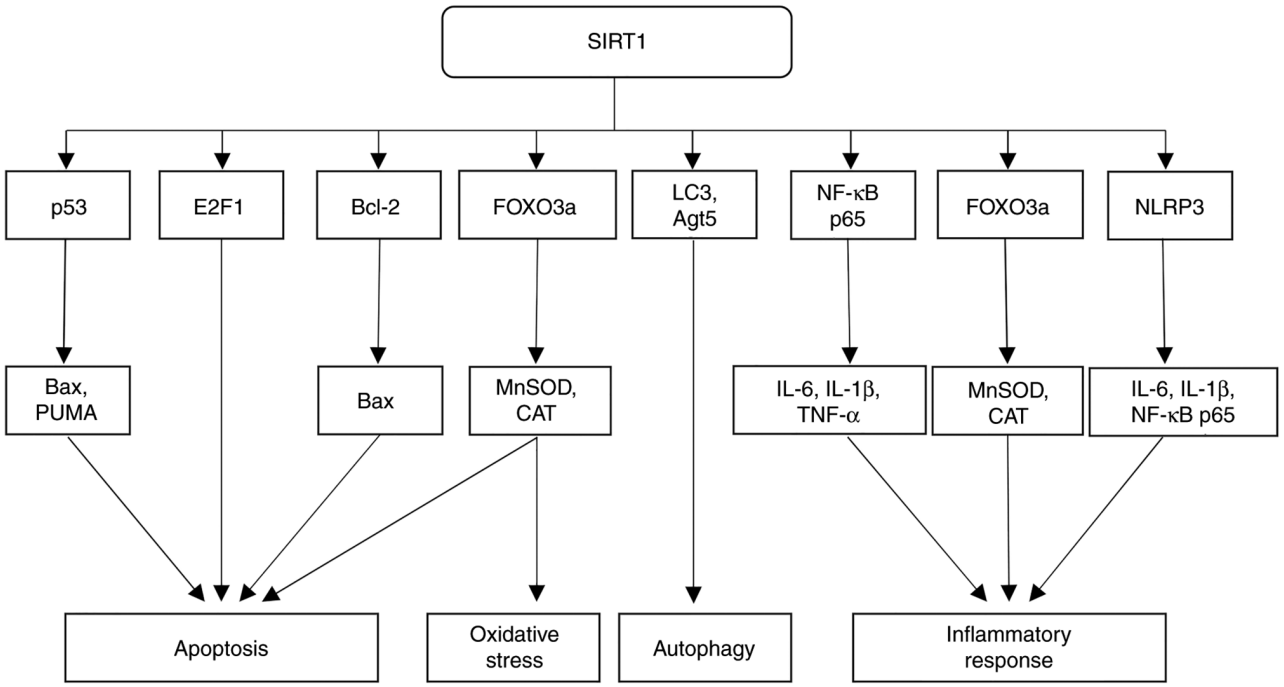

Figure 1. Schematic figure, illustrating how SIRT1 regulates apoptosis, oxidative stress, autophagy and inflammation via its deacetylation activity. SIRT1 primarily exerts its regulatory effects by modifying proteins such as p53, and reducing the levels of pro-apoptotic factors, including Bax and PUMA, to prevent cell death. Additionally, it enhances E2F1 activity, which further promotes cell survival. SIRT1 also modulates Bcl-2 levels to inhibit Bax, thereby reinforcing apoptosis suppression. Through activation of FOXO3a, SIRT1 increases the levels of antioxidant enzymes, including MnSOD and CAT, thereby decreasing oxidative stress. SIRT1 also promotes autophagy via proteins such as LC3 and Agt5, thereby exerting a role in the clearance of damaged organelles. Inflammatory responses are diminished via SIRT1's deacetylation of NF-κB p65 and NLRP3, with the resultant reduction in pro-inflammatory cytokine production. SIRT1, sirtuin 1; p53, tumor protein p53; E2F1, E2F transcription factor 1; Bcl-2, B-cell lymphoma 2; FOXO3a, Forkhead box O3a; LC3, microtubule-associated protein 1A/1B-light chain 3; Agt5, autophagy protein 5; NF-κB p65, nuclear factor-κB subunit p65; NLRP3, nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3; Bax, Bcl2-associated X protein; PUMA, p53 upregulated modulator of apoptosis; MnSOD, manganese superoxide dismutase; CAT, catalase; IL-6, interleukin-6; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor-α.

negatively influence mood, and contribute to cardiovascular risk factors, such as high blood pressure, platelet reactivity, endothelial dysfunction, diabetes and metabolic syndrome, all of which may increase the likelihood of depression (72). Additionally, these biochemical imbalances cause alterations in immune function, leading to an overproduction of cytokines such as IL-1, IL-6 and TNF-α (73). A study based on populations with CHD demonstrated that inflammation is a common factor linking mood disorders and cardiovascular diseases, potentially contributing to plaque formation and acute coronary events (74). An additional study suggested that shared genetic pathways across the neuroendocrine, immune and inflammatory systems may underlie an increased risk of both depression and CHD (21).

Brain regions involved in mood disorders and cardiovascular regulation, particularly those associated with stress and memory, have been shown to be altered in patients with severe depression (75). A previous study demonstrated that acute psychological stress reduces baroreflex sensitivity, whereas asymmetric sympathetic signaling from the brain to the heart may increase the risk of CHD (76). In human neuroimaging studies analyzing the amygdala and arterial inflammation, it was found that amygdala activity is able to independently predict cardiovascular events, suggesting a link between emotional stress and cardiovascular disease (77,78). Another clinical study showed that individuals with depression face a significantly higher CHD risk, with increased symptom severity further elevating this risk (79). Depression not only increases the likelihood of CHD, but also increases the incidence of adverse cardiovascular events and mortality among patients with CHD (80). Certain subtypes of depression, such as new-onset depression following acute coronary syndrome, refractory depression or depression with somatic symptoms, are more likely to result in negative CHD outcomes and a diminished quality of life (81). After adjusting for factors such as functional limitations and clinical variables (including stable angina and congestive heart failure), improvements in depressive symptoms were found to be the strongest predictors of improved health-associated quality of life at 1 year (82,83). A large clinical study revealed that depression independently predicts cardiovascular events in patients with CHD, with the risk increasing alongside symptom severity. Moreover, the mortality rate among patients with CHD who were depressed was found to be more than double that of their non-depressed counterparts (84).

The mechanisms via which depression causes atherosclerosis are multifaceted, although these mainly include chronic psychological stress and the inflammatory response (21). Depression has been shown to be closely associated with chronic psychological stress, and this condition is a major risk factor for atherosclerosis, which comprises the thickening of artery walls due to the buildup of plaque (85). A study encompassing both animal and human studies revealed that chronic psychological stress triggers numerous physiological

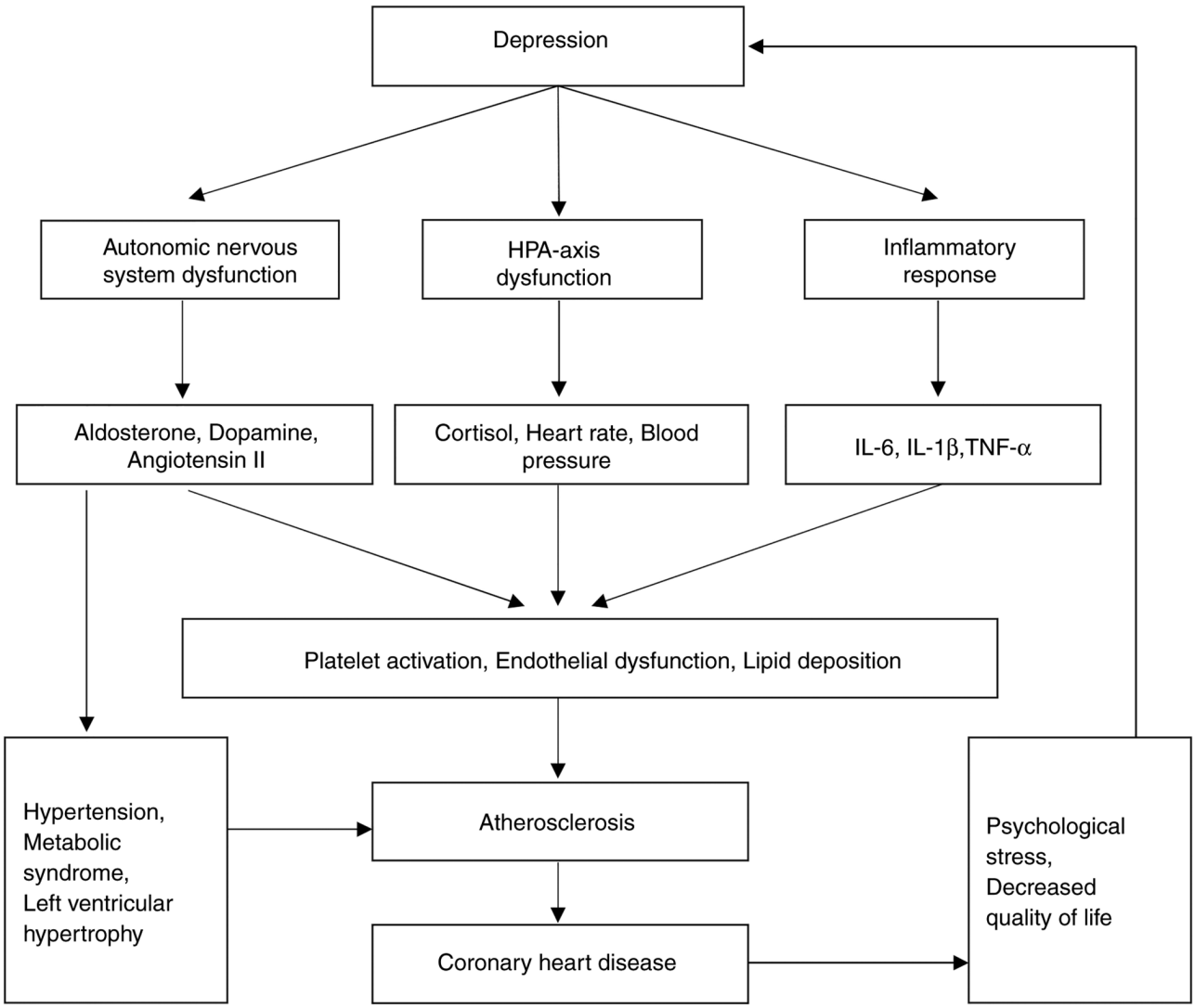

Figure 2. Schematic figure, illustrating the complex association between depression and coronary heart disease. Depression leads to CHD through multiple pathways, including autonomic nervous system dysfunction, HPA axis dysfunction and inflammatory responses. These disturbances result in hormonal imbalances, such as elevated levels of aldosterone, dopamine, angiotensin II and cortisol, along with an increased heart rate and a heightening of blood pressure. Additionally, depression leads to increases in levels of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α. Hormonal imbalances resulting from autonomic dysfunction further contribute to hypertension, metabolic syndrome and left ventricular hypertrophy. These alterations, in turn, promote platelet activation, disrupt endothelial function and increase lipid deposition, all of which lead to an increased risk of CHD. CHD, coronary heart disease; HPA-axis, hypothalamic-pituitary-adrenal axis; IL-6, interleukin-6; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor-α.

shifts, including elevated levels of stress hormones and heightened sympathetic nervous system activity, largely driven by hypothalamic-pituitary-adrenal (HPA) axis activation (86). A clinical study also revealed that prolonged psychological stress results in increased cortisol levels, with resultant damage caused to vascular endothelial cells, and other effects, including increasing vascular wall permeability and fostering lipid accumulation in the vascular walls, ultimately contributing to atherosclerosis (84). Persistent sympathetic nervous system activation also leads to increases in heart rate and blood pressure, which elevates cardiac workload and vascular wall stress, factors that also contribute to the development of atherosclerosis (87).

Low-grade chronic inflammation, which is common in depressed patients, significantly contributes to atherosclerosis onset and progression (88). High levels of pro-inflammatory markers and oxidative stress drive this inflammatory response (89). In individuals with depression, markers such as C-reactive protein, IL-6 and TNF-α are found at elevated levels (90). These inflammatory factors are able to promote atherosclerosis through various pathways (91). Not only in human studies, but also in animal models, inflammatory factors have been shown to activate vascular endothelial cells, cause an upregulation of the expression of adhesion molecules, and facilitate the adhesion of monocytes to the vascular wall and their subsequent transformation into macrophages, which subsequently further engulf lipids to form foam cells, a process that is pivotal in the formation of atherosclerotic plaques (92). Additionally, depression has been shown to be closely associated with oxidative stress, which not only causes direct damage to vascular endothelial cells, but also triggers multiple inflammatory pathways, further promoting the development of atherosclerosis (92,93). Therefore, depression increases the risk of CHD through multiple mechanisms (Fig. 2).

4. Role of SIRT1 in depression

Depression is a multifaceted mental disorder, with its causes rooted in biological, genetic and environmental factors (94). A previous study utilizing a mouse model of depression identified SIRT1 as performing a crucial role in the development of depression (95). Another study also demonstrated that SIRT1 affects neurogenesis, especially within areas of the brain critical for emotional and cognitive processes, such as the hippocampus and prefrontal cortex (96). Extensive studies in both animal and human models have explored the molecular role of SIRT1 in mood disorders (97,98). SIRT1 has been shown to regulate multiple transcription factors, including peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α), p53 and NF-κB, which have crucial roles in modulating processes such as oxidative stress, inflammation and apoptosis (95). These pathways are often dysregulated in patients with depression, suggesting that SIRT1 has a pivotal role in the pathogenesis of the disorder (99). Both SIRT1 and SIRT2 have been implicated in regulating inflammatory responses within the brain, indicating their potential as therapeutic targets for anti-inflammatory treatments for depression (100). Via reduction of neuroinflammation, SIRT1 may alleviate the biological stress that exacerbates depressive symptoms (101).

In animal models of depression, SIRT1 expression in hippocampal tissue has been found to be markedly reduced (102). The hippocampus, a brain region essential for learning and memory, is often affected in the state of depression, and its dysfunction is one of the primary pathological features of the disorder (103). A previously published study on hippocampal neuroplasticity in patients with depression showed that low expression of SIRT1 may impair neuroplasticity, neurogenesis and synaptic function, thereby exacerbating depressive symptoms (104). Similarly, in depressive mouse models, decreased SIRT1 expression was found to be associated with reduced neurogenesis in the hippocampus (105). Activation of SIRT1 was also shown to enhance the proliferation and differentiation of neural stem cells, thereby increasing the number of new neurons and alleviating depressive symptoms (106). In rats subjected to chronic unpredictable mild stress (CUMS), hippocampal SIRT1 expression was shown to be significantly reduced, which correlated with depressive-like behaviors (107). In the CUMS mouse model, overexpression of SIRT1 in the hippocampus was found to significantly mitigate depressive-like behaviors, emphasizing the role of SIRT1 in depression (108).

The potential antidepressant effects of SIRT1 activation have been demonstrated in numerous studies. Research in CUMS mouse models has shown that activating SIRT1 improves neuronal function, enhancing neuroplasticity and promoting neurogenesis, thereby producing antidepressant-like effects (109). SIRT1 modulates the expression of various genes through deacetylation, promoting synaptic plasticity and the formation of functional synapses (110). In animal models of depression, activation of SIRT1 has been shown to increase the expression of brain-derived neurotrophic factor (BDNF), a protein critical for neuronal survival, synaptic plasticity and neurogenesis (111). Elevated BDNF levels were demonstrated to improve hippocampal function and alleviate depressive symptoms (112).

In a different study, researchers assessed postpartum depressive-like behaviors in a depression model of ovariectomized mice, and found that resveratrol, a SIRT1 activator, could alleviate depressive-like behaviors in mice, drawing significant attention to its potential role as a therapeutic agent for treating depression (113). Resveratrol, a natural polyphenolic compound found in fruit such as grapes, berries and peanuts, exhibits antioxidant, anti-inflammatory and anticancer properties (114). In animal models of depression, the antidepressant-like effects of resveratrol have been widely confirmed (113). Through the activation of SIRT1, resveratrol was shown to enhance neuroplasticity and neurogenesis in the hippocampus, thereby mitigating depressive-like behavior (115). In CUMS models, treatment with resveratrol also led to a marked increase in SIRT1 expression, an elevation in the level of BDNF, and the alleviation of depressive symptoms (116). The proposed mechanism is that resveratrol regulates various depression-associated molecules and pathways through SIRT1-mediated deacetylation (116). Furthermore, resveratrol has an important role in a variety of neurological diseases, including depression, via activation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy balance. The activation of AMPK may not only affect the behavioral effects of antidepressants, but it may also have a role in the occurrence of depression by regulating the expression or function of glucocorticoids (117).

SIRT1 significantly influences depression by acting on the nucleus accumbens, a brain region crucial for motivation and reward processing (118). The regulation of this region mediated by SIRT1 is considered to influence emotional regulation and depressive-like behaviors (25). In animal models, manipulating SIRT1 expression in the nucleus accumbens leads to marked changes in anxiety- and depression-associated behaviors (119). This underscores the potential of SIRT1 as a molecular target for novel antidepressant therapies, especially for patients experiencing symptoms such as anhedonia or lack of motivation (119). Chronic stress is a major depression risk factor, and SIRT1 is pivotal in modulating the body's stress response (120). It affects the body's response to stress by regulating glucocorticoid receptors, which are essential for stress responses (121). In a CUMS mouse model, numerous studies have identified that dysregulation of SIRT1 exacerbates stress-associated depressive behaviors (122,123). In a study conducted on male mice with depression, it was discovered that chronic stress leads to downregulation of SIRT1 in the amygdala. Fluoxetine, a widely used antidepressant, is able to reverse this downregulation and ameliorate depressive-like behaviors, demonstrating that SIRT1 may mediate the antidepressant effects of certain medications (124). In conclusion, SIRT1 regulates oxidative stress, inflammation, neurogenesis and neuroplasticity, influencing both the onset and prevention of depression (Fig. 3).

5. Role of SIRT1 in CHD

A study that employed an acute myocardial infarction rat model highlighted the role of SIRT1 in mitigating inflammation, oxidative stress and vascular dysfunction, which all act as contributing factors in CHD and atherosclerosis (125). A cohort study on patients post-coronary artery bypass graft surgery

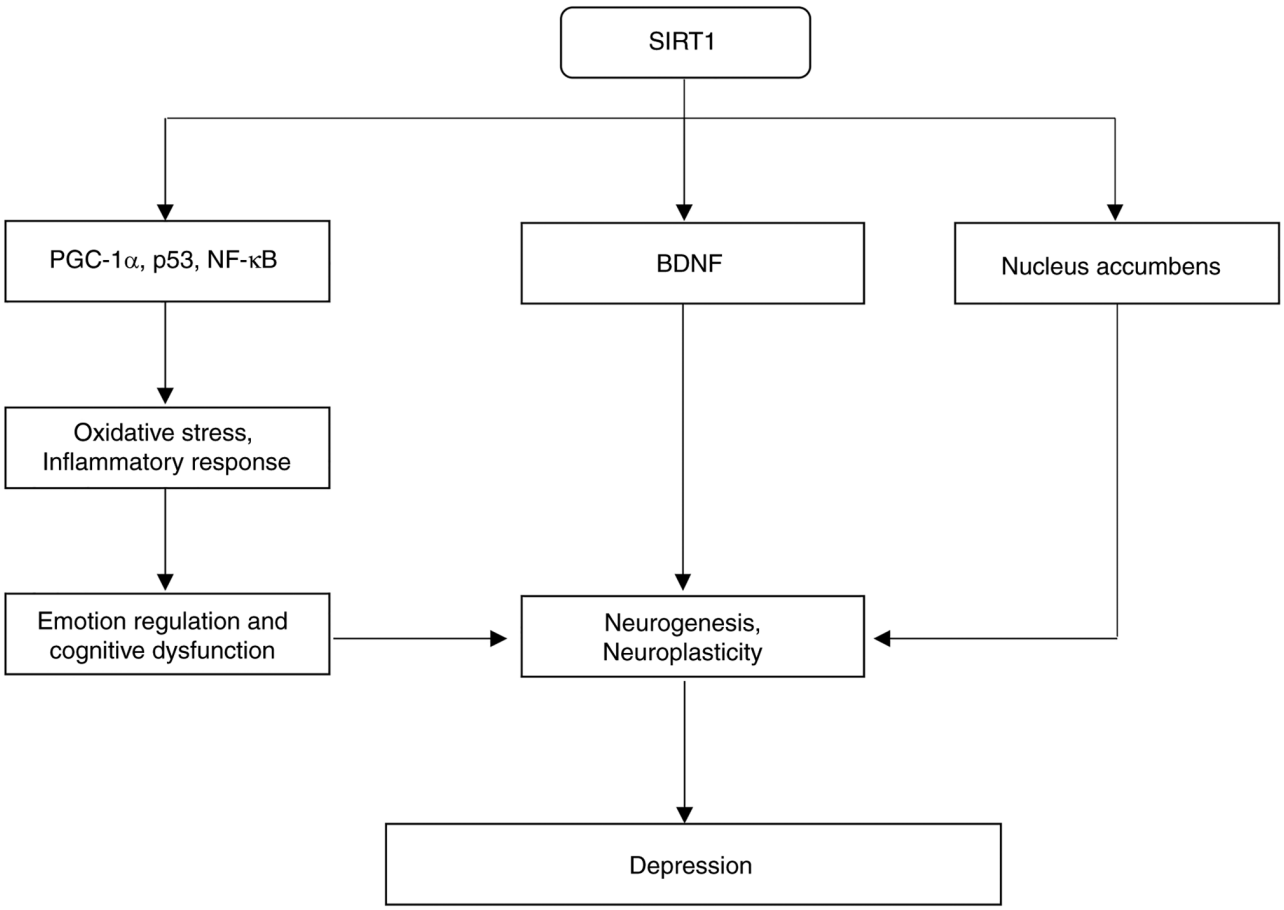

Figure 3. Schematic figure, illustrating the association between SIRT1 and depression. Through the regulation of PGC-1α, p53, and NF-κB, SIRT1 impacts oxidative stress and inflammation, which subsequently influences emotional and cognitive functions. These imbalances may disrupt neurogenesis and neuroplasticity, increasing the risk of depression. On the other hand, SIRT1 is able to lower the risk of depression by enhancing neurogenesis and plasticity via BDNF modulation. Additionally, the role of SIRT1 in the nucleus accumbens, where it governs neurogenesis and plasticity, helps to reduce oxidative stress and inflammation, thereby decreasing depression susceptibility. These mechanisms establish SIRT1 as a pivotal factor in both the onset and prevention of depression. SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; p53, tumor protein p53; NF-κB, nuclear factor kappa B; BDNF, brain-derived neurotrophic factor.

and after aortic valve replacement revealed high expression levels of SIRT1 in endothelial cells, vascular smooth muscle cells (VSMCs) and cardiomyocytes, where it was found to confer protective benefits (126). Its function in maintaining endothelial homeostasis is especially important, as endothelial dysfunction is an early event in the development of atherosclerosis (127). A previous *in vivo* study with mice revealed that activating SIRT1 boosts the production of nitric oxide (NO), reduces oxidative stress and decreases inflammation, thereby improving endothelial function. Additionally, SIRT1 protects against atherosclerosis by either activating endothelial NO synthase or reducing NF-κB activity in endothelial cells and macrophages (128).

These effects are crucial, as impaired NO bioavailability and increased oxidative stress are characteristic of endothelial dysfunction, and contribute to the progression of atherosclerosis (129). A study that investigated atherosclerosis using cultured human smooth muscle cells showed that SIRT1 is able to reduce vascular wall inflammation, a major contributor to atherosclerosis (130). In an *in vitro* cell culture study, SIRT1 deacetylation was found to cause downregulation of NF-κB, a central transcription factor in inflammatory responses, which thereby reduced the levels of pro-inflammatory cytokines, including TNF-α and IL-6 (131). This anti-inflammatory action reduces the recruitment of immune cells, such as monocytes and macrophages, to the arterial wall, thereby limiting the formation of atherosclerotic plaques (132). Furthermore, moderate overexpression of SIRT1 in mice has been shown to reduce oxidative stress, thereby preventing lipid oxidation, which is a key step both in terms of halting plaque formation and slowing the progression of atherosclerosis (133).

Studies in both animals and human models have underscored the importance of SIRT1 in lipid metabolism, directly associating it with atherosclerosis prevention (134-136). Experiments that analyzed SIRT1 expression in the rat hippocampus showed that SIRT1 activates PGC-1α, a coactivator essential for mitochondrial formation and fatty acid oxidation (137). Through the promotion of efficient lipid utilization, SIRT1 was found to decrease the accumulation of low-density lipoprotein cholesterol, a primary risk factor for atherosclerosis, in the bloodstream (138). Moreover, a study on human U937 monocytes revealed that SIRT1 modulates liver X receptor (LXR) activity, with LXRs having a key role in cholesterol clearance and reverse transport, which are essential roles for cholesterol removal from arterial plaques (139). The association between SIRT1 and atherosclerosis has also been

confirmed in both animal models and human studies (140,141). SIRT1 activation has been shown to reduce atherosclerotic plaque formation in mouse models of the disease (142). Moreover, a retrospective case-control study revealed an association between gene variants of SIRT1 and a reduced risk of atherosclerotic coronary artery disease, suggesting that the cardiovascular protective role of SIRT1 may be genetically influenced (143). Additionally, in a rat model of cardiac hypertrophy, another study found that activating SIRT1 using sirtuin activators such as resveratrol led to a reduction in vascular inflammation, which caused a delay in the progression of atherosclerosis (144).

In addition to its anti-inflammatory and antioxidant effects, SIRT1 has also been shown to have a crucial role in regulating the proliferation and migration of VSMCs, processes that are essential for neointimal hyperplasia and the stability of atherosclerotic plaques (145). A further study revealed that, in a mouse model with SIRT1 overexpression, SIRT1 helped to stabilize atherosclerotic plaques, thereby reducing the risk of plaque rupture and subsequent thrombotic events, such as myocardial infarction or stroke, through inhibition of the proliferation of VSMCs and promotion of their differentiation (146). Another key aspect of the protective role of SIRT1 in the cardiovascular system involves its interaction with metabolic pathways (147). SIRT1 has been shown to be able to improve insulin sensitivity and to regulate glucose metabolism, processes that are especially significant in metabolic diseases such as type 2 diabetes, which is a known risk factor for CHD (148). In diabetic patients, SIRT1 activation was found to improve endothelial function, with a mitigation of coronary atherosclerosis (149).

Furthermore, the cardioprotective effects of SIRT1 have been shown to extend beyond atherosclerosis; for example, it has been shown to protect against cardiac hypertrophy, a common complication in patients with hypertension and CHD (150). In a rat model of myocardial hypertrophy, SIRT1 was found to regulate the hypertrophic response of cardiomyocytes via inhibiting the transforming growth factor-β1 (TGF-β1)/p-Smad3 signaling pathway, which is implicated in cardiac fibrosis and hypertrophy (144). This anti-hypertrophic effect helps to preserve cardiac function and to prevent heart failure, a frequent complication in CHD. In conclusion, the available evidence suggests that SIRT1 exerts protective effects against CHD by modulating the growth of VSMCs, oxidative stress, lipid metabolism and inflammation (Fig. 4).

6. Mechanism of action of SIRT1 in the development of CHD caused by depression

Studies in both animal models and humans have shown that the role of SIRT1 in depression-induced CHD involves its complex regulation of cardiovascular molecular pathways, including oxidative stress, inflammation and metabolism (151). As part of the sirtuin family, SIRT1 performs a key role in the cellular response to various forms of stress, including emotional and psychological stressors, such as depression (152). Extensive longitudinal studies and meta-analyses have confirmed that depression is a known risk factor for cardiovascular diseases, including CHD, primarily due to its detrimental effects on the autonomic nervous system, inflammatory processes and cardiac function (153-155). SIRT1 has been shown to mitigate these harmful effects by affecting the core mechanisms underlying depression-induced CHD (156).

One of the primary mechanisms through which SIRT1 influences CHD in the context of depression is by regulating oxidative stress (151). A previous study using the CUMS mouse model has shown that depression leads to an increase in the production of reactive oxygen species and the compromise of antioxidant defenses, resulting in oxidative damage to endothelial cells, which are critical contributors to atherosclerosis and CHD progression (157). Furthermore, studies *in vitro* have demonstrated that SIRT1 exerts protective antioxidant and anti-apoptotic effects, which are achieved by enhancing antioxidant gene expression and effecting the downregulation of pro-oxidative pathways (158). SIRT1 specifically activates FOXO transcription factors, which causes the upregulation of antioxidant stress genes such as MnSOD, contributing to its role in oxidative stress defense (159). A study that utilized a mouse model of myocardial ischemia demonstrated that SIRT1 reduces the risk of plaque formation and slows down atherosclerosis progression through mitigation of oxidative damage to vascular endothelial cells (160).

In addition to its role in reducing oxidative stress, SIRT1 also regulates inflammatory pathways that are often activated by depression (151). Clinical evidence has shown that chronic inflammation is a shared characteristic of depression and CHD, with SIRT1 having a crucial role in reducing inflammatory responses (161,162). Studies in mice with overexpressed SIRT1 have shown that the deacetylase function of SIRT1 inhibits the activation of NF-κB, a key transcription factor that promotes the production of pro-inflammatory cytokines such as IL-6 and TNF-α. By dampening the inflammatory response, SIRT1 reduces immune cell recruitment to the vessel wall, which thereby prevents atherosclerotic plaque formation and decreases the risk of CHD in patients with depression (163,164). Furthermore, SIRT1 regulates disrupted metabolic processes in both depression and CHD (165). A cross-sectional study demonstrated that depression frequently occurs concomitantly with metabolic syndrome, which involves processes such as insulin resistance and dyslipidemia (166) and obesity, all of which are significant risk factors for CHD. Analysis of cholesterol and triglyceride levels in mouse tissues has suggested that SIRT1 regulates lipid metabolism via activation of PGC-1α and LXRs, which are both integral to cholesterol efflux and fatty acid oxidation (167). Through the promotion of lipid homeostasis, SIRT1 has been shown to reduce cholesterol accumulation in the arterial walls, thereby decreasing the risk of atherosclerosis and CHD, especially in individuals with depression (168).

Depression-induced CHD is also associated with disruptions in autonomic nervous system function; specifically, an increase in sympathetic activity and a reduction in parasympathetic activity (169). These autonomic imbalances may lead to increased blood pressure, an accelerated heart rate and heightened vascular tone, all of which contribute to the risk of CHD, especially in women with depression (170). In a study that utilized a hypertensive rat model, activating SIRT1 in the hypothalamus led to the regulation of sympathetic nervous activity, thereby reducing blood pressure (171). Activation

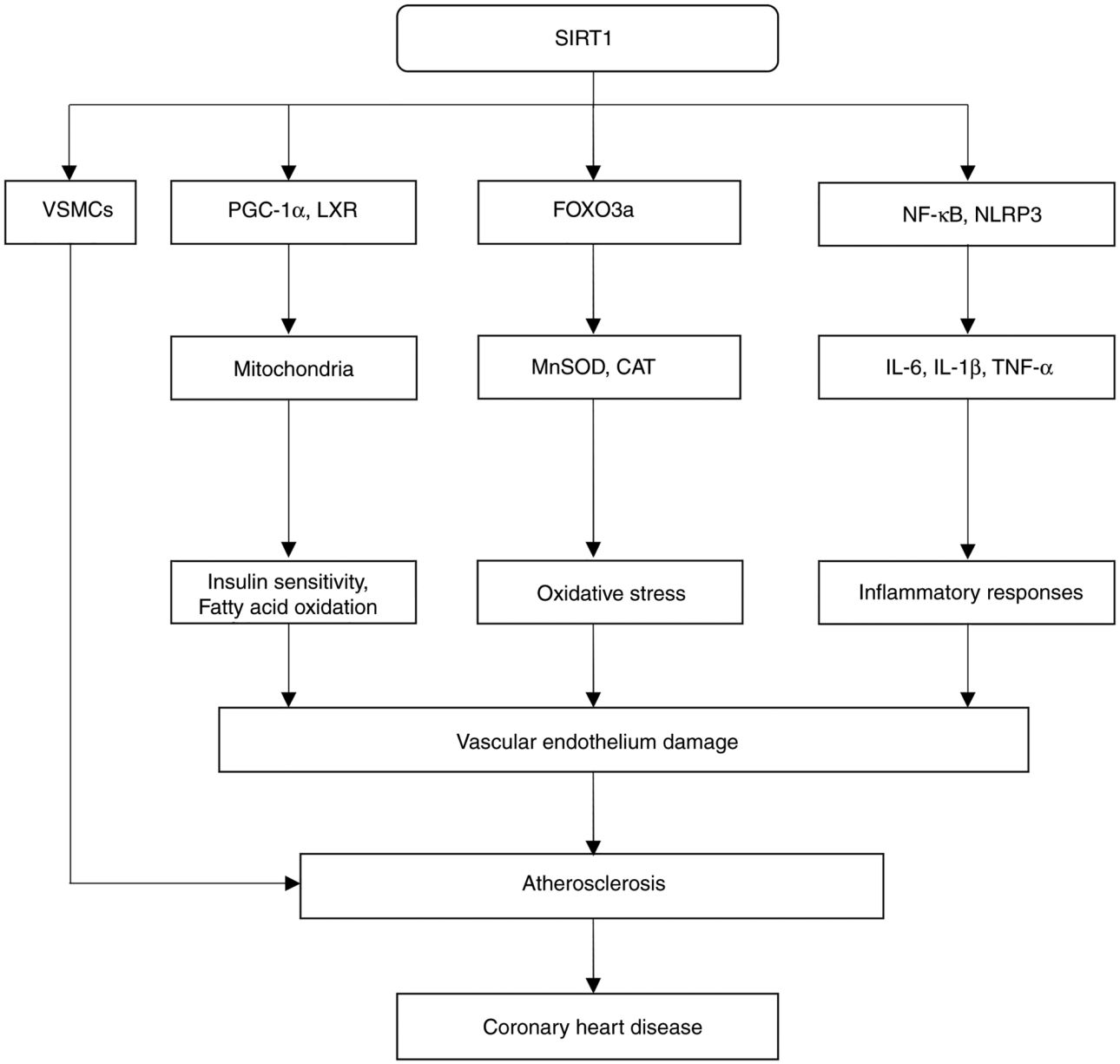

Figure 4. Schematic figure, illustrating the association between SIRT1 and coronary heart disease. Through the regulation of a number of cellular and molecular pathways, SIRT1 influences CHD development and progression. It regulates VSMC growth and degradation, thereby affecting atherosclerosis or plaque stability. Through its interactions with PGC-1α and LXR, SIRT1 enhances mitochondrial function and fatty acid oxidation, thereby improving insulin sensitivity and reducing the accumulation of lipids, and helping to prevent atherosclerosis. Activation of FOXO3a by SIRT1 upregulates the expression of antioxidants such as MnSOD and CAT, thereby reducing oxidative stress and supporting endothelial health, and minimizing the risk of plaque formation by reducing vascular endothelium damage. Deacetylation of NF-κB and NLRP3 by SIRT1 lowers the levels of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α, which, in turn, reduces the levels of inflammation and protects endothelial function, and collectively, these processes cause a slowing down of atherosclerosis and a lowering of the CHD risk. SIRT1, sirtuin 1; VSMCs, vascular smooth muscle cells; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; LXR, liver X receptor; FOXO3a, Forkhead box O3a; NF-κB, nuclear factor-κB; NLRP3, nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3; MnSOD, manganese superoxide dismutase; CAT, catalase; IL-6, interleukin-6; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor-α; CHD, coronary heart disease.

of SIRT1 in the hypothalamus has been shown to modulate sympathetic outflow and to reduce blood pressure, mitigating one of the key mechanisms through which depression leads to CHD (172). Another critical role of SIRT1 in depression-associated CHD involves its effect on cardiac remodeling and fibrosis (173). In a clinical observational study of hypertension, depression was often found to be associated with increased cardiac stress and hypertrophy, which, if left uncontrolled, may lead to heart failure (174).

In animal studies, SIRT1 was found to inhibit the TGF-β1 signaling pathway, thereby alleviating cardiac fibrosis in mice and leading to the protection of the heart from hypertrophic stress, a pathway that is a significant driver of cardiac fibrosis and remodeling (175,176). Additionally, SIRT1 was shown to support cardiac health by limiting the accumulation of extracellular matrix proteins in the heart, potentially lowering the risk of heart failure in patients with depression-associated CHD (177). Additionally, SIRT1 has been shown to have a

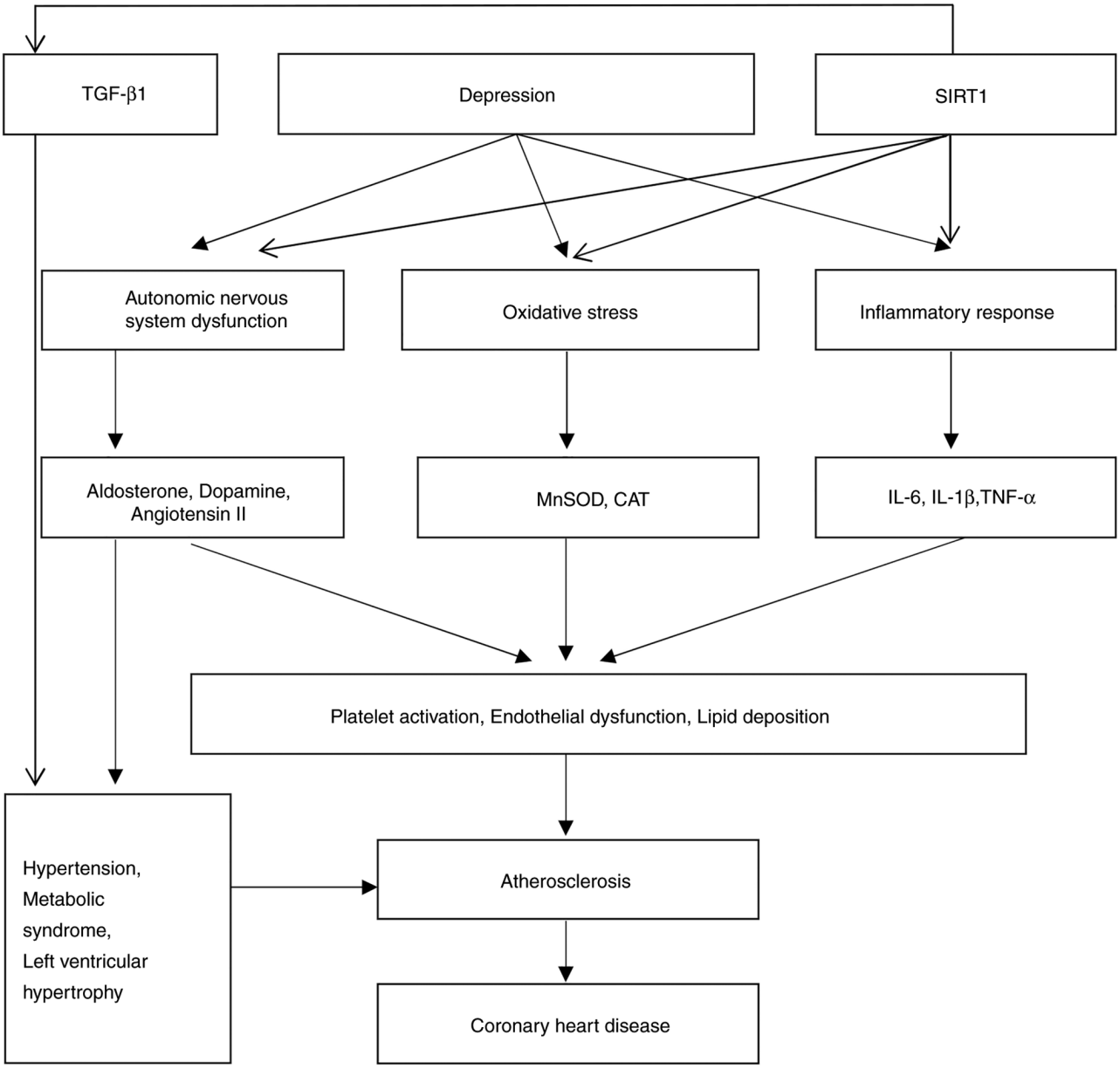

Figure 5. Schematic figure, illustrating the association between SIRT1, depression and coronary heart disease. Depression increases the risk of CHD by disrupting autonomic function, increasing the level of oxidative stress and triggering inflammation, which collectively contribute to endothelial dysfunction, platelet activation and the accumulation of lipids, driving atherosclerosis. SIRT1 regulates these processes by supporting autonomic function, increasing the levels of antioxidant enzymes such as MnSOD and CAT, and decreasing the levels of pro-inflammatory cytokines. Additionally, SIRT1 modulates TGF-β1 to further mitigate cardiovascular damage, helping to lower the risk of CHD associated with depression. SIRT1, sirtuin 1; TGF-β1, transforming growth factor-β1; MnSOD, manganese superoxide dismutase; CAT, catalase; IL-6, interleukin-6; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor-α; CHD, coronary heart disease.

vital role in regulating autophagy, a cellular process essential for maintaining cardiovascular health (178). Autophagy helps to eliminate damaged cellular components, thereby preventing the accumulation of toxic proteins, which can lead to cardiovascular diseases (179). A study that employed a mouse depression model showed that depression compromises cardiac autophagy, increasing the likelihood of ischemic injury and heart failure (180). SIRT1 has also been shown to facilitate autophagy by deacetylating essential autophagy-associated proteins, which improved the removal of damaged mitochondria and reduced the chance of ischemia-reperfusion injury in cardiac tissue (181). In conclusion, a number of studies have shown that SIRT1 decreases the risk of CHD by mitigating cardiovascular damage associated with depression, primarily by strengthening autonomic function, boosting antioxidant defense mechanisms and reducing inflammation (Fig. 5).

7. Therapeutic potential of SIRT1 in depression-induced CHD

The potential of SIRT1 in managing depression and CHD is increasingly supported by robust preclinical and clinical data, highlighting its ability to regulate inflammation, oxidative stress and metabolic pathways, which serve as key pathological mechanisms implicated in both CHD and depression (104,108,128,130). As a prominent NAD^+-dependent

deacetylase, SIRT1 exerts protective effects on the cardiovascular and central nervous systems, suggesting its suitability as a dual-targeted therapeutic intervention. The findings from animal experiments have suggested that natural and synthetic SIRT1 activators, such as resveratrol and SRT1720, confer substantial cardioprotective and neuroprotective effects, indicating their potential for use in patients with co-morbid CHD and depression (182,183).

In experiments with ApoE$^{(-/-)}$ mice, resveratrol, a SIRT1 activator, showed significant anti-atherosclerotic effects under standard dietary conditions. This included alleviating endothelial dysfunction and inhibiting atherosclerotic plaque formation, which are two critical components in the development of CHD (184). This compound activates SIRT1 to suppress the pro-inflammatory transcription factor NF-κB, which subsequently downregulates the expression of cytokines such as TNF-α and IL-6, which have key roles in vascular inflammation and plaque development. Additionally, resveratrol exhibits notable anti-inflammatory and antioxidant effects in the brain, modulating neuroinflammation markers and oxidative stress in depression models, thereby easing behavioral and cognitive symptoms associated with depression (185). These pleiotropic effects highlight the potential of resveratrol in modulating systemic inflammation and neuroinflammation, supporting the potential application of SIRT1 activators in the treatment of cardiovascular diseases associated with depression.

Similarly, SRT1720 is a synthetic SIRT1 agonist that has shown great potential in supporting cardiac and neurological health (186,187). Animal studies have shown that SRT1720 may promote mitophagy, decrease oxidative stress and regulate inflammation, which may help to slow the progression of atherosclerosis (188,189). This is particularly beneficial in CHD models, where atherosclerosis poses a significant risk. Experimental evidence *in vitro* has demonstrated that SRT1720 exhibits neuroprotective effects by mitigating oxidative stress in neural tissues and regulating mitochondrial function, potentially reducing the depressive symptoms associated with chronic neuroinflammation (190).

Other SIRT1 activators, such as quercetin, have further underscored the therapeutic utility of SIRT1 in cardiovascular and mental health settings (191,192). Quercetin, another polyphenol, has been observed to activate SIRT1 and decrease lipid peroxidation, while enhancing antioxidant enzyme activity in preclinical cardiovascular models (188). This modulation has been associated with improved vascular health and reduced CHD risk (193). In a mouse model of depression, quercetin was shown to effectively reduce neuroinflammatory responses, suggesting that it may alleviate depressive symptoms and improve overall neurological resilience in patients with concurrent CHD (194).

These findings provide a strong basis for exploring the therapeutic potential of SIRT1 in treating CHD associated with depression. However, transitioning from preclinical to clinical application requires extensive research. Future studies should focus on large-scale, multi-center trials to confirm the effectiveness of SIRT1 activators such as resveratrol and SRT1720 in diverse patient groups. Such trials should carefully evaluate biomarkers that are associated with inflammation, oxidative stress and mitochondrial health to better understand the impact of SIRT1 on these interlinked pathways in patients with co-occurring CHD and depression. Additionally, identifying consistent biomarkers, such as specific cytokines and mitochondrial activity markers, will aid in personalizing treatment and guiding SIRT1-based interventions for individual patients. Finally, combining SIRT1-targeted approaches with existing cardiovascular and antidepressant therapies may improve outcomes in both physical and mental health for these patients.

8. Conclusions

SIRT1 is a key factor linking the pathophysiology of depression and CHD that has shown therapeutic potential in terms of its ability to regulate inflammation, oxidative stress and metabolic pathways. Preclinical studies of SIRT1 activators, such as resveratrol and SRT1720, have demonstrated their positive effects on cardiac protection and mood improvement, laying the foundation for further clinical research. However, the complexity of SIRT1 signaling poses challenges for direct clinical translation, especially in patients with co-morbid CHD and depression. Continued advancements in SIRT1-targeted therapies are expected to enhance the treatment outcomes for this dual condition.

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Authors' contributions

SZ and JL designed and conceived this review. SZ wrote the manuscript. LY, QD and XL collected and analyzed the data required for the article, and TM and JL reviewed and edited the manuscript. The authors have carefully reviewed, analyzed, and adapted the content of all referenced studies to ensure accuracy and relevance within the context of this review. All authors read and approved the final manuscript. Data authentication is applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Goldston K and Baillie AJ: Depression and coronary heart disease: A review of the epidemiological evidence, explanatory mechanisms and management approaches. Clin Psychol Rev 28: 288-306, 2008.
2. Pearce M, Garcia L, Abbas A, Strain T, Schuch FB, Golubic R, Kelly P, Khan S, Utukuri M, Laird Y, *et al*: Association between physical activity and risk of depression: A systematic review and meta-analysis. JAMA Psychiatry 79: 550-559, 2022.
3. Li R and Ödell J: Environmental, genetic factors and depression. J Stud Res 12: 1-5 2023.
4. Scott KM, de Jonge P, Stein DJ and Kessler RC: Mental Disorders Around the World: Facts and Figures from the WHO World Mental Health Surveys. Scott KM, de Jonge P, Stein DJ and Kessler RC (eds). Cambridge University Press, 2018.
5. Moffitt TE, Caspi A, Taylor A, Kokaua J, Milne BJ, Polanczyk G and Poulton R: How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol Med 40: 899-909, 2010.
6. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, *et al*: Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 70: 1-25, 2017.
7. Mensah GA, Fuster V, Murray CJL and Roth GA; Global Burden of Cardiovascular Diseases and Risks Collaborators: Global burden of cardiovascular diseases and risks, 1990-2022. J Am Coll Cardiol 82: 2350-2473, 2023.
8. World Health Organization: Cardiovascular diseases (CVDs). Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
9. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, *et al*: Heart disease and stroke statistics-2020 update: A report from the American Heart Association. Circulation 141: E139-E596, 2020.
10. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, *et al*: Forecasting the future of cardiovascular disease in the United States: A policy statement from the American Heart Association. Circulation 123: 933-944, 2011.
11. Li A, Rosella LC, Kurdyak P and Wodchis WP: Depression as a risk factor for physical illness and multimorbidity in a cohort with no prior comorbidity. Can J Psychiatry 66: 726-736, 2021.
12. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, Furukawa TA, Kessler RC, Kohrt BA, Maj M, *et al*: Time for united action on depression: A lancet-world psychiatric association commission. Lancet 399: 957-1022, 2022.
13. Penninx BW, Milaneschi Y, Lamers F and Vogelzangs N: Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. BMC Med 11: 129, 2013.
14. Dantzer R, O'Connor JC, Freund GG, Johnson RW and Kelley KW: From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci 9: 46-56, 2008.
15. Sichko S, Bui TQ, Vinograd M, Shields GS, Saha K, Devkota S, Olvera-Alvarez HA, Carroll JE, Cole SW, Irwin MR and Slavich GM: Psychobiology of stress and adolescent depression (PSY SAD) study: Protocol overview for an fMRI-based multi-method investigation. Brain Behav Immun Health 17: 100334, 2021.
16. Bansal Y and Kuhad A: Mitochondrial dysfunction in depression. Curr Neuropharmacol 14: 610-618, 2016.
17. Tan C, Yan Q, Ma Y, Fang J and Yang Y: Recognizing the role of the vagus nerve in depression from microbiota-gut brain axis. Front Neurol 13: 1015175, 2022.
18. Yuan M, Yang B, Rothschild G, Mann JJ, Sanford LD, Tang X, Huang C, Wang C and Zhang W: Epigenetic regulation in major depression and other stress-related disorders: Molecular mechanisms, clinical relevance and therapeutic potential. Signal Transduct Target Ther 8: 309, 2023.
19. Shen R, Zhao N, Wang J, Guo P, Shen S, Liu D and Zou T: Association between level of depression and coronary heart disease, stroke risk and all-cause and cardiovascular mortality: Data from the 2005-2018 National health and nutrition examination survey. Front Cardiovasc Med 9: 954563, 2022.
20. Cao H, Zhao H and Shen L: Depression increased risk of coronary heart disease: A meta-analysis of prospective cohort studies. Front Cardiovasc Med 9: 913888, 2022.
21. Xu L, Zhai X, Shi D and Zhang Y: Depression and coronary heart disease: Mechanisms, interventions, and treatments. Front Psychiatry 15: 1328048, 2024.
22. Harshfield EL, Pennells L, Schwartz JE, Willeit P, Kaptoge S, Bell S, Shaffer JA, Bolton T, Spackman S, Wassertheil-Smoller S, *et al*: Association between depressive symptoms and incident cardiovascular diseases. JAMA 324: 2396-2405, 2020.
23. Zhang Y, Cui G, Wang Y, Gong Y and Wang Y: SIRT1 activation alleviates brain microvascular endothelial dysfunction in peroxisomal disorders. Int J Mol Med 44: 995-1005, 2019.
24. Jha MK, Qamar A, Vaduganathan M, Charney DS and Murrough JW: Screening and management of depression in patients with cardiovascular disease. J Am Coll Cardiol 73: 1827-1845, 2019.
25. Lu G, Li J, Zhang H, Zhao X, Yan LJ and Yang X: Role and possible mechanisms of Sirt1 in depression. Oxid Med Cell Longev 2018: 8596903, 2018.
26. Chan SH, Hung CH, Shih JY, Chu PM, Cheng YH, Lin HC and Tsai KL: SIRT1 inhibition causes oxidative stress and inflammation in patients with coronary artery disease. Redox Biol 13: 301-309, 2017.
27. Singh V and Ubaid S: Role of silent information regulator 1 (SIRT1) in regulating oxidative stress and inflammation. Inflammation 43: 1589-1598, 2020.
28. Campagna R, Mazzanti L, Pompei V, Alia S, Vignini A and Emanuelli M: The multifaceted role of endothelial Sirt1 in vascular aging: An update. Cells 13: 1469, 2024.
29. Mao Y and Jiang P: The crisscross between p53 and metabolism in cancer. Acta Biochim Biophys Sin (Shanghai) 55: 914-922, 2023.
30. Mijit M, Caracciolo V, Melillo A, Amicarelli F and Giordano A: Role of p53 in the regulation of cellular senescence. Biomolecules 10: 420, 2020.
31. Yi J and Luo J: SIRT1 and p53, effect on cancer, senescence and beyond. Biochim Biophys Acta Proteins Proteom 1804: 1684-1689, 2010.
32. Sullivan A and Lu X: ASPP: A new family of oncogenes and tumour suppressor genes. Br J Cancer 96: 196-200, 2007.
33. Brockmueller A, Buhrmann C, Shayan P and Shakibaei M: Resveratrol induces apoptosis by modulating the reciprocal crosstalk between p53 and Sirt-1 in the CRC tumor microenvironment. Front Immunol 14: 1225530, 2023.
34. Sivakumar KK, Stanley JA, Behlen JC, Wuri L, Dutta S, Wu J, Arosh JA and Banu SK: Inhibition of Sirtuin-1 hyperacetylates p53 and abrogates Sirtuin-1-p53 interaction in Cr(VI)-induced apoptosis in the ovary. Reprod Toxicol 109: 121-134, 2022.
35. Dilmac S, Kuscu N, Caner A, Yildirim S, Yoldas B, Farooqi AA and Tanriover G: SIRT1/FOXO signaling pathway in breast cancer progression and metastasis. Int J Mol Sci 23: 10227, 2022.
36. Mizani S, Keshavarz A, Vazifeh Shiran N, Bashash D and Allahbakhshian Farsani M: Expression changes of SIRT1 and FOXO3a significantly correlate with oxidative stress resistance genes in AML patients. Indian J Hematol Blood Transfus 39: 392-401, 2023.
37. Chen L, Li S, Zhu J, You A, Huang X, Yi X and Xue M: Mangiferin prevents myocardial infarction-induced apoptosis and heart failure in mice by activating the Sirt1/FoxO3a pathway. J Cell Mol Med 25: 2944-2955, 2021.
38. Zhao X, Liu Y, Zhu G, Liang Y, Liu B, Wu Y, Han M, Sun W, Han Y, Chen G and Jiang J: SIRT1 downregulation mediated Manganese-induced neuronal apoptosis through activation of FOXO3a-Bim/PUMA axis. Sci Total Environ 646: 1047-1055, 2019.
39. Alves-Fernandes DK and Jasiulionis MG: The role of SIRT1 on DNA damage response and epigenetic alterations in cancer. Int J Mol Sci 20: 3153, 2019.
40. Qi F, Jiang X, Tong T, Chang H and Li RX: MiR-204 inhibits inflammation and cell apoptosis in retinopathy rats with diabetic retinopathy by regulating Bcl-2 and SIRT1 expressions. Eur Rev Med Pharmacol Sci 24: 6486-6493, 2020.
41. Wu QJ, Zhang TN, Chen HH, Yu XF, Lv JL, Liu YY, Liu YS, Zheng G, Zhao JQ, Wei YF, *et al*: The sirtuin family in health and disease. Signal Transduct Target Ther 7: 402, 2022.
42. Chen G, Zhang B, Xu H, Sun Y, Shi Y, Luo Y, Jia H and Wang F: Suppression of Sirt1 sensitizes lung cancer cells to WEE1 inhibitor MK-1775-induced DNA damage and apoptosis. Oncogene 36: 6863-6872, 2017.

43. Wang C, Chen L, Hou X, Li Z, Kabra N, Ma Y, Nemoto S, Finkel T, Gu W, Cress WD and Chen J: Interactions between E2F1 and SirT1 regulate apoptotic response to DNA damage. Nat Cell Biol 8: 1025-1031, 2006.
44. Imperatore F, Maurizio J, Vargas Aguilar S, Busch CJ, Favret J, Kowenz-Leutz E, Cathou W, Gentek R, Perrin P, Leutz A, *et al*: SIRT1 regulates macrophage self-renewal. EMBO J 36: 2353-2372, 2017.
45. Yang S, Moon S, Hur SC and Jeong SM: Fatty acid oxidation regulates cellular senescence by modulating the autophagy-SIRT1 axis. BMB Rep 56: 651-656, 2023.
46. Liu S, Yao S, Yang H, Liu S and Wang Y: Autophagy: Regulator of cell death. Cell Death Dis 14: 648, 2023.
47. Guo H, Ding H, Tang X, Liang M, Li S, Zhang J and Cao J: Quercetin induces pro-apoptotic autophagy via SIRT1/AMPK signaling pathway in human lung cancer cell lines A549 and H1299 in vitro. Thorac Cancer 12: 1415-1422, 2021.
48. Abate M, Festa A, Falco M, Lombardi A, Luce A, Grimaldi A, Zappavigna S, Sperlongano P, Irace C, Caraglia M and Misso G: Mitochondria as playmakers of apoptosis, autophagy and senescence. Semin Cell Dev Biol 98: 139-153, 2020.
49. Ding X, Zhu C, Wang W, Li M, Ma C and Gao B: SIRT1 is a regulator of autophagy: Implications for the progression and treatment of myocardial ischemia-reperfusion. Pharmacol Res 199: 106957, 2024.
50. Jiang Y, Botchway BOA, Hu Z and Fang M: Overexpression of SIRT1 inhibits corticosterone-induced autophagy. Neuroscience 411: 11-22, 2019.
51. Chung S, Yao H, Caito S, Hwang JW, Arunachalam G and Rahman I: Regulation of SIRT1 in cellular functions: Role of polyphenols. Arch Biochem Biophys 501: 79-90, 2010.
52. Korbecki J, Bobiński R and Dutka M: Self-regulation of the inflammatory response by peroxisome proliferator-activated receptors. Inflamm Res 68: 443-458, 2019.
53. Tian Y, Ma J, Wang W, Zhang L, Xu J, Wang K and Li D: Resveratrol supplement inhibited the NF-κB inflammation pathway through activating AMPKα-SIRT1 pathway in mice with fatty liver. Mol Cell Biochem 422: 75-84, 2016.
54. Sun HJ, Xiong SP, Cao X, Cao L, Zhu MY, Wu ZY and Bian JS: Polysulfide-mediated sulfhydration of SIRT1 prevents diabetic nephropathy by suppressing phosphorylation and acetylation of p65 NF-κB and STAT3. Redox Biol 38: 101813, 2021.
55. Murphy CE, Lawther AJ, Webster MJ, Asai M, Kondo Y, Matsumoto M, Walker AK and Weickert CS: Nuclear factor kappa B activation appears weaker in schizophrenia patients with high brain cytokines than in non-schizophrenic controls with high brain cytokines. J Neuroinflammation 17: 215, 2020.
56. Liu T, Zhang L, Joo D and Sun SC: NF-κB signaling in inflammation. Signal Transduct Target Ther 2: 17023, 2017.
57. Kauppinen A, Suuronen T, Ojala J, Kaarniranta K and Salminen A: Antagonistic crosstalk between NF-κB and SIRT1 in the regulation of inflammation and metabolic disorders. Cell Signal 25: 1939-1948, 2013.
58. Jalgaonkar MP, Parmar UM, Kulkarni YA and Oza MJ: SIRT1-FOXOs activity regulates diabetic complications. Pharmacol Res 175: 106014, 2022.
59. Jia D, Ping W, Wang M, Wang D, Zhang L and Cao Y: SIRT1 mediates the inflammatory response of macrophages and regulates the TIMP3/ADAM17 pathway in atherosclerosis. Exp Cell Res 442: 114253, 2024.
60. Chen H, Deng J, Gao H, Song Y, Zhang Y, Sun J and Zhai J: Involvement of the SIRT1-NLRP3 pathway in the inflammatory response. Cell Commun Signal 21: 185, 2023.
61. Hardeland R: Aging, melatonin, and the pro-and anti-inflammatory networks. Int J Mol Sci 20: 1223, 2019.
62. Rovira-Llopis S, Apostolova N, Bañuls C, Muntané J, Rocha M and Victor VM: Mitochondria, the NLRP3 inflammasome, and sirtuins in type 2 diabetes: New therapeutic targets. Antioxid Redox Signal 29: 749-791, 2018.
63. Zhang Y, Zhang H, Li S, Huang K, Jiang L and Wang Y: Metformin alleviates LPS-induced acute lung injury by regulating the SIRT1/NF-κB/NLRP3 pathway and inhibiting endothelial cell pyroptosis. Front Pharmacol 13: 801337, 2022.
64. Luo XY, Qu SL, Tang ZH, Zhang Y, Liu MH, Peng J, Tang H, Yu KL, Zhang C, Ren Z and Jiang ZS: SIRT1 in cardiovascular aging. Clin Chim Acta 437: 106-114, 2014.
65. Das A, Huang GX, Bonkowski MS, Longchamp A, Li C, Schultz MB, Kim LJ, Osborne B, Joshi S, Lu Y, *et al*: Impairment of an endothelial NAD+-H2S signaling network is a reversible cause of vascular aging. Cell 173: 74-89. e20, 2018.
66. Zhu YJ, Huang J, Chen R, Zhang Y, He X, Duan WX, Zou YL, Sun MM, Sun HL, Cheng SM, *et al*: Autophagy dysfunction contributes to NLRP1 inflammasome-linked depressive-like behaviors in mice. J Neuroinflammation 21: 6, 2024.
67. Strothers HS III: Depression in the primary care setting. Ethn Dis 12: S28-S30, 2002.
68. Schmauβ M: Depression and Parkinson's disease. Fortschr Neurol Psychiatr 90: 145-146, 2022 (In German).
69. El-Battrawy I, Behnes M and Akin I: Depression and incident cardiovascular disease. JAMA 325: 1679-1680, 2021.
70. Taqueti VR and Di Carli MF: Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. J Am Coll Cardiol 72: 2625-2641, 2018.
71. Halaris A: Inflammation-associated co-morbidity between depression and cardiovascular disease. Curr Top Behav Neurosci 31: 45-70, 2017.
72. Hackett RA and Steptoe A: Psychosocial factors in diabetes and cardiovascular risk. Curr Cardiol Rep 18: 95, 2016.
73. Lawrence S and Scofield RH: Post traumatic stress disorder associated hypothalamic-pituitary-adrenal axis dysregulation and physical illness. Brain Behav Immun Health 41: 100849, 2024.
74. Wirtz PH and von Känel R: Psychological stress, inflammation, and coronary heart disease. Curr Cardiol Rep 19: 111, 2017.
75. Tonhajzerova I, Sekaninova N, Bona Olexova L and Visnovcova Z: Novel insight into neuroimmune regulatory mechanisms and biomarkers linking major depression and vascular diseases: The dilemma continues. Int J Mol Sci 21: 2317, 2020.
76. Ramachandruni S, Handberg E and Sheps DS: Acute and chronic psychological stress in coronary disease. Curr Opin Cardiol 19: 494-499, 2004.
77. Gianaros PJ, Hariri AR, Sheu LK, Muldoon MF, Sutton-Tyrrell K and Manuck SB: Preclinical atherosclerosis covaries with individual differences in reactivity and functional connectivity of the amygdala. Biol Psychiatry 65: 943-950, 2009.
78. Levin A: Amygdala activity may predict future cardiovascular events. Psychiatr News 52: 1-1, 2017.
79. Pizzi C, Manzoli L, Mancini S, Bedetti G, Fontana F and Costa GM: Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. Atherosclerosis 212: 292-298, 2010.
80. Pan Y, Chen Y, Wu S, Ying P, Zhang Z, Tan X and Zhu J: Prevalence and management of depressive symptoms in coronary heart disease patients and relationship with cardiovascular prognosis: A prospective cohort study. BMC Psychiatry 24: 644, 2024.
81. Compare A, Proietti R, Germani E and Janeway D: Anxiety and depression: Risk factors for cardiovascular disease. In: Stress Proof the Heart: Behavioral Interventions for Cardiac Patients. Vol 9781441956507. Springer, New York, NY, pp139-166, 2012.
82. Dickens C: Depression in people with coronary heart disease: Prognostic significance and mechanisms. Curr Cardiol Rep 17: 83, 2015.
83. De Martini GA, Grisante DL, Gonçalves ALP, D'Agostino F, Lopes JL, Santos VB and Lopes CT: Relationships between depressive symptoms, appetite, and quality of life in heart failure. West J Nurs Res 45: 416-424, 2023.
84. Xu Q, Chen C, You R, Ni L, Chen S and Peng B: Causal association between major depressive disorder and coronary heart disease: A two-sample bidirectional mendelian randomization study. BMC Med Genomics 16: 183, 2023.
85. Meng LB, Zhang YM, Luo Y, Gong T and Liu DP: Chronic Stress A Potential Suspect Zero of Atherosclerosis: A Systematic Review. Front Cardiovasc Med: Dec 20, 2021 (Epub ahead of print). doi: 10.3389/fcvm.2021.738654.
86. Mbiydzenyuy NE and Qulu LA: Stress, hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis, and aggression. Metab Brain Dis 39: 1613-1636, 2024.
87. Hering D, Seravalle G, Grassi G and Narkiewicz K: Sympathetic Activity in Hypertension and Heart Failure. Springer Nature, Heidelberg, pp107-126, 2023.
88. Osimo EF, Baxter LJ, Lewis G, Jones PB and Khandaker GM: Prevalence of low-grade inflammation in depression: A systematic review and meta-analysis of CRP levels. Psychol Med 49: 1958-1970, 2019.
89. Correia AS, Cardoso A and Vale N: Oxidative stress in depression: The link with the stress response, neuroinflammation, serotonin, neurogenesis and synaptic plasticity. Antioxidants (Basel) 12: 470, 2023.
90. Chocano-Bedoya PO, Mirzaei F, O'Reilly EJ, Lucas M, Okereke OI, Hu FB, Rimm EB and Ascherio A: C-reactive protein, interleukin-6, soluble tumor necrosis factor α receptor 2 and incident clinical depression. J Affect Disord 163: 25-32, 2014.

91. Li G, Zhang L and Liu M: Meta-analysis on inflammation and autonomic nervous system of coronary heart disease combined with depression. BMJ Open 14: e079980, 2024.
92. Higashi Y: Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease. Antioxidants (Basel) 11: 1958, 2022.
93. Gao F, Zhao Y, Zhang B, Xiao C, Sun Z, Gao Y and Dou X: Orientin alleviates ox-LDL-induced oxidative stress, inflammation and apoptosis in human vascular endothelial cells by regulating Sestrin 1 (SESN1)-mediated autophagy. J Mol Histol 55: 109-120, 2024.
94. Kwong ASF, López-López JA, Hammerton G, Manley D, Timpson NJ, Leckie G and Pearson RM: Genetic and environmental risk factors associated with trajectories of depression symptoms from adolescence to young adulthood. JAMA Netw Open 2: e196587, 2019.
95. Lei Y, Wang J, Wang D, Li C, Liu B, Fang X, You J, Guo M and Lu XY: SIRT1 in forebrain excitatory neurons produces sexually dimorphic effects on depression-related behaviors and modulates neuronal excitability and synaptic transmission in the medial prefrontal cortex. Mol Psychiatry 25: 1094-1111, 2020.
96. Abe-Higuchi N, Uchida S, Yamagata H, Higuchi F, Hobara T, Hara K, Kobayashi A and Watanabe Y: Hippocampal Sirtuin 1 signaling mediates depression-like behavior. Biol Psychiatry 80: 815-826, 2016.
97. Singh P, Hanson PS and Morris CM: SIRT1 ameliorates oxidative stress induced neural cell death and is down-regulated in Parkinson's disease. BMC Neurosci 18: 46, 2017.
98. Qiu X, Lu P, Zeng X, Jin S and Chen X: Study on the mechanism for SIRT1 during the process of exercise improving depression. Brain Sci 13: 719, 2023.
99. Wang R, Wu Y, Liu R, Liu M, Li Q, Ba Y and Huang H: Deciphering therapeutic options for neurodegenerative diseases: insights from SIRT1. J Mol Med (Berl) 100: 537-553, 2022.
100. Zhang Y, Anoopkumar-Dukie S and Davey AK: Sirt1 and sirt2 modulators: Potential anti-inflammatory treatment for depression? Biomolecules 11: 353, 2021.
101. Dang R, Wang M, Li X, Wang H, Liu L, Wu Q, Zhao J, Ji P, Zhong L, Licinio J and Xie P: Edaravone ameliorates depressive and anxiety-like behaviors via Sirt1/Nrf2/HO-1/Gpx4 pathway. J Neuroinflammation 19: 41, 2022.
102. Ma Z, Feng D, Rui W and Wang Z: Baicalin attenuates chronic unpredictable mild stress-induced hippocampal neuronal apoptosis through regulating SIRT1/PARP1 signaling pathway. Behav Brain Res 441: 114299, 2023.
103. Geng M, Shao Q, Fu J, Gu J, Feng L, Zhao L, Liu C, Mu J, Zhang X, Zhao M, *et al*: Down-regulation of MKP-1 in hippocampus protects against stress-induced depression-like behaviors and neuroinflammation. Transl Psychiatry 14: 130, 2024.
104. Tartt AN, Mariani MB, Hen R, Mann JJ and Boldrini M: Dysregulation of adult hippocampal neuroplasticity in major depression: Pathogenesis and therapeutic implications. Mol Psychiatry 27: 2689-2699, 2022.
105. Zhang K, Wang F, Zhai M, He M, Hu Y, Feng L, Li Y, Yang J and Wu C: Hyperactive neuronal autophagy depletes BDNF and impairs adult hippocampal neurogenesis in a corticosterone-induced mouse model of depression. Theranostics 13: 1059-1075, 2023.
106. Saharan S, Jhaveri DJ and Bartlett PF: SIRT1 regulates the neurogenic potential of neural precursors in the adult subventricular zone and hippocampus. J Neurosci Res 91: 642-659, 2013.
107. Shen J, Hao C, Yuan S, Chen W, Tong T, Chen Y, Shahzad Aslam M, Yan S, Li J, Zeng J, *et al*: Acupuncture alleviates CUMS-induced depression-like behaviors of rats by regulating oxidative stress, neuroinflammation and ferroptosis. Brain Res 1826: 148715, 2024.
108. Li C, Wang F, Miao P, Yan L, Liu S, Wang X, Jin Z and Gu Z: miR-138 increases depressive-like behaviors by targeting SIRT1 in hippocampus. Neuropsychiatr Dis Treat 16: 949-957, 2020.
109. Wu X, Zhang Y, Wang J, Qin L, Li Y, He Q, Zhang T, Wang Y, Song L, Ji L, *et al*: Role of SIRT1-mediated synaptic plasticity and neurogenesis: Sex-differences in antidepressant-like efficacy of catalpol. Phytomedicine 135: 156120, 2024.
110. Michán S, Li Y, Chou MM, Parrella E, Ge H, Long JM, Allard JS, Lewis K, Miller M, Xu W, *et al*: SIRT1 is essential for normal cognitive function and synaptic plasticity. J Neurosci 30: 9695-9707, 2010.
111. Guo H, Deji C, Peng H, Zhang J, Chen Y, Zhang Y and Wang Y: The role of SIRT1 in the basolateral amygdala in depression-like behaviors in mice. Genes Brain Behav 20: e12765, 2021.
112. Erickson KI, Miller DL and Roecklein KA: The aging hippocampus: Interactions between exercise, depression, and BDNF. Neuroscientist 18: 82-97, 2012.
113. Ye S, Fang L, Xie S, Hu Y, Chen S, Amin N, Fang M and Hu Z: Resveratrol alleviates postpartum depression-like behavior by activating autophagy via SIRT1 and inhibiting AKT/mTOR pathway. Behav Brain Res 438: 114208, 2023.
114. Wang J, Li J, Cao N, Li Z, Han J and Li L: Resveratrol, an activator of SIRT1, induces protective autophagy in non-small-cell lung cancer via inhibiting Akt/mTOR and activating p38-MAPK. Onco Targets Ther 11: 7777-7786, 2018.
115. Tabassum S, Misrani A, Huang HX, Zhang ZY, Li QW and Long C: Resveratrol attenuates chronic unpredictable mild stress-induced alterations in the SIRT1/PGC1α/SIRT3 pathway and associated mitochondrial dysfunction in mice. Mol Neurobiol 60: 5102-5116, 2023.
116. Shen J, Xu L, Qu C, Sun H and Zhang J: Resveratrol prevents cognitive deficits induced by chronic unpredictable mild stress: Sirt1/miR-134 signalling pathway regulates CREB/BDNF expression in hippocampus in vivo and in vitro. Behav Brain Res 349: 1-7, 2018.
117. Takahashi K, Kurokawa K, Hong L, Miyagawa K, Mochida-Saito A, Takeda H and Tsuji M: Hippocampal and gut AMPK activation attenuates enterocolitis-like symptoms and co-occurring depressive-like behavior in ulcerative colitis model mice: Involvement of brain-gut autophagy. Exp Neurol 373: 114671, 2024.
118. Kim HD, Wei J, Call T, Call T, Ma X, Quintus NT, Summers AJ, Carotenuto S, Johnson R, Nguyen A, *et al*: SIRT1 coordinates transcriptional regulation of neural activity and modulates depression-like behaviors in the nucleus accumbens. Biol Psychiatry 96: 495-505, 2024.
119. Kim HD, Hesterman J, Call T, Magazu S, Keeley E, Armenta K, Kronman H, Neve RL, Nestler EJ and Ferguson D: SIRT1 mediates depression-like behaviors in the nucleus accumbens. J Neurosci 36: 8441-8452, 2016.
120. Nowacka-Chmielewska M, Grabowska K, Grabowski M, Meybohm P, Burek M and Małecki A: Running from stress: Neurobiological mechanisms of exercise-induced stress resilience. Int J Mol Sci 23: 13348, 2022.
121. Yamamoto M and Takahashi Y: The essential role of sirt1 in hypothalamic-pituitary axis. Front Endocrinol (Lausanne) 9: 605, 2018.
122. Yu X, Hu Y, Huang W, Ye N, Yan Q, Ni W and Jiang X: Role of AMPK/SIRT1-SIRT3 signaling pathway in affective disorders in unpredictable chronic mild stress mice. Neuropharmacology 165: 107925, 2020.
123. Takaba R, Ibi D, Watanabe K, Hayakawa K, Nakasai G and Hiramatsu M: Role of sirtuin1 in impairments of emotion-related behaviors in mice with chronic mild unpredictable stress during adolescence. Physiol Behav 257: 113971, 2022.
124. Cordner ZA, Marshall-Thomas I, Boersma GJ, Lee RS, Potash JB and Tamashiro KLK: Fluoxetine and environmental enrichment similarly reverse chronic social stress-related depression- and anxiety-like behavior, but have differential effects on amygdala gene expression. Neurobiol Stress 15: 100392, 2021.
125. Ma B, Guo B, Chen Z and Li Y: SIRT1 regulates hypoxia-induced oxidative stress in cardiomyocytes via PI3K/MTOR signaling. Cell Mol Biol (Noisy-le-grand) 68: 48-53, 2022.
126. Opstad TB, Papotti B, Åkra S, Hansen CH, Braathen B, Tønnessen T, Solheim S and Seljeflot I: Sirtuin1, not NAMPT, possesses anti-inflammatory effects in epicardial, pericardial and subcutaneous adipose tissue in patients with CHD. J Transl Med 21: 644, 2023.
127. Kida Y and Goligorsky MS: Sirtuins, cell senescence, and vascular aging. Can J Cardiol 32: 634-641, 2016.
128. Winnik S, Auwerx J, Sinclair DA and Matter CM: Protective effects of sirtuins in cardiovascular diseases: From bench to bedside. Eur Heart J 36: 3404-3412, 2015.
129. Stein S, Schäfer N, Breitenstein A, Besler C, Winnik S, Lohmann C, Heinrich K, Brokopp CE, Handschin C, Landmesser U, *et al*: SIRT1 reduces endothelial activation without affecting vascular function in ApoE-/-mice. Aging (Albany NY) 2: 353-360, 2010.

130. Gorenne I, Kumar S, Gray K, Figg N, Yu H, Mercer J and Bennett M: Vascular smooth muscle cell sirtuin 1 protects against DNA damage and inhibits atherosclerosis. Circulation 127: 386-396, 2013.
131. Yang H, Zhang W, Pan H, Feldser HG, Lainez E, Miller C, Leung S, Zhong Z, Zhao H, Sweitzer S, *et al*: SIRT1 activators suppress inflammatory responses through promotion of p65 deacetylation and inhibition of NF-κB activity. PLoS One 7: e46364, 2012.
132. Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X, Tang D and Chen R: Research progress on the relationship between atherosclerosis and inflammation. Biomolecules 8: 80, 2018.
133. Kitada M, Ogura Y and Koya D: The protective role of Sirt1 in vascular tissue: Its relationship to vascular aging and atherosclerosis. Aging (Albany NY) 8: 2290-2307, 2016.
134. Guarente L: Franklin H. Epstein Lecture: Sirtuins, aging, and medicine. N Engl J Med 364: 2235-2244, 2011.
135. Houtkooper RH, Pirinen E and Auwerx J: Sirtuins as regulators of metabolism and healthspan. Nat Rev Mol Cell Biol 13: 225-238, 2012.
136. Yang X, Wei J, He Y, Jing T, Li Y, Xiao Y, Wang B, Wang W, Zhang J and Lin R: SIRT1 inhibition promotes atherosclerosis through impaired autophagy. Oncotarget 8: 51447-51461, 2017.
137. Wang SJ, Zhao XH, Chen W, Bo N, Wang XJ, Chi ZF and Wu W: Sirtuin 1 activation enhances the PGC-1α/mitochondrial antioxidant system pathway in status epilepticus. Mol Med Rep 11: 521-526, 2015.
138. Dong YT, Cao K, Xiang J, Qi XL, Xiao Y, Yu WF, He Y, Hong W and Guan ZZ: Resveratrol attenuates the disruption of lipid metabolism observed in amyloid precursor protein/presenilin 1 mouse brains and cultured primary neurons exposed to Aβ. Neuroscience 521: 134-147, 2023.
139. Zeng HT, Fu YC, Yu W, Lin JM, Zhou L, Liu L and Wang W: SIRT1 prevents atherosclerosis via liver-X-receptor and NF-κB signaling in a U937 cell model. Mol Med Rep 8: 23-28, 2013.
140. Li L, Zhang HN, Chen HZ, Gao P, Zhu LH, Li HL, Lv X, Zhang QJ, Zhang R, Wang Z, *et al*: SIRT1 acts as a modulator of neointima formation following vascular injury in mice. Circ Res 108: 1180-1189, 2011.
141. Xu W, Deng YY, Yang L, Zhao S, Liu J, Zhao Z, Wang L, Maharjan P, Gao S, Tian Y, *et al*: Metformin ameliorates the proinflammatory state in patients with carotid artery atherosclerosis through sirtuin 1 induction. Transl Res 166: 451-458, 2015.
142. Chen YX, Zhang M, Cai Y, Zhao Q and Dai W: The Sirt1 activator SRT1720 attenuates angiotensin II-induced atherosclerosis in apoE-/-mice through inhibiting vascular inflammatory response. Biochem Biophys Res Commun 465: 732-738, 2015.
143. Nasiri M, Rauf M, Kamfiroozie H, Zibaeenezhad MJ and Jamali Z: SIRT1 gene polymorphisms associated with decreased risk of atherosclerotic coronary artery disease. Gene 672: 16-20, 2018.
144. Chen Y, He T, Zhang Z and Zhang J: Activation of SIRT1 by resveratrol alleviates pressure overload-induced cardiac hypertrophy via suppression of TGF-β1 signaling. Pharmacology 106: 667-681, 2021.
145. Zhang MJ, Zhou Y, Chen L, Wang X, Long CY, Pi Y, Gao CY, Li JC and Zhang LL: SIRT1 improves VSMC functions in atherosclerosis. Prog Biophys Mol Biol 121: 11-15, 2016.
146. Qiang L, Lin HV, Kim-Muller JY, Welch CL, Gu W and Accili D: Proatherogenic abnormalities of lipid metabolism in SirT1 transgenic mice are mediated through Creb deacetylation. Cell Metab 14: 758-767, 2011.
147. Liu YP, Wen R, Liu CF, Zhang TN and Yang N: Cellular and molecular biology of sirtuins in cardiovascular disease. Biomed Pharmacother 164: 114931, 2023.
148. Liang F, Kume S and Koya D: SIRT1 and insulin resistance. Nat Rev Endocrinol 5: 367-373, 2009.
149. Gong H, Liu J, Xue Z, Wang W, Li C, Xu F, Du Y and Lyu X: SIRT3 attenuates coronary atherosclerosis in diabetic patients by regulating endothelial cell function. J Clin Lab Anal 36: e24586, 2022.
150. Yu H, Gan D, Luo Z, Yang Q, An D, Zhang H, Hu Y, Ma Z, Zeng Q, Xu D and Ren H: α-Ketoglutarate improves cardiac insufficiency through NAD+-SIRT1 signaling-mediated mitophagy and ferroptosis in pressure overload-induced mice. Mol Med 30: 15, 2024.
151. Rodriguez-Miguelez P and Pollock JS: Adverse childhood events and cardiovascular diseases: The potential role of Sirt1. Am J Physiol Heart Circ Physiol 321: H577-H579, 2021.
152. Lo Iacono L, Visco-Comandini F, Valzania A, Viscomi MT, Coviello M, Giampà A, Roscini L, Bisicchia E, Siracusano A, Troisi A, *et al*: Adversity in childhood and depression: Linked through SIRT1. Transl Psychiatry 5: e629, 2015.
153. Vicario A and Cerezo GH: The heart and brain connection: Contribution of cardiovascular disease to vascular depression-A narrative review. Heart and Mind 7: 126-131, 2023.
154. Piantella S, Dragano N, Marques M, McDonald SJ and Wright BJ: Prospective increases in depression symptoms and markers of inflammation increase coronary heart disease risk - The Whitehall II cohort study. J Psychosom Res 151: 110657, 2021.
155. Liu RT, Hernandez EM, Trout ZM, Kleiman EM and Bozzay ML: Depression, social support, and long-term risk for coronary heart disease in a 13-year longitudinal epidemiological study. Psychiatry Res 251: 36-40, 2017.
156. Yu H, Li X, Ning B, Feng L, Ren Y, Li S, Kang Y, Ma J and Zhao M: SIRT1: A potential therapeutic target for coronary heart disease combined with anxiety or depression. J Drug Target: Dec 23, 2024 (Epub ahead of print).
157. Stanley SC, Brooks SD, Butcher JT, d'Audiffret AC, Frisbee SJ and Frisbee JC: Protective effect of sex on chronic stress- and depressive behavior-induced vascular dysfunction in BALB/cJ mice. J Appl Physiol 117: 959-970, 2014.
158. Hori YS, Kuno A, Hosoda R and Horio Y: Regulation of FOXOs and p53 by SIRT1 modulators under oxidative stress. PLoS One 8: e73875, 2013.
159. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, Tran H, Ross SE, Mostoslavsky R, Cohen HY, *et al*: Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science 303: 2011-2015, 2004.
160. Hsu CP, Zhai P, Yamamoto T, Maejima Y, Matsushima S, Hariharan N, Shao D, Takagi H, Oka S and Sadoshima J: Silent information regulator 1 protects the heart from ischemia/reperfusion. Circulation 122: 2170-2182, 2010.
161. Starodubtseva I, Meshkova M and Zuikova A: Pathogenetic mechanisms of repeated adverse cardiovascular events development in patients with coronary heart disease: The role of chronic inflammation. Folia Med (Plovdiv) 65: 863-870, 2023.
162. Kofod J, Elfving B, Nielsen EH, Mors O and Köhler-Forsberg O: Depression and inflammation: Correlation between changes in inflammatory markers with antidepressant response and long-term prognosis. Eur Neuropsychopharmacol 54: 116-125, 2022.
163. Pfluger PT, Herranz D, Velasco-Miguel S, Serrano M and Tschöp MH: Sirt1 protects against high-fat diet-induced metabolic damage. Proc Natl Acad Sci USA 105: 9793-9798, 2008.
164. Fan J, Guang H, Zhang H, Chen D, Ding L, Fan X, Xue F, Gan Z, Wang Y, Mao S, *et al*: SIRT1 mediates apelin-13 in ameliorating chronic normobaric hypoxia-induced anxiety-like behavior by suppressing NF-κB pathway in mice hippocampus. Neuroscience 381: 22-34, 2018.
165. Askin L, Tibilli H, Tanriverdi O and Turkmen S: The relationship between coronary artery disease and SIRT1 protein. North Clin Istanb 7: 631-635, 2020.
166. Sugimoto K, Yamada T, Kitazawa A and Fukuda Y: Metabolic syndrome and depression: Evidence from a cross-sectional study of real-world data in Japan. Environ Health Prev Med 29: 33, 2024.
167. Li X, Zhang S, Blander G, Tse JG, Krieger M and Guarente L: SIRT1 deacetylates and positively regulates the nuclear receptor LXR. Mol Cell 28: 91-106, 2007.
168. Feige JN and Auwerx J: DisSIRTing on LXR and cholesterol metabolism. Cell Metab 6: 343-345, 2007.
169. Wang Y, Zhao X, O'Neil A, Turner A, Liu X and Berk M: Altered cardiac autonomic nervous function in depression. BMC Psychiatry 13: 187, 2013.
170. Rome D, Sales A, Leeds R, Usseglio J, Cornelius T, Monk C, Smolderen KG and Moise N: A narrative review of the association between depression and heart disease among women: Prevalence, mechanisms of action, and treatment. Curr Atheroscler Rep 24: 709-720, 2022.
171. Yan J, Tang X, Zhou ZQ, Zhang J, Zhao Y, Li S and Luo A: Sirtuins functions in central nervous system cells under neurological disorders. Front Physiol 13: 886087, 2022.
172. Vinciguerra M, Santini MP, Martinez C, Pazienza V, Claycomb WC, Giuliani A and Rosenthal N: mIGF-1/JNK1/SirT1 signaling confers protection against oxidative stress in the heart. Aging Cell 11: 139-149, 2012.

173. Wang Y, Zhao R, Wu C, Liang X, He L, Wang L and Wang X: Activation of the sirtuin silent information regulator 1 pathway inhibits pathological myocardial remodeling. Front Pharmacol 14: 1111320, 2023.
174. Shi S, Guan G, Wang J, Hui R, Zhang Y, Cui Q, Zhao J and Zhu L: Association of depression with hypertensive left ventricular hypertrophy in age, sex, and education level-specific differences. J Clin Hypertens (Greenwich) 25: 715-724, 2023.
175. Liu ZH, Zhang Y, Wang X, Fan XF, Zhang Y, Li X, Gong YS and Han LP: SIRT1 activation attenuates cardiac fibrosis by endothelial-to-mesenchymal transition. Biomed Pharmacother 118: 109227, 2019.
176. Piao S, Lee I, Jin SA, Kim S, Nagar H, Choi SJ, Jeon BH and Kim CS: SIRT1 activation attenuates the cardiac dysfunction induced by endothelial cell-specific deletion of CRIF1. Biomedicines 9: 52, 2021.
177. Pintaningrum Y, Humaera NN, Rafiq A and Tanti A: OR10. Association between heart functional capacity with depression severity on patient with coronary artery disease. Eur Heart J Suppl 23 2021.
178. Wang Y, Li Y, Ding H, Li D, Shen W and Zhang X: The current state of research on sirtuin-mediated autophagy in cardiovascular diseases. J Cardiovasc Dev Dis 10: 382, 2023.
179. Luo G, Jian Z, Zhu Y, Zhu Y, Chen B, Ma R, Tang F and Xiao Y: Sirt1 promotes autophagy and inhibits apoptosis to protect cardiomyocytes from hypoxic stress. Int J Mol Med 43: 2033-2043, 2019.
180. Jiang G, Wang Y, Liu Q, Gu T, Liu S, Yin A and Zhang L: Autophagy: A new mechanism for esketamine as a depression therapeutic. Neuroscience 498: 214-223, 2022.
181. Song X, Wei C, Huang H, Cao X, Chen Z, Chen Y and Wu B: Effects of resveratrol on tolerance to ischemia/reperfusion injury in aged male mice: Role of autophagy and apoptosis. Food Sci Nutr 11: 5938-5947, 2023.
182. Do GM, Kwon EY, Kim HJ, Jeon SM, Ha TY, Park T and Choi MS: Long-term effects of resveratrol supplementation on suppression of atherogenic lesion formation and cholesterol synthesis in apo E-deficient mice. Biochem Biophys Res Commun 374: 55-59, 2008.
183. Shukla P, Akotkar L and Aswar U: Resveratrol attenuates early life stress induced depression in rats: Behavioural and neurochemical evidence. Neurosci Lett 820: 137606, 2024.
184. Raj P, Thandapilly SJ, Wigle J, Zieroth S and Netticadan T: A comprehensive analysis of the efficacy of resveratrol in atherosclerotic cardiovascular disease, myocardial infarction and heart failure. Molecules 26: 6600, 2021.
185. Gu Z, Chu L and Han Y: Therapeutic effect of resveratrol on mice with depression. Exp Ther Med 17: 3061-3064, 2019.
186. Piao S, Kim S, Vu G, Lee M, Kim M, Jeon BH and Kim CS: SRT1720 alleviates endothelial crif1 deficiency-induced cardiac function. J Hypertens 41 (Suppl 3): e161, 2023.
187. Wen S, Xu M, Zhang W, Song R, Zou H, Gu J, Liu X, Bian J, Liu Z and Yuan Y: Cadmium induces mitochondrial dysfunction via SIRT1 suppression-mediated oxidative stress in neuronal cells. Environ Toxicol 38: 743-753, 2023.
188. Sung JY, Kim SG, Kang YJ, Park SY and Choi HC: SIRT1-dependent PGC-1α deacetylation by SRT1720 rescues progression of atherosclerosis by enhancing mitochondrial function. Biochim Biophys Acta Mol Cell Biol Lipids 1869: 159453, 2024.
189. Wang Q, Wang Y, Liu S, Sha X, Song X, Dai Y, Zhao M, Cai L, Xu K and Li J: Theranostic nanoplatform to target macrophages enables the inhibition of atherosclerosis progression and fluorescence imaging of plaque in ApoE(-/-) mice. J Nanobiotechnology 19: 222, 2021.
190. Rabelo TK, Zeidán-Chuliá F, Caregnato FF, Schnorr CE, Gasparotto J, Serafini MR, de Souza Araújo AA, Quintans-Junior LJ, Moreira JCF and Gelain DP: In vitro neuroprotective effect of shikimic acid against hydrogen peroxide-induced oxidative stress. J Mol Neurosci 56: 956-965, 2015.
191. Agrawal K, Chakraborty P, Dewanjee S, Arfin S, Das SS, Dey A, Moustafa M, Mishra PC, Jafari SM, Jha NK, *et al*: Neuropharmacological interventions of quercetin and its derivatives in neurological and psychological disorders. Neurosci Biobehav Rev 144: 104955, 2023.
192. Korzh OM: The application of quercetin in liposomal form for optimization of metabolic therapy of coronary artery disease. National Academy of Sciences of Ukraine, pp118-123, 2021.
193. Nazari-Khanamiri F and Ghasemnejad-Berenji M: Quercetin and heart health: From molecular pathways to clinical findings. J Food Biochem, 2023.
194. Ge C, Wang S, Wu X and Lei L: Quercetin mitigates depression-like behavior via the suppression of neuroinflammation and oxidative damage in corticosterone-induced mice. J Chem Neuroanat 132: 102313, 2023.