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REVIEW ARTICLE

AGE-RAGE Axis and Cardiovascular Diseases: Pathophysiologic Mechanisms and Prospects for Clinical Applications

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Abstract

Advanced glycation end products (AGE), a diverse array of molecules generated through non-enzymatic glycosylation, in conjunction with the receptor of advanced glycation end products (RAGE), play a crucial role in the pathogenesis of diabetes and its associated complications. Recent studies have revealed that the AGE-RAGE axis potentially accelerated the progression of cardiovascular diseases, including heart failure, atherosclerosis, myocarditis, pulmonary hypertension, hypertension, arrhythmia, and other related conditions. The AGE-RAGE axis is intricately involved in the initiation and progression of cardiovascular diseases, independently of its engagement in diabetes. The mechanisms include oxidative stress, inflammation, alterations in autophagy flux, and mitochondrial dysfunction. Conversely, inhibition of AGE production, disruption of the binding between RAGE and its ligands, or silencing of RAGE expression could effectively impair the function of AGE-RAGE axis, thereby delaying or ameliorating the aforementioned diseases. AGE and the soluble receptor for advanced glycation end products (sRAGE) have the potential to be novel predictors of cardiovascular diseases. In this review, we provide an in-depth overview towards the biosynthetic pathway of AGE and elucidate the pathophysiological implications in various cardiovascular diseases. Furthermore, we delve into the profound role of RAGE in cardiovascular diseases, offering novel insights for further exploration of the AGE-RAGE axis and potential strategies for the prevention and management of cardiovascular disorders.

Keywords Advanced glycation end products · RAGE · SRAGE · Inflammation · Oxidative stress · Cardiovascular diseases

Introduction

Diabetes mellitus (DM) is the most common chronic disorder effecting regular carbohydrate metabolism [1]. By the characteristic of insulin secretion deficiency, insulin resistance, or the combination of both, persistent hyperglycemia is the most typical clinical symptom of DM [2]. Studies have showed that such symptom strongly associated with heart failure, atherosclerosis, and other cardiovascular diseases [3]. Patients with diabetes have a significantly higher incidence of heart failure, and diabetes itself also acts as an independent predictor for adverse cardiovascular events and cardiovascular mortality [3–5]. The regulation of blood glucose levels may be able to lower morbidity and mortality associated with atherosclerosis, myocardial infarction, stroke, and other cardiovascular and cerebrovascular diseases [6–8]. Diabetic patients exhibit a significantly higher incidence of cardiovascular disease compared with non-diabetic individuals, which can be partially attributed to higher level of advanced glycation end products (AGE) the receptor

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of advanced glycation end products (RAGE) [9]. However, it has been revealed that the pathogenic impact of AGE and RAGE on cardiovascular diseases is not completely dependent on the presence of diabetes [10, 11]. In addition to direct cross-linking with collagen and extracellular matrix, AGE induce alterations in multiple cellular signaling pathways that contribute to oxidative stress and inflammatory reactions [12]. By interacting with RAGE, AGE contributes to the development of cardiovascular diseases such as myocardial fibrosis, atherosclerosis, and myocardial ischemia–reperfusion injury [12, 13]. Exploring the mechanism of both AGE and RAGE in cardiovascular diseases will offer us novel strategies for the prevention and treatment of such disorders.

Advanced Glycation End Products (AGE)

The formation of AGE involves a diverse array of compounds resulting from the glycosylation reaction with various precursors. These intricate and non-enzymatic processes were initially elucidated by Louis Camille Maillard in 1912, thus earning its name as "Maillard reaction" [13, 14]. As the primary mechanism underlying AGE formation, the Maillard reaction consists of the following stages: (1) Reducing sugars react with residues on proteins, peptides, lipids, and nucleic acids to form a class of unstable compounds known as Schiff base. These compounds undergo rearrangement to modify its chemical properties and transform into early glycation end products (Amadori products) which are more stable. (2) The early glycation end products further undergo rearrangement, dehydration, and other reactions forming highly reactive carbonyls which continuously interact with lysine, histidine, arginine, or cysteine residues in proteins. (3) The highly reactive carbonyl compounds combine with cellular components, undergo oxidation, dehydration, and cyclization, eventually forming AGE [15, 16]. The formation of AGE is influenced by various factors, of which oxidative stress facilitates the generation of AGE [17].

The formation of AGE involves a series of intricate reactions, as we have partially mentioned above. AGE are generated from both endogenous and exogenous sources. In fact, both endogenous and exogenous AGE can be formed through multiple pathways from various precursors, including glucose, fructose, glycolaldehyde, glyceraldehyde, methylglyoxal, glyoxal-derived compounds, and 3-deoxyglucosone-derived compounds. The excessive accumulation of these AGE can lead to diseases [13]. Endogenous AGE, formed in human tissues and body fluids, play a pivotal role in cellular glucose metabolism. AGE are produced and accumulated in various tissues during the natural aging process, and these mechanisms are significantly expedited in individuals with diabetes mellitus [18]. AGE can also be synthesized and secreted by pathological cells in the human body, thereby facilitating the development of specific diseases [18]. For instance, a portion of the AGE produced by diabetic patients is generated by β-cells and subsequently contributes to their own damage [19]. The AGE synthesized and secreted by macrophages plays a role in inducing muscle cell death during ischemia–reperfusion injury [20]. Exogenous AGE are directly obtained from dietary and other external substances, which are independent of synthesis in the human body [16]. AGE naturally exist in foods and multiply through Maillard reaction process causing by frying, baking, or grilling. In comparison to high-fiber foods, high-fat and high-protein foods not only contain higher AGE levels but also demonstrate a greater propensity for generating novel AGE during cooking. Moreover, compounds produced during smoking are another source of exogenous AGE [21, 22]. Previously, it was believed that exogenous AGE could not enter the human body and exert their pathogenic results. However, a recent study revealed that the expressions of AGE, RAGE, and vascular endothelial growth factor (VEGF) in the livers of mice are upregulated by feeding them with a diet rich in AGE [23], indicating that exogenous intake of AGE contributes to an increase in AGE levels within the body [14]. Despite the diversity in the sources of AGE, both exogenous and endogenous AGE ultimately bind to their receptors or directly cross-link with extracellular matrix, thereby instigating a multitude of pathological processes [24]. However, not all AGE contribute to the pathogenesis of diseases. In light of this, some researchers have proposed categorizing AGE into non-toxic AGE and toxic AGE [13]. The formation of non-toxic AGE may involve the active sequestration of highly reactive aldehyde and carbonyl compounds by proteins. Consequently, the generation of non-toxic AGE may represent a detoxification mechanism employed by the body to mitigate excessive glycation and carbonylation processes. Thus, non-toxic AGE are distinct from their toxic counterparts and may possess specific physiological roles [23]. Our article will specifically examine the pathogenic effects of toxic AGE in the human body, and the term "AGE" used throughout this article refers exclusively to toxic AGE (Figs. 1).

Receptors of AGE

AGE initiate various pathophysiological processes mainly by binding to their receptors [25, 26]. There are several types of AGE receptors, including RAGE, the AGE-R1, AGE-R2, and AGE-R3 receptors and a group of scavenger receptors. These different types of receptors interact with AGE, resulting in a wide range of pathophysiological effects [13, 27, 28]. As multi-ligand receptors, RAGE, AGE-related scavenger receptors, and AGE-R not only bind to AGE but also interact with other ligands to initiate

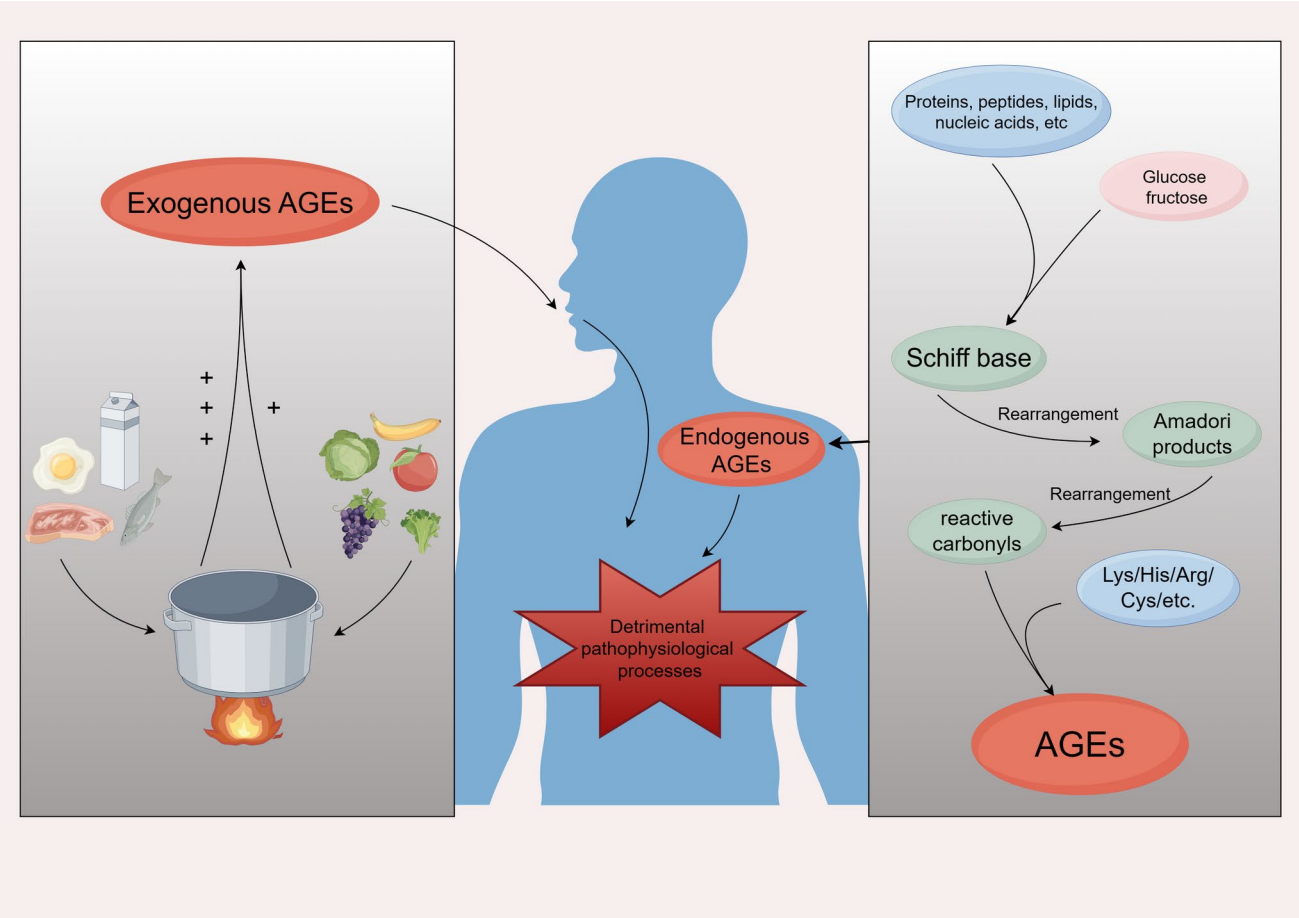

Fig. 1 The two major sources of AGE. Endogenous AGE are formed in human tissues and body fluids throughout the glycosylation reaction with various precursors. While the exogenous AGE are directly obtained from diet, both exogenous and endogenous AGE ultimately instigate a multitude of pathological processes

multiple intracellular signaling pathways, subsequently triggering a range of pathophysiological processes [16, 29]. High mobility group box 1 protein (HMGB1), S100 proteins, lysophosphatidic acid (LPA), amyloid beta (Aβ), and phosphatidylserine (PS) are capable of binding to receptors such as RAGE, thereby initiating a cascade of cellular signal transduction processes [29]. For example, $A\beta_{1\text{-}42}$ triggers endoplasmic reticulum stress in endothelial cells via its interaction with RAGE, thereby contributing to the disruption of the blood–brain barrier and the onset of Alzheimer's disease [30]. The association between HMGB1 and RAGE contributes to acute kidney injury resulting from ischemia–reperfusion injury [31]. The complex network among AGE, AGE receptors, and other ligands of AGE receptors allows AGE and their receptors to participate in physiological and pathophysiological processes of many diseases.

Receptor for Advanced Glycation End Products (RAGE)

RAGE, a member of the immunoglobulin superfamily, is the receptor for AGE that has been most extensively investigated. RAGE is initially discovered in bovine lung endothelial cells. Later, RAGE was identified in humans and ultimately recognized as a multi-ligand receptor on the endothelium [13, 32]. In the subsequent decades, RAGE has been found in various types of cells, including monocytes, macrophages, dendritic cells, T lymphocytes, fibroblasts, neurons, and glial cells [16, 24, 33–38]. The recognition of AGE by RAGE leads to various intracellular signal transductions, including the activation of transcription factors such as nuclear factor kappa B (NF-κB), the generation of reactive oxygen species, and the recruitment of proinflammatory cells. Moreover, RAGE are also associated with oxidative

stress and endothelial dysfunction [13, 39]. Besides, RAGE also interacts with other ligands like HMGB1, the S100 protein family, β-peptide amyloid, LPA, and PS. As a result, it plays a crucial and indispensable role in the pathogenesis of various chronic inflammatory diseases beyond diabetes mellitus, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, myasthenia gravis, heart failure, atherosclerosis, myocardial infarction, hypertension, and aortic diseases [12, 33, 35, 37, 40–47]. Furthermore, RAGE can directly interact with DNA, facilitating its internalization and modulating its concentration threshold for DNA-induced inflammatory responses [13, 32, 34, 36, 41].

The AGE-Receptor Complex (AGE-R)

The AGE-R family includes AGE-R1, AGE-R2, and AGE-R3, each of which appears to have different roles after binding with AGE. Activation of AGE-R1 mainly suppress RAGE, thereby preventing cellular oxidative stress. AGE-R3 is located in the cytoplasm, nucleus, and on the cell surface. The interaction between AGE-R3 and AGE promotes the transport and degradation of various types of AGE. Both AGE-R1 and AGR-R3 participate in the detoxification of AGE, thereby preventing the development of diseases related to AGE-RAGE axis [13, 48]. AGE-R1 exerts a beneficial effect on the development of diabetic kidney disease [13]. In mice with high expression of AGE-R1 receptor, the absorption and metabolism of AGE-modified bovine serum albumin (AGE-BSA) were enhanced in renal mesangial cells, accompanied by a decrease in transcriptional activity of NF-κB and other inflammatory factors, while the opposite results was obtained when the AGE-R1 gene was silenced. This suggests that AGE-R1 may be involved in AGE metabolism and clearance [28]. This appears to provide evidence, to some degree, that AGE-R family plays a role in the clearance and metabolism of AGE, antagonizing the adverse pathophysiological reactions caused by AGE-RAGE axis. This may represent a potential compensatory mechanism to mitigate the detrimental effects of glycation products [27]. However, unlike AGE-R1 and AGE-R3, it seems that AGE-R2 may contribute to adverse effects such as inflammation and altered metabolic effects caused by AGE [13, 16]. The role of the AGE-R family in metabolic diseases requires further investigation for clarification.

Scavenger Receptors of AGE

In addition to RAGE and the AGE-R family, some scavenger receptors have also been reported to bind with AGE. The scavenger receptors share a common affinity for some modified proteins, such as oxidized low-density lipoprotein (OxLDL) and acetylated LDL (AcLDL), which facilitates their uptake and degradation. Scavenger receptor class A (SR-A) is described as an AGE-binding receptor that mediates the endocytic uptake of AGE-modified proteins, potentially playing a crucial role in the development of atherosclerosis [49]. Other scavenger receptors, such as platelet glycoprotein 4 (CD36), scavenger receptor class B type I (SR-BI), and lectin-like oxidized LDL receptor-1 (LOX-1), can also be associated with AGE and accelerated atherosclerosis. Among them, CD36 is not directly responsible for the endocytic uptake of circulating AGE, but it plays a crucial role in inducing cellular oxidative stress [49]. It has also been demonstrated that proteins modified by AGE affect the uptake of high-density lipoprotein (HDL) by SR-BI, suggesting a potential pathological effect on the cholesterol transport system [50]. The binding of LOX-1, a type II scavenger receptor from the E class, to oxLDL results in an increased production of reactive oxygen species within the cell, subsequently activating NF-κB. Concurrently, the presence of AGE further enhances LOX-1 expression, thereby amplifying the cellular signaling pathway [51]. However, the interaction between AGE and their scavenger receptors does not exclusively lead to pathogenic consequences. Some of the scavenger receptors for AGE, such as Stab1 and Stab2, are the endocytic receptors for AGE and may participate in the elimination of AGE in hepatic sinusoidal Kupffer and endothelial cells [13, 16].

Soluble Receptor for Advanced Glycation End Products (sRAGE)

Unlike RAGE, soluble receptor for AGE (sRAGE) is a type of receptor with free structure outside the cells. There are two sources of sRAGE: One is endogenous secreted RAGE (esRAGE), which is derived from the extracellular domain of RAGE cutting by metalloproteinases and shedding from cells. Another is cleaved RAGE (cRAGE), which is directly released from cells during alternative pre-mRNA splicing and protein synthesis and modification processes [14, 52]. Since sRAGE is not directly connected to cells, AGE-sRAGE interaction do not activate any intracellular signal pathways. Therefore, the involvement of sRAGE in the diagnosis and treatment of cardiovascular disease has captured the attention of many researchers. Elevated levels of esRAGE or cRAGE have been observed in patients suffering from heart failure, pulmonary hypertension, chronic kidney disease, end-stage renal disease, and other disorders [52–55]. It is worth noting that the correlation between sRAGE and various pathologies, such as atherosclerosis, chronic heart failure, fatal cardiovascular events, chronic obstructive pulmonary disease, acute respiratory distress syndrome, and cancers, has been consistently corroborated by some studies, suggesting that sRAGE be considered a prognostic marker for certain diseases [54, 56–58]. Additionally, sRAGE has been identified as possessing

therapeutic potential. In a rodent study, the concentration of sRAGE in the blood demonstrated a downward trend as mice aged, while the administration of exogenous sRAGE was found to alleviate myocardial fibrosis [59]. Furthermore, sRAGE significantly suppressed autophagy and ischemia/reperfusion (I/R) injury, leading to decreased infarct size and improved heart function in a myocardial infarction model [60]. Liu et al. found that sRAGE effectively impedes the upregulation of RAGE mRNA and protein expression in myocardium in the transverse aortic constriction (TAC) model, thereby ameliorating oxidative stress and endoplasmic reticulum stress and suppressing inflammation in the myocardium [61]. There is a view that sRAGE decrease the integration of AGE and RAGE by competitively binding to AGE, thus inhibiting the following intracellular signaling pathways activation and reducing RAGE-associated damage [62]. However, another view is that sRAGE might be implicated in sustaining inflammation [56] (Fig. 2).

AGE-RAGE Axis and the Induction of Cell Death

AGE generation and their accumulation can induce neuronal cell damage, hepatocellular damage, pancreatic ductal epithelial cell damage, cardiomyocyte pulsation arrest, and cell death and myoblast cell death [18]. AGE have been shown to increase the production of intracellular reactive oxygen species (ROS), leading to cellular dysfunction and apoptosis. However, a portion of intracellular AGEs that contribute to β-cell death may be endogenously generated within the β-cells themselves [19, 63]. Similar endogenous formation of AGE and cellular self-damage has also been observed in other types of cells, including hepatocytes, cardiomyocytes, and skeletal muscle cells [19]. The accumulation of AGE in cells ultimately results in hepatocyte death, potentially through direct DNA damage caused by AGE. At this juncture, it is noteworthy that the demise of hepatic cells may be attributed to necrosis as opposed to apoptosis [64]. AGE-modified bovine serum albumin (AGE-BSA) stimulates the upregulation of $p27^{Kip1}$, a gene involved in cell cycle regulation, in podocytes. This leads to cell cycle arrest, cell hypertrophy, and an increase of necrosis [65]. Damage to podocytes may also be associated with AGE-induced inflammation, oxidative stress, and a certain level of autophagy inhibition, which can be partially mitigated by dapagliflozin [66]. AGE-induced renal cell apoptosis is also correlated with mitochondrial dysfunction and endoplasmic reticulum stress [67]. Furthermore, diabetes represents a significant risk factor for Alzheimer's disease, which is also thought to be associated with AGE-induced neuronal cell damage [68]. In terms of cardiac damage, AGE possess the capacity to suppress cardiomyocyte pulsation and induce cell death in cardiomyocytes, as well as an augmentation of cardiac fibroblasts [18]. In conclusion, cell damage induced by AGE occurs in multiple organs and systems of the human body. Furthermore, AGE-induced cell damage encompasses diverse mechanisms of cellular demise, including autophagic cell death, necroptosis, pyroptosis, ferroptosis, and cuprotosis. These processes involves diverse cytokines and intracellular signaling pathways such as NF-κB, TNFa, TNFR1, class III phosphatidylinositol-3 kinase/Beclin-1,

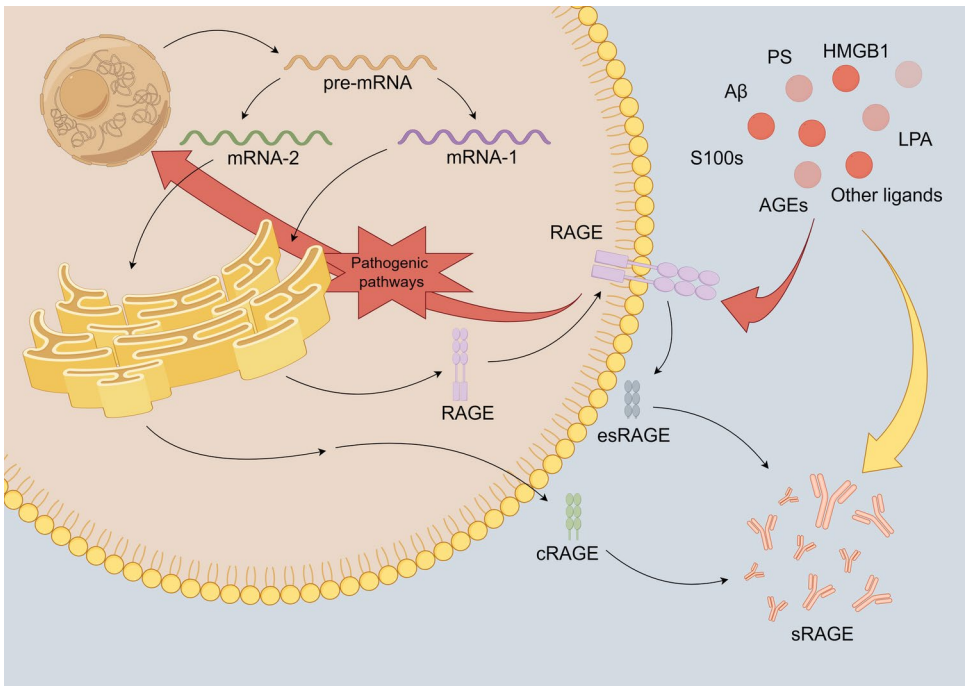

Fig. 2 The formation of RAGE and sRAGE. The extracellular domain of RAGE is cleaved by metalloproteinases and shed from the cell surface, eventually forming esRAGE. cRAGE is directly released from the cell through different mRNA splicing and protein transcription and modification processes. cRAGE and esRAGE together constitute sRAGE and competitively inhibit the binding of RAGE to its ligands, thereby reducing RAGE-associated cell damage

phosphatidylinositol-3 kinase/protein kinase B/mammalian target of rapamycin ((PI3K/AKT/mTOR), Janus kinase/signal transducer and activator of transcription(JAK/STAT), and nuclear factor erythropoietin-2-related factor 2/heme oxygenase 1(Nrf2/HO-1) [69]. This implies that AGE-induced cell death is not only associated with direct DNA damage, oxidative stress, inflammatory responses, endoplasmic reticulum stress, and mitochondrial damage, but also leads to aberrant cellular metal ion metabolism [69, 70].

Pathogenic Mechanism of AGE-RAGE Axis

The AGE-RAGE axis regulates intracellular signal transduction pathways by activating multiple cytokines, which lead to inflammation, oxidative stress, angiogenesis, proliferation, migration, leukocyte aggregation, and other processes in tissue and cells, ultimately promoting the occurrence and development of diseases [29]. Upon binding to its ligands, RAGE activates a multitude of cellular signaling pathways, including JAK/STAT, PI3K/AKT/mTOR, extracellular regulated protein kinases 1/2 (ERK1/2), p38 mitogen-activated protein kinase (p38 MAPK), and stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK). This cascade ultimately leads to the activation of downstream transcription factors such as NF-κB and activator protein-1(AP-1), among others. They cause changes in the expression of related genes and cell function and induce pathophysiological changes and the development of diseases [32, 71–74] (Fig. 3).

Oxidative Stress and Inflammation

Oxidative stress and inflammation have been demonstrated to be involved in pathogenesis of diabetes and cardiovascular disease. Studies have shown that oxidative stress also plays an important role in AGE-related diseases [75]. The occurrence of oxidative stress in organisms intimately links to the concentration of reactive oxygen species (ROS), encompassing superoxide anion radicals (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (HO·). Excessive ROS leads to oxidative damage to proteins, lipids and nucleic acids, as well as triggers the accumulation of inflammatory factors such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) [13, 14, 29, 76, 77]. Under physiological conditions, the antioxidant system can effectively neutralize endogenously produced ROS, thereby maintaining their levels at a low threshold. Upon binding with AGE, RAGE activates nicotinamide adenine dinucleotide phosphate(NADPH) oxidase, resulting in the generation of ROS. Reactive nitrogen species (RNS) like nitric oxide (NO·) is also involved in the oxidative stress stimulated by the AGE-RAGE axis. Excessive ROS and RNS promote the formation of peroxynitrite ($ONOO^-$), which possesses oxidizing and nitrating abilities that lead to the inactivation of biomolecules, such as proteins [16]. Moreover, the accumulation of ROS and RNS induces the upregulation of NOS, further exacerbating oxidation and nitrification processes, forming a vicious cycle that exacerbates oxidative redox signal transduction and cellular molecular damage, and concurrently promoting the accumulation of inflammatory

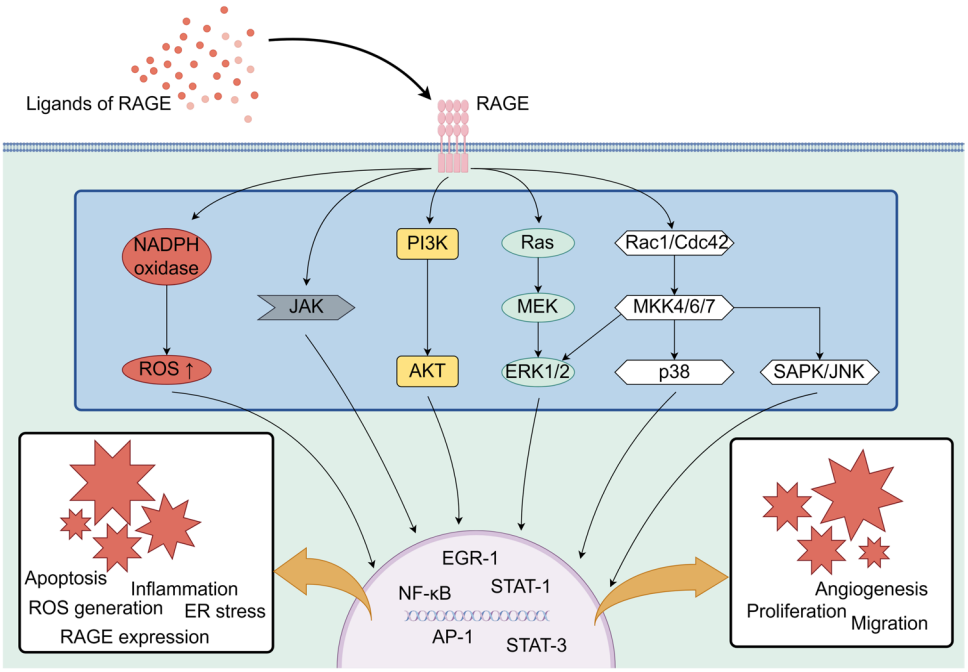

Fig. 3 The RAGE-mediated cellular signaling pathways. After binding to its ligands, RAGE initiates multiple cell signaling pathways, including JAK-STAT, PI3K-AKT, ERK1/2, p38, and SAPK/JNK, thereby activating downstream NF-κB, AP-1, ECR-1, and other transcription factors, ultimately leading to inflammation, oxidative stress, angiogenesis, proliferation, migration, leukocyte aggregation, and other processes in tissue and cells, promoting the occurrence and development of diseases

factors [78, 79]. Under physiological conditions, peroxidated proteins are typically degraded by 20S proteasome of the ubiquitin–proteasome system (UPS). However, AGE-RAGE hinder the formation of this proteasome, resulting in the accumulation of oxidatively damaged proteins and increased ROS levels. Excessive ROS diminish cellular antioxidant and repair capacities, promote the oxidation of lipids and glucose, and induce lipid peroxidation as well as glycation by targeting free amino groups in proteins, in turn facilitating the formation of AGE [16, 80].

Besides, RAGE engages in the adhesion and recruitment of inflammatory cells within the body and further exacerbates the inflammatory response [12]. The interaction between AGE and RAGE transduces signals through multiple pathways, including JAK2/STAT1, PI3K/AKT, mitogen-activated protein kinase/extracellular regulated protein kinases (MAPK/ERK), and NADPH oxidase–mediated ROS production. Ultimately, phosphorylated NF-κB translocates to the nucleus to regulate the transcription of genes associated with proinflammatory cytokines, growth factors, and oxidative stress responses. Consequently, the AGE-RAGE axis contributes to cellular damage across various tissue types and organs [81]. AGE has been shown to promote the synthesis of IL-6 in monocytes/macrophages, thereby inducing the onset of active inflammation, mediated by the MAPK-ERK and NF-κB p50 signaling pathways [82]. In a mouse model of myocardial ischemia–reperfusion, RAGE knockout mice exhibited a reduction in inflammatory cell aggregation compared with the control group, while their left ventricular developed pressure was also notably elevated relative to that of the controls [83]. HMGB1, as another ligand for RAGE, is capable of interacting with both RAGE and Toll-like receptor 4 (TLR4) to activate NF-κB, thereby eliciting inflammatory responses that further compromise the integrity of the retinal vascular barrier [29]. The extent of atherosclerosis is intricately associated with RAGE, as RAGE-mediated inflammation correlates with the upregulation of various inflammatory mediators, including monocyte chemotactic protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), cyclooxygenase-2 (COX-2), nitrotyrosine epitopes, and p38 mitogen-activated protein kinase. Following competitive inhibition of RAGE by sRAGE, there is a notable reduction in the expression of those inflammatory factors, leading to a decrease in the size of atherosclerotic plaques [84]. AGE can also trigger cellular inflammation and facilitate pyroptosis of endothelial cells via the hypoxia-inducible factors-α (HIF-α)/RAGE/NOD-like receptor thermal protein domain associated protein 3 (NLRP3) signaling pathway, thereby exacerbating brain injury. In both in vitro cellular assays and in vivo mouse models, AGE were found to upregulate the expression of hypoxia-inducible factor-α (HIF-α), NLRP3, and RAGE, elevate inflammatory factor levels, and diminish the expression of Zonula Occludens Protein 1 (ZO-1) and platelet endothelial cell adhesion molecule-1 (CD31). This cascade ultimately leads to endothelial cell pyroptosis and further promotes brain injury. Treatment with a HIF-α inhibitor or siRNA targeting NLRP3 effectively mitigated pyroptosis and reduced inflammatory factor levels [85]. NLRP3, along with the inflammatory mediators, such as IL-1β, also facilitates various mechanisms of cell death—including pyroptosis and autophagy—during disease processes like diabetes and lung endothelial injury [69].

AGE trigger oxidative stress and stimulate the production of inflammatory mediators, which leads to cellular damage and promotes the development of diseases. Meanwhile, oxidative stress in turn augments the generation of AGE, establishing a vicious cycle of inflammation that exacerbates the pathological process.

Autophagy

Autophagy is an essential cellular mechanism that sustains cellular homeostasis by degrading aged or damaged proteins and organelles. This process involves the formation of autophagosomes, which subsequently fuse with lysosomes to form autolysosomes [14]. Autophagy has been established to be involved in the pathogenesis of diseases triggered by the AGE-RAGE axis [14, 86]. Liang et al. found that AGE-RAGE axis promoted the expressions of autophagy related proteins and increased autophagy flux, thus promoting the process of myocardial fibrosis [11]. In this study, treatment with AGE resulted in a significant upregulation of mRNA expression levels of fibrosis-related genes, including collagen I, collagen III, fibronectin, connective tissue growth factor (CTGF), vimentin, and α-smooth muscle actin (α-SMA). Concurrently, autophagy-related gene expression—specifically light chain 3 beta (LC3B), Beclin1, and Bcl-2 adenovirus E1B 19 kDa-interacting protein (BNIP)—was also elevated in cardiac fibroblasts treated with AGE. The application of the autophagy inhibitor 3-methyladenine (3MA) significantly reduced the expression of fibrosis-associated genes and inhibited the activation of cardiac fibroblasts [11]. Furthermore, sRAGE has been demonstrated to inhibit cellular autophagy through modulation of STAT3-dependent pathways, thereby conferring protection against cardiac ischemia/reperfusion (I/R) injury [60]. However, during the course of cellular damage, autophagic flux is not consistently elevated. Generally, induction of autophagy results in an upregulation of the ratio of LC3-II/LC3-I [87]. Takata and colleagues observed a reduction in the ratio of LC3-II/LC3-I during AGE-induced cardiomyocyte death, suggesting that AGE exert detrimental effects on cardiomyocytes by suppressing autophagy [88]. AGE was also associated with vascular calcification by inhibiting autophagy through the AMPK/mTOR signaling pathway [89]. Besides, autophagy was revealed to play a pivitol role in the clearance of AGE.

In conditions characterized by excessive AGE, an increase in lysosomal biogenesis was observed within the proximal tubular epithelial cells of the kidney. While inhibition of cellular autophagy resulted in the accumulation of AGE [90]. Therefore, the relationship of the AGE-RAGE axis and autophagy is complex and varies in different situation, the underlying mechanisms need to be further elucidated.

Endoplasmic Reticulum Stress (ERS)

Under normal conditions, the endoplasmic reticulum (ER) performs a vital function in protein synthesis, protein folding and trafficking, cholesterol biosynthesis, calcium storage, and carbohydrate metabolism [14]. When ER's capacity for protein synthesis and folding is perturbed by certain conditions, such as nutrient overload, insulin resistance, inflammation, calcium homeostasis disruption, energy deficiency, changes in ROS levels, ischemia, mutations, and viral infections, misfolded proteins accumulate within the ER and elicit a complex adaptive response. This disruption of ER homeostasis is commonly referred to as endoplasmic reticulum stress (ERS) [47, 91]. The activation of ERS elicits a spectrum of defensive responses, including endoplasmic reticulum-associated degradation (ERAD), the unfolded protein response (UPR), and reticulophagy. Protracted and excessive ERS may contribute to the progression of various diseases [92]. In diabetes, elevated blood glucose levels stimulate the generation of AGE, which triggers ERS, thereby contributing to the exacerbation of diabetes and its complications [93]. AGE can directly instigate ERS or indirectly provoke it through oxidative stress and inflammatory responses. Inhibition of AGE system aids in preserving the homeostasis of the endoplasmic reticulum [91]. The pathogenesis of cardiovascular diseases are also intimately associated with ERS triggered by AGE. The binding of AGE to RAGE or toll-like receptors (TLR) activates the ERS response. AGE promote abnormal lipid metabolism, leading to cholesterol accumulation, which contributes to the production of ROS, inflammation, and ERS. These factors participate in the development of cardiovascular disease. Ventricular arrhythmias secondary to myocardial infarction are also linked to AGE-induced activation of ERS [93]. AGE may trigger the ERS pathway via the nuclear factor kappa B/protein kinase R—like ER kinase/C/EBP homologous protein (NF-κβ/PERK/CHOP) signaling cascade, promoting the progression of diabetic cardiomyopathy. Sacubitril/valsartan effectively reduced AGE generation and RAGE expression, thereby alleviating ERS and improving myocardial inflammation [94]. In addition, a substantial upsurge in RAGE expression was detected in renal tissue in acute kidney injury concurrent with intestinal ischemia/reperfusion, which instigated ERS in renal tissue and progressively culminated in renal damage [31].

Mitochondrial Dysfunction

Mitochondrial dysfunction plays a crucial role in the pathogenesis of diabetic cardiomyopathy and heart failure. This dysfunction triggers an excessive ROS production and impaired oxidative phosphorylation, which promotes mitochondrial respiratory dysfunction and leads to cellular demise. Furthermore, mitochondrial dysfunction induces calcium overload, exacerbating myocardial autophagy and necrosis [95]. AGE-RAGE axis induces cellular oxidative stress and mitochondrial dysfunction, which subsequently exacerbates the production of ROS, thereby establishing a vicious cycle that ultimately leads to cell death. Furthermore, increased levels of reducing sugars, such as glucose-6-phosphate, fructose, and fructose-3-phosphate, promote their own entry into the mitochondrial electron transport chain, thereby enhancing the formation of AGE [96]. Besides, the AGE-RAGE axis has been shown to independently impair mitochondrial function by increasing JNK expression [97]. Exogenous AGE disrupt mitochondrial function in chondrocytes through the inhibition of the AMPKα-SIRT1-PGC-1α pathway. These indicate that mitochondrial dysfunction plays an important part in the pathogenesis of AGE-induced diseases [98] (Fig. 4).

The AGE-RAGE Axis and Cardiovascular Diseases

The intricate physiological and pathophysiological network established between AGE and RAGE plays a crucial role in the onset and progression of various cardiovascular disorders.

Atherosclerosis

Arteriosclerosis, characterized by foam cells accumulation and atherosclerotic plaques formation, is a chronic inflammatory disease accompanied by oxidative stress and subsequent cascading oxidation reactions [7, 12]. The AGE-RAGE axis initiates receptor-mediated signaling pathways that are involve in endothelial damage, modifications in vascular smooth muscle cell function, and alterations in platelet activity. Those processes collectively contribute to arterial injury [99]. The AGE-RAGE axis amplifies the progression of atherosclerotic plaques via multiple mechanisms, such as inhibition of endothelial NO production, promotion of oxidative stress, inflammatory reactions in vascular endothelial cells, impairment of reverse cholesterol transport, stimulation of vascular endothelial growth factor production, and induction of pathological angiogenesis [99, 100]. The AGE-RAGE axis induced vascular calcification, while treatment with anti-RAGE

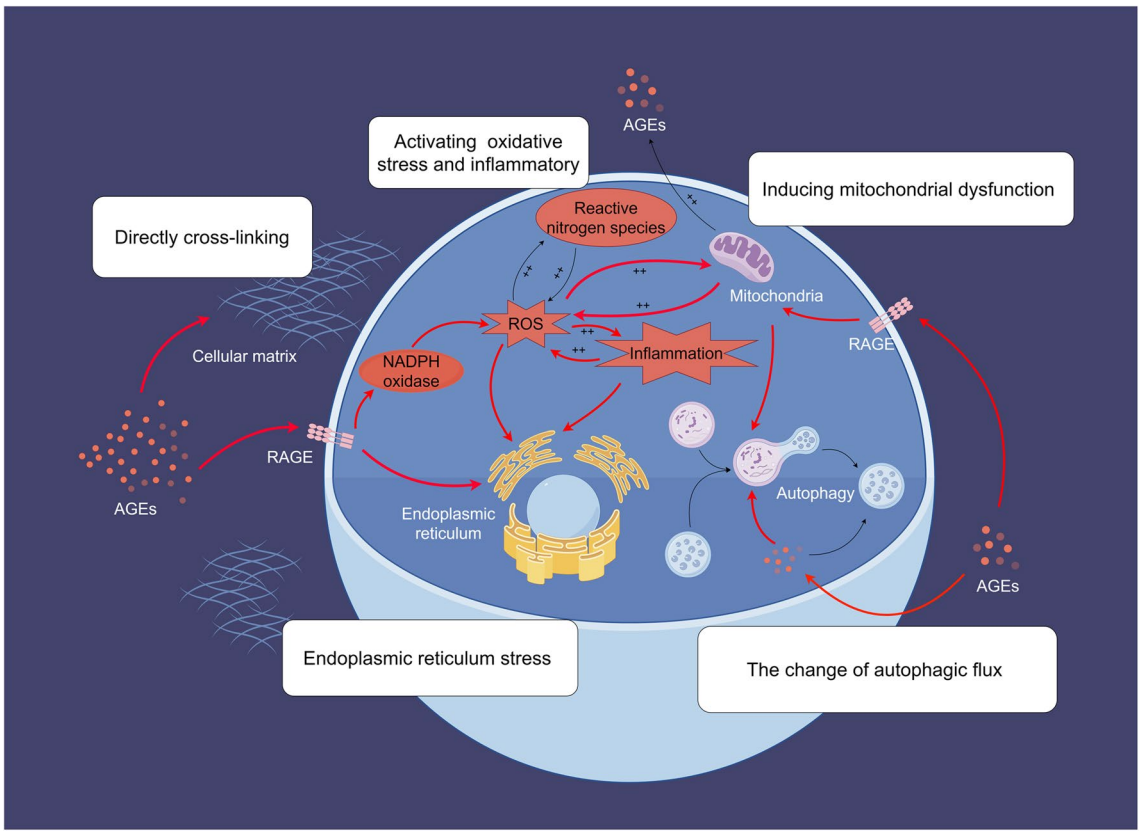

Fig. 4 Pathogenic mechanism of the AGE-RAGE axis. (1) AGE directly cross-link with collagen and other substances to promote tissue fibrosis; (2) RAGE activates intracellular oxidative stress and inflammatory pathways; (3) RAGE induces mitochondrial dysfunction, which aggravates cell damage and the formation of AGE, and also affects the process of oxidative stress and autophagy; (4) endoplasmic reticulum stress can be directly induced by RAGE or be indirectly induced by oxidative stress and inflammatory response; (5) cell death induced by the AGE-RAGE axis is related to the change of autophagic flux; meanwhile, some AGE are cleared by autophagy

antibodies effectively mitigated the impact of AGE on vascular calcification [77]. AGE induced the activation of the RAGE/TLR4/forkhead box C2 (FOXC2) signaling pathway, promoting macrophage infiltration and phenotypic transformation of vascular smooth muscle cells. Inhibition of RAGE with siRNA or TLR4 antagonists effectively suppressed macrophage infiltration and phenotypic transformation of vascular smooth muscle cell, thereby ameliorating vascular stenosis [101]. In individuals with subclinical atherosclerosis, a significant correlation has been demonstrated between the concentrations of AGE and the severity of bilateral carotid plaque [102]. In a 10-year follow-up study, various AGE, including Nε-carboxymethyl lysine (CML), Nε-carboxyethyl lysine (CEL), glyoxal hydroimidazolone (G-H1), methylglyoxal hydroimidazolone (MG-H1), and 3-deoxyglucosone hydroimidazolone (3DG-H), were found to exhibit positive correlation with arterial atherosclerosis indicators, such as intima-media thickness (CIMT), coronary artery calcification (CAC), and abdominal aortic artery calcification (AAC). This association between AGE and arterial atherosclerosis indicators persists even in case of effective blood glucose control and reduced overall HbA1c levels [17]. Despite rigorous glycemic control, individuals exhibiting elevated levels of AGE continued to demonstrate a significantly increased incidence of both microvascular and macrovascular complications. This implies the presence of a "metabolic memory" mechanism within the human body, which contributes to the correlation between AGE and atherosclerosis [103]. In addition, the direct crosslinking of extracellular matrix proteins with AGE further contributes to the progression of atherosclerosis [100]. There are various factors that influence the effect of AGE on atherosclerosis. For instance, the oxidative derivative and 2-aminoaipic acid (2-AAA) exhibit a synergistic effect on coronary artery calcification lesions associated with AGE [17]. Age represents an additional factor that influences the positive correlation between AGE and atherosclerosis [104]. The correlation between AGE and atherosclerosis renders AGE to be a potentially valuable novel predictive factor and therapeutic target in the future.

Myocardial Fibrosis

Myocardial fibrosis, an important pathological process in the development of heart failure, suggests an adverse prognosis. Diabetic cardiomyopathy is a serious cardiovascular complication of diabetes, in which increased plasma AGE was shown to be independent predictors of mortality and hospitalization of heart failure [95]. In diabetic cardiomyopathy, AGE interact with RAGE on the surface of myocardial cells and initiate JAK/MAPK signaling cascades that facilitate an inflammatory response, resulting in production of extracellular matrix proteins and connective tissue. Meanwhile, AGE activate the TGF-β1/Smad pathway, which ultimately contributes to myocardial fibrosis [95]. However, diabetes is not the necessary condition for the AGE-RAGE axis to cause myocardial fibrosis. The correlation between AGE-RAGE and myocardial fibrosis also exists in the non-diabetic [11]. Liang et al. demonstrated that the severity of myocardial fibrosis was associated with AGE-RAGE axis, independent of the diabetic status in mice. In the myocardium of TAC mice, endothelium-to-mesenchymal cell transformation (EndMT) promoted myocardial fibrosis and heart failure, while RAGE knockout resulted in a decrease of EndMT and a remission of myocardial fibrosis [105]. Furthermore, AGE triggered myocardial fibrosis via activation of the TGF-β/Smad signaling pathway which can be blocked by AGE antibodies and SB431542 (a potent TGF-β/Smad signaling pathway inhibitor) [106]. MG-H1, a type of AGE derived from methylglyoxal (MG), was markedly elevated in the myocardium of wild-type (WT) mice 6 h following myocardial infarction. Promoting the metabolism of MG-H1 effectively reduced myocardial infarct size and augmented left ventricular ejection fraction after myocardial infarction. This study highlights the crucial role of AGE in adverse myocardial remodeling and cardiac dysfunction subsequent to myocardial infarction [107]. Besides, AGE can directly bind to extracellular matrix and modify collagen proteins, rendering them resistant to hydrolysis, thereby contributing to accumulation of extracellular matrix proteins. The cross-linking between extracellular matrix induced and AGE exacerbates the progression of myocardial fibrosis [46, 95]. These results indicate that the AGE-RAGE axis is implicated in the pathogenesis of myocardial fibrosis. Therefore, targeting the cellular signaling cascade associated with the AGE-RAGE axis may offer a promising therapeutic strategy for reversing myocardial fibrosis.

Ischemia/Reperfusion (I/R) Injury

Ischemia/reperfusion (I/R) injury is linked to an augmented infarct size and a decline in cardiac function following reperfusion therapy in the context of myocardial infarction. The AGE-RAGE axis plays an important role in I/R injury, potentially by eliciting oxidative stress, augmenting the generation of inflammatory mediators, and recruiting inflammatory cells. The inhibition of RAGE can effectively mitigate myocardial cell death and reduce ventricular remodeling induced by I/R [83, 108]. The pathophysiological mechanisms underlying the AGE-RAGE axis in I/R injury involve the engagement of multiple cellular and molecular pathways. Upon the occurrence of I/R injury, activated macrophages induced the secretion of AGE-modified albumin (AGE-albumin), resulting in elevated expression of RAGE, ultimately driving cell apoptosis via the activation of the AGE-RAGE signaling pathway [62]. RAGE might serve as an upstream receptor of MAPK signaling pathway. During I/R injury, RAGE initiated oxidative stress and cellular apoptosis by decreasing phosphorylation of MAPKs, including p38, JNK, and ERK [109]. The mammalian diaphanous-related formin 1 (DIAPH1), which acts as an effector for Rho small GTP-binding proteins and participates in signal transduction progress in multiple cells, was found to contribute to the regulation of cellular responses to I/R by interacting with RAGE. I/R injury increased the expression of DIAPH1, while deletion of DIAPH1 effectively reduced infarct size and damage after I/R [110]. Besides, the underlying mechanism of RAGE-induced cardiomyocyte death is intimately linked to the sympathetic nervous system. Although the sympathetic nervous system and RAGE triggered cardiomyocyte death independently, inhibition of RAGE could attenuate sympathetic nerve-induced cardiomyocyte death [111]. Future therapeutic strategies targeting the blockade of the AGE-RAGE axis may possess significant potential to mitigate I/R injury and ameliorate ventricular remodeling following myocardial infarction.

Hypertension

Hypertension, marked by persistently elevated arterial pressure levels, is a multifactorial and highly prevalent clinical condition. It has been revealed that the plasma AGE level is positively correlated with central systolic blood pressure in patients with diabetes and prediabetes. Increased AGE activate their receptors, leading to oxidative stress, chronic inflammation, endothelial dysfunction, and activation of the renin-angiotensin system, promoting the development of hypertension [112]. In addition to primary hypertension, the AGE-RAGE system upregulates the expressions of interleukin-6 (IL-6) and C–C motif chemokine ligand 2 (CCL2), which are related to the progression of gestational hypertension [113]. Furthermore, the sympathetic nervous system, a key contributor to the pathogenesis of hypertension, influences the balance between sRAGE and RAGE. By regulating sympathetic nerve activity and the sRAGE/RAGE balance, it might be feasible to mitigate AGE/RAGE-mediated

cardiac damage in patients suffering from hypertension and metabolic syndrome [114].

Other Cardiovascular Diseases

The AGE-RAGE axis was also found to be involved in the pathogenesis of myocarditis, atrial fibrillation, pulmonary hypertension, and other cardiovascular diseases. In autoimmune and inflammatory heart disease, the expression of sRAGE was significantly elevated, and inhibition of RAGE has been demonstrated to effectively mitigate myocardial damage [115]. The progression of atrial fibrillation is intimately associated with the activation of the sympathetic adrenal system and RAGE-mediated inflammation. Inhibition of renal sympathetic nerve activity has the potential to reduce the expression of RAGE and increase the sRAGE level, which alleviates inflammatory responses and mitigates atrial remodeling, thereby diminishing the incidence of atrial fibrillation [116]. Besides, AGE might be used as an indicator to predict the long-term outcome of catheter ablation in patients with paroxysmal atrial fibrillation [117]. The concentrations of sRAGE are elevated in patients with pulmonary arterial hypertension [55]. However, following balloon pulmonary angioplasty treatment, sRAGE levels were observed to decrease [118]. RAGE accelerated the progression of pulmonary arterial hypertension by triggering ERK1/2, JNK and p38 kinase, and subsequently activating the TGF-β1 signaling pathway. The inhibition of RAGE resulted in a reduced expression of these proteins [119]. Therefore, RAGE may be a therapeutic target for pulmonary hypertension. During the natural aging process, there is a marked increase in the levels of AGE within human tissues. Concurrently, the expression of RAGE also rises with age, likely due to the progressive accumulation of its ligands [18]. As aging progresses, the turnover rate of RAGE significantly declines, accompanied by a reduction in sRAGE levels. Consequently, in aged myocardium and other tissues, cellular signaling pathways become increasingly activated, which may be implicated in the pathogenesis of multiple diseases [16]. In addition to its interaction with RAGE, the direct cross-linking of proteins by AGE has emerged as a crucial component of their pathogenic mechanisms. Glucosepane, a notable member of the AGE family, has garnered increasing attention due to its ease of quantification and its association with various diseases, including microvascular complications related to diabetes, chronic kidney disease, neurological disorders, retinal pathologies, and osteoarthritis [120–122]. Current perspectives suggest that glucosepane differs from many other AGE in that its mechanism primarily involves cross-linking with the extracellular matrix (ECM), which reduces ECM turnover rates and increases stiffness; this process may subsequently facilitate disease progression and play a significant role in the pathogenesis of multiple metabolic disorders [123, 124].

AGE and Cardiovascular Diseases in the Setting of Chronic Kidney Disease (CKD)

The AGE load in the human body is contingent upon the equilibrium between their production, absorption, and clearance. As previously discussed, AGE are produced and absorbed through various pathways. Their clearance involves cellular protein degradation processes, during which a portion of AGE is hydrolyzed into AGE peptides. The liver and kidneys serve as the primary organs responsible for the elimination of AGE, effectively clearing the carbonyl precursors, AGE peptides, and AGE themselves. Notably, there exists a negative correlation between AGE concentrations in the body and renal function; this relationship may contribute to an increased susceptibility of renal tissues to damage mediated by AGE [125]. AGE plays a multifaceted role in the pathogenesis of diabetes-related organ damage, encompassing diabetic cardiomyopathy, diabetic nephropathy (DKD), and atherosclerosis [126]. Individuals with diabetes exhibit a significantly elevated risk of cardiovascular disease and chronic kidney disease, attributable in part to the formation of AGE and the subsequent activation of RAGE. The interplay between these resultant conditions further exacerbates one another, establishing a detrimental cycle of heart-kidney metabolic disorders [127]. Ciobanu et al. identified that the ratio of AGE to nicotinamide adenine dinucleotide hydride (NADH) may serve as a predictive biomarker for diabetes-related CKD and cardiovascular disease, following their assessment of AGE and NADH levels in patients with type 2 diabetes [128]. The accumulation of AGE within the arterial significantly enhances medial calcification in peripheral arteries and exhibits a positive correlation with cardiovascular mortality among patients with CKD [129]. Calprotectin, a circulating damage-associated molecular pattern protein, has been shown to facilitate arterial calcification and is independently correlated with cardiovascular outcomes and mortality. Inhibition of RAGE can partially mitigate arterial calcification induced by calprotectin [130]. Belmokhtar and colleagues further elucidated that the ligands of RAGE, including AGE and S100 proteins, were significantly elevated in CKD mice. Additionally, in vitro stimulation of vascular smooth muscle cells with phosphates or S100 protein was found to induce mineralization and osteoblastic transformation. Inhibition or suppression of either RAGE or the sodium phosphate co-transporter PIT-1 mitigated these changes, indicating that PIT-1 plays a crucial role in RAGE-mediated vascular calcification [131]. In patients with CKD, left ventricular dysfunction, cardiomyopathy, atherosclerosis, stroke, heart failure, peripheral artery disease, and other cardiovascular conditions are also closely associated with

AGE. These associations are linked to the various pathophysiological mechanisms mediated by the AGE-RAGE axis as discussed above. Furthermore, muscle wasting in CKD patients is also correlated with elevated levels of AGE; this phenomenon may involve inflammation, endothelial cell dysfunction, increased stiffness of connective tissue proteins, and insulin resistance secondary to CKD [132]. In the context of uremia, the expression of Krüppel-like factor 2 (KLF2), a crucial regulator of endothelial function and activation, is diminished, exacerbating endothelial dysfunction and ultimately contributing to cardiovascular disease; AGE may play a significant role in the downregulation of KLF2 in patients with uremia [133]. There exists a profound and widespread association between CKD and cardiovascular disease attributable to various mechanisms including activation of the renin–angiotensin–aldosterone system (RAAS), stimulation of the sympathetic nervous system, insulin resistance, inflammatory processes, and oxidative stress. The AGE-RAGE axis also contributes to the progression of heart-kidney metabolic disorders, offering new insights for future research in cardiovascular disease and CKD.

Prospects for Clinical Applications

Systematic reviews have indicated that AGE may serve as predictors for cardiovascular and all-cause mortality in high-risk individuals [134]. Interventions targeting the AGE-RAGE axis potentially delayed or even reversed the progression of cardiovascular diseases, providing novel insights into the treatment of these diseases. Systematic studies have indicated that the implemented strategies for pharmacological intervention of the AGE-RAGE axis encompass but are not limited to the following: (i) inhibiting the formation of reactive precursors and AGE; (ii) disrupting the cross-linking between AGE and proteins within the organism; and (iii) antagonizing the activation of RAGE [135]. However, further research and clinical trials are warranted to validate their safety and effectiveness [135, 136].

Drugs and sRAGE

To date, several drugs and pharmacological compounds have been demonstrated to exert beneficial effects on preventing or reversing AGE-RAGE-related cardiovascular diseases. RAGE antagonists, including TTP488 and FPS-ZM1, also played a vital role in inhibiting the incidence and progression of various RAGE-associated chronic diseases [32]. In addition to drug research, the findings on sRAGE are equally promising [62]. The pharmacological effects of sRAGE may be attributed to its competitive inhibition of RAGE, as we previously discussed.

1) Advancements in the Management of Heart Failure.

Aminoguanidine (AG) has been demonstrated to ameliorate myocardial fibrosis by blocking AGE, thereby enhancing left ventricular ejection fraction in diabetic mice [40]. The administration of atorvastatin effectively downregulated the expression of RAGE and α-SMA and inhibited AGE-induced ERK1/2 phosphorylation and fibroblast proliferation, resulting in an improvement of myocardial fibrosis and cardiac function [137]. Long-term use of rosiglitazone significantly reduced both mRNA and protein levels of RAGE, as well as the levels of connective tissue growth factor (CTGF), leading to an amelioration of myocardial fibrosis in type 2 diabetic mice [138]. FPS-ZM1 effectively downregulated the mRNA and protein expressions of RAGE in the hearts of TAC mice, thereby ameliorating oxidative stress and endoplasmic reticulum stress, further mitigating inflammation in cardiac tissues [61]. SB431542, as another RAGE antagonist, attenuates the expression of TGF-β1, phosphorylated Smad2/3, and matrix metalloproteinases-2 induced by AGE in cardiomyocytes, thereby ameliorating AGE-induced myocardial fibrosis [106].

2) Advancements in the Management of Coronary Heart Disease.

Pioglitazone demonstrated the capacity to decrease both the mRNA and protein expressions of RAGE and suppressed the interaction between AGE and RAGE, thereby effectively reducing atherosclerotic plaque area as well as complex plaque numbers in diabetic mice [139]; however, its use may be limited by recent studies showing it increases hospitalizations for heart failure [140]. Other drugs or pharmacological components, such as irbesartan, mangiferin, and traditional Chinese medicine Sanqi, also exerted beneficial effects on cardiovascular diseases by intervening the AGE-RAGE axis [141–143]. Through the artificial cultivation of mesenchymal stem cells (MSCs) capable of secreting sRAGE and their application in a rat model of acute myocardial infarction, it was discovered that elevated levels of sRAGE exhibit a remarkable anti-myocardial fibrosis effect [62]. In the porcine I/R model, the administration of sRAGE markedly attenuated RAGE-mediated myocardial fibrosis and I/R injury, while preserving ventricular ejection function [144].

3) Advancements in the Management of Hypertension.

sRAGE has the potential to modulate the balance between Ang II and Ang-(1–7), suppress oxidative stress and inflammatory responses, and activate the peroxisome proliferator-activated receptor-c (PPAR-c) pathway to mitigate adverse vascular remodeling in primary hypertension [145].

RAGE-Targeted Molecular Therapy

Molecular targeted therapy against RAGE exhibits considerable application potential. Silencing RAGE expression with siRNA could effectively reduce the release of inflammatory factors, cardiomyocyte apoptosis, and mitigate myocardial fibrosis following myocardial injury, indicating that siRNA targeting RAGE is of significant potential as a novel therapeutic approach for post-myocardial injury [146, 147]. Inhibition of RAGE overexpression also demonstrated a certain anti-arrhythmic effect in I/R injury following myocardial infarction [148]. Anti-RAGE antibodies have been shown to significantly ameliorate vascular calcification through the attenuation of oxidative stress [77]. The concurrent administration of RAGE siRNA and sRAGE has demonstrated a synergistic cardioprotective effect following myocardial infarction, thereby offering a promising therapeutic strategy for the management of post-myocardial infarction [108].

The direct deletion of the RAGE gene in murine models has demonstrated a cardiovascular protective effect, as previously discussed. However, the direct deletion of the corresponding human gene for therapeutic applications is currently not feasible; thus, we will refrain from further discussion on this matter.

Although blocking the AGE-RAGE axis has been identified as a promising novel therapeutic approach for managing various associated diseases, there are limited drugs for effectively intervening this axis. To date, lifestyle modifications continue to be the most cost-effective and efficacious method for modulating the AGE-RAGE axis. Dietary AGE directly or indirectly influence the development of chronic diseases, either by being absorbed through the intestines or by interfering with gut microbiota and their metabolites. Non-pharmacological interventions, such as reducing high-temperature and high-fat cooking methods, increasing physical exercise, and smoking cessation, can effectively decrease exogenous AGE intake. Moreover, appropriate exercise assist in reducing accumulation of AGE in heart and preventing myocardial fibrosis [136, 149].

Summary and Outlook

AGE and their receptor RAGE, crucial molecules pervasively distributed throughout the human body, are implicated in various pathological processes, including oxidative stress, inflammatory response, cellular autophagy, endoplasmic reticulum stress, and mitochondrial dysfunction. They exert a profound impact on the development of various cardiovascular diseases such as atherosclerosis, I/R injury, myocardial fibrosis, hypertension, myocarditis, atrial fibrillation, and pulmonary arterial hypertension. Based on the existing research, we can deduce that targeting the AGE-RAGE axis may offer novel strategies for the diagnosis and management of a range of diseases. Reducing intake of AGE compounds, inhibiting the formation of AGE, and antagonizing the AGE-RAGE axis might emerge as novel approaches for preventing and treating cardiovascular diseases. Furthermore, sRAGE has the potential to serve as an innovative biomarker for the prediction of specific diseases. The therapeutic effects of sRAGE have also been preliminarily validated in conditions such as myocardial fibrosis and myocardial I/R injury. The application of siRNA targeting RAGE also demonstrates considerable potential for clinical utility. Therefore, further research aimed at elucidating the pathological and pathophysiological mechanisms underlying the AGE-RAGE axis, as well as its relationship with clinical diseases, will facilitate the development of drugs targeting this axis and provide novel diagnostic and therapeutic strategies for cardiovascular diseases.

Author Contribution All authors contributed to the study conception and design. The manuscript was mainly written by BW. The remaining authors participated in the revision of the draft and the adjustment of the structure of the article to varying degrees. The whole writing process was supervised by SZ, who put forward many valuable suggestions for optimizing the article. SZ also provided valuable language support for this article. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

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References

1. Kharroubi AT, Darwish HM. Diabetes mellitus: the epidemic of the century. World J Diabetes. 2015;6(6):850–67. https://doi.org/10.4239/wjd.v6.i6.850.
2. Luo X, Wu J, Jing S, Yan LJ. Hyperglycemic stress and carbon stress in diabetic glucotoxicity. Aging Dis. 2016;7(1):90–110. https://doi.org/10.14336/ad.2015.0702.
3. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. Lancet (London, England). 2015;385(9982):2107–17. https://doi.org/10.1016/s0140-6736(14)61402-1.
4. Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: cellular effectors, molecular mechanisms and therapeutic opportunities. J Mol Cell Cardiol. 2016;90:84–93. https://doi.org/10.1016/j.yjmcc.2015.12.011.
5. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J. 2008;29(11):1377–85. https://doi.org/10.1093/eurheartj/ehn153.
6. Di Pino A, DeFronzo RA. Insulin resistance and atherosclerosis: implications for insulin-sensitizing agents. Endocr Rev. 2019;40(6):1447–67. https://doi.org/10.1210/er.2018-00141.
7. Yuan T, Yang T, Chen H, et al. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biol. 2019;20:247–60. https://doi.org/10.1016/j.redox.2018.09.025.
8. Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol. 2018;71(23):2628–39. https://doi.org/10.1016/j.jacc.2018.03.009.
9. Yang PS, Lee SH, Park J, et al. Atrial tissue expression of receptor for advanced glycation end-products (RAGE) and atrial fibrosis in patients with mitral valve disease. Int J Cardiol. 2016;220:1–6. https://doi.org/10.1016/j.ijcard.2016.06.137.
10. Kosmopoulos M, Drekolias D, Zavras PD, Piperi C, Papavassiliou AG. Impact of advanced glycation end products (AGEs) signaling in coronary artery disease. Biochim Biophys Acta. 2019;1865(3):611–9. https://doi.org/10.1016/j.bbadis.2019.01.006.
11. Liang B, Zhou Z, Yang Z, et al. AGEs-RAGE axis mediates myocardial fibrosis via activation of cardiac fibroblasts induced by autophagy in heart failure. Exp Physiol. 2022;107(8):879–91. https://doi.org/10.1113/ep090042.
12. Park S, Yoon SJ, Tae HJ, Shim CY. RAGE and cardiovascular disease. Front Biosci (Landmark edition). 2011;16(2):486–97. https://doi.org/10.2741/3700.
13. Twarda-Clapa A, Olczak A, Białkowska AM, Koziołkiewicz M. Advanced glycation end-products (AGEs): formation, chemistry, classification, receptors, and diseases related to AGEs. Cells. 2022;11(8):1312. https://doi.org/10.3390/cells11081312.
14. Sruthi CR, Raghu KG. Advanced glycation end products and their adverse effects: the role of autophagy. J Biochem Mol Toxicol. 2021;35(4): e22710. https://doi.org/10.1002/jbt.22710.
15. Vistoli G, De Maddis D, Cipak A, et al. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. Free Radical Res. 2013;47(Suppl 1):3–27. https://doi.org/10.3109/10715762.2013.815348.
16. Ott C, Jacobs K, Haucke E, et al. Role of advanced glycation end products in cellular signaling. Redox Biol. 2014;2:411–29. https://doi.org/10.1016/j.redox.2013.12.016.
17. Saremi A, Howell S, Schwenke DC, et al. Advanced glycation end products, oxidation products, and the extent of atherosclerosis during the VA diabetes trial and follow-up study. Diabetes Care. 2017;40(4):591–8. https://doi.org/10.2337/dc16-1875.
18. Takeuchi M, Sakasai-Sakai A, Takata T, et al. Intracellular toxic AGEs (TAGE) triggers numerous types of cell damage. Biomolecules. 2021;11(3):387. https://doi.org/10.3390/biom11030387.
19. Takata T, Sakasai-Sakai A, Takeuchi M. Intracellular toxic advanced glycation end-products in 1.4E7 cell line induce death with reduction of microtubule-associated protein 1 light chain 3 and p62. Nutrients. 2022;14(2):332. https://doi.org/10.3390/nu14020332.
20. Son M, Kang WC, Oh S, et al. Advanced glycation end-product (AGE)-albumin from activated macrophage is critical in human mesenchymal stem cells survival and post-ischemic reperfusion injury. Sci Rep. 2017;7(1):11593. https://doi.org/10.1038/s41598-017-11773-1.
21. Sharma C, Kaur A, Thind SS, Singh B, Raina S. Advanced glycation end-products (AGEs): an emerging concern for processed food industries. J Food Sci Technol. 2015;52(12):7561–76. https://doi.org/10.1007/s13197-015-1851-y.
22. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc. 2010;110(6):911-16.e12. https://doi.org/10.1016/j.jada.2010.03.018.
23. Takeuchi M. Toxic AGEs (TAGE) theory: a new concept for preventing the development of diseases related to lifestyle. Diabetol Metab Syndr. 2020;12(1):105. https://doi.org/10.1186/s13098-020-00614-3.
24. Rungratanawanich W, Qu Y, Wang X, Essa MM, Song BJ. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. Exp Mol Med. 2021;53(2):168–88. https://doi.org/10.1038/s12276-021-00561-7.
25. Simm A. Protein glycation during aging and in cardiovascular disease. J Proteomics. 2013;92:248–59. https://doi.org/10.1016/j.jprot.2013.05.012.
26. Deluyker D, Ferferieva V, Noben JP, et al. Cross-linking versus RAGE: How do high molecular weight advanced glycation products induce cardiac dysfunction? Int J Cardiol. 2016;210:100–8. https://doi.org/10.1016/j.ijcard.2016.02.095.
27. Zhuang A, Forbes JM. Diabetic kidney disease: a role for advanced glycation end-product receptor 1 (AGE-R1)? Glycoconj J. 2016;33(4):645–52. https://doi.org/10.1007/s10719-016-9693-z.
28. Lu C, He JC, Cai W, et al. Advanced glycation endproduct (AGE) receptor 1 is a negative regulator of the inflammatory response to AGE in mesangial cells. Proc Natl Acad Sci USA. 2004;101(32):11767–72. https://doi.org/10.1073/pnas.0401588101.
29. Dong H, Zhang Y, Huang Y, Deng H. Pathophysiology of RAGE in inflammatory diseases. Front Immunol. 2022;13:931473. https://doi.org/10.3389/fimmu.2022.931473.
30. Chen W, Chan Y, Wan W, Li Y, Zhang C. Aβ(1–42) induces cell damage via RAGE-dependent endoplasmic reticulum stress in bEnd.3 cells. Exp Cell Res. 2018;362(1):83–9. https://doi.org/10.1016/j.yexcr.2017.11.005.
31. Lai HJ, Zhan YQ, Qiu YX, et al. HMGB1 signaling-regulated endoplasmic reticulum stress mediates intestinal ischemia/reperfusion-induced acute renal damage. Surgery. 2021;170(1):239–48. https://doi.org/10.1016/j.surg.2021.01.042.
32. Hudson BI, Lippman ME. Targeting RAGE signaling in inflammatory disease. Annu Rev Med. 2018;69:349–64. https://doi.org/10.1146/annurev-med-041316-085215.
33. Ohashi K, Takahashi HK, Mori S, et al. Advanced glycation end products enhance monocyte activation during human

mixed lymphocyte reaction. Clin Immunol (Orlando, Fla). 2010;134(3):345–53. https://doi.org/10.1016/j.clim.2009.10.008.
34. Akirav EM, Preston-Hurlburt P, Garyu J, et al. RAGE expression in human T cells: a link between environmental factors and adaptive immune responses. PLoS ONE. 2012;7(4):e34698. https://doi.org/10.1371/journal.pone.0034698.
35. Pollreisz A, Hudson BI, Chang JS, et al. Receptor for advanced glycation endproducts mediates pro-atherogenic responses to periodontal infection in vascular endothelial cells. Atherosclerosis. 2010;212(2):451–6. https://doi.org/10.1016/j.atherosclerosis.2010.07.011.
36. Tian J, Avalos AM, Mao SY, et al. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol. 2007;8(5):487–96. https://doi.org/10.1038/ni1457.
37. Liu Y, Liang C, Liu X, et al. AGEs increased migration and inflammatory responses of adventitial fibroblasts via RAGE MAPK and NF-kappaB. Pathways Atherosclerosis. 2010;208(1):34–42. https://doi.org/10.1016/j.atherosclerosis.2009.06.007.
38. Nah SS, Choi IY, Yoo B, et al. Advanced glycation end products increases matrix metalloproteinase-1, -3, and -13, and TNF-alpha in human osteoarthritic chondrocytes. FEBS Lett. 2007;581(9):1928–32. https://doi.org/10.1016/j.febslet.2007.03.090.
39. Kislinger T, Fu C, Huber B, et al. N(epsilon)-(carboxymethyl) lysine adducts of proteins are ligands for receptor for advanced glycation end products that activate cell signaling pathways and modulate gene expression. J Biol Chem. 1999;274(44):31740–9. https://doi.org/10.1074/jbc.274.44.31740.
40. Heydari AH, Fathi M, Heydari S, Heidari ME. Advanced glycation end product blocker drugs have a great potential to prevent diabetic cardiomyopathy in an animal model of diabetes mellitus type-2. Cardiovasc Ther. 2022;2022:7014680. https://doi.org/10.1155/2022/7014680.
41. Sirois CM, Jin T, Miller AL, et al. RAGE is a nucleic acid receptor that promotes inflammatory responses to DNA. J Exp Med. 2013;210(11):2447–63. https://doi.org/10.1084/jem.20120201.
42. Momeni Z, Neapetung J, Pacholko A, et al. Hyperglycemia induces RAGE-dependent hippocampal spatial memory impairments. Physiol Behav. 2021;229: 113287. https://doi.org/10.1016/j.physbeh.2020.113287.
43. Rahmadi A, Steiner N, Münch G. Advanced glycation endproducts as gerontotoxins and biomarkers for carbonyl-based degenerative processes in Alzheimer's disease. Clin Chem Lab Med. 2011;49(3):385–91. https://doi.org/10.1515/cclm.2011.079.
44. Kim SJ, Ryu MJ, Han J, et al. Non-cell autonomous modulation of tyrosine hydroxylase by HMGB1 released from astrocytes in an acute MPTP-induced Parkinsonian mouse model. Lab Inv. 2019;99(9):1389–99. https://doi.org/10.1038/s41374-019-0254-5.
45. Hehir MK, Silvestri NJ. Generalized myasthenia gravis: classification, clinical presentation, natural history, and epidemiology. Neurol Clin. 2018;36(2):253–60. https://doi.org/10.1016/j.ncl.2018.01.002.
46. Zhao J, Randive R, Stewart JA. Molecular mechanisms of AGE/RAGE-mediated fibrosis in the diabetic heart. World J Diabetes. 2014;5(6):860–7. https://doi.org/10.4239/wjd.v5.i6.860.
47. Yue Q, Song Y, Liu Z, et al. Receptor for advanced glycation end products (RAGE): a pivotal hub in immune diseases. Molecules (Basel, Switzerland). 2022;27(15):4922. https://doi.org/10.3390/molecules27154922.
48. Miyazaki A, Nakayama H, Horiuchi S. Scavenger receptors that recognize advanced glycation end products. Trends Cardiovasc Med. 2002;12(6):258–62. https://doi.org/10.1016/s1050-1738(02)00171-8.
49. Horiuchi S, Sakamoto Y, Sakai M. Scavenger receptors for oxidized and glycated proteins. Amino Acids. 2003;25(3–4):283–92. https://doi.org/10.1007/s00726-003-0029-5.
50. Kumar Pasupulati A, Chitra PS, Reddy GB. Advanced glycation end products mediated cellular and molecular events in the pathology of diabetic nephropathy. Biomol Concepts. 2016;7(5–6):293–309. https://doi.org/10.1515/bmc-2016-0021.
51. Jono T, Miyazaki A, Nagai R, et al. Lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) serves as an endothelial receptor for advanced glycation end products (AGE). FEBS Lett. 2002;511(1–3):170–4. https://doi.org/10.1016/s0014-5793(01)03325-7.
52. Paradela-Dobarro B, Agra RM, Álvarez L, et al. The different roles for the advanced glycation end products axis in heart failure and acute coronary syndrome settings. Nutr Metab Cardiovasc Dis. 2019;29(10):1050–60. https://doi.org/10.1016/j.numecd.2019.06.014.
53. Rebholz CM, Astor BC, Grams ME, et al. Association of plasma levels of soluble receptor for advanced glycation end products and risk of kidney disease: the Atherosclerosis Risk in Communities study. Nephrol, Dialysis, Transp. 2015;30(1):77–83. https://doi.org/10.1093/ndt/gfu282.
54. Raposeiras-Roubín S, Rodiño-Janeiro BK, Grigorian-Shamagian L, et al. Relation of soluble receptor for advanced glycation end products to predict mortality in patients with chronic heart failure independently of Seattle Heart Failure Score. Am J Cardiol. 2011;107(6):938–44. https://doi.org/10.1016/j.amjcard.2010.11.011.
55. Diekmann F, Chouvarine P, Sallmon H, et al. Soluble receptor for advanced glycation end products (sRAGE) is a sensitive biomarker in human pulmonary arterial hypertension. Int J Mole Sci. 2021;22(16):8591. https://doi.org/10.3390/ijms22168591.
56. Erusalimsky JD. The use of the soluble receptor for advanced glycation-end products (sRAGE) as a potential biomarker of disease risk and adverse outcomes. Redox Biol. 2021;42: 101958. https://doi.org/10.1016/j.redox.2021.101958.
57. Lindsey JB, de Lemos JA, Cipollone F, et al. Association between circulating soluble receptor for advanced glycation end products and atherosclerosis: observations from the Dallas Heart Study. Diabetes Care. 2009;32(7):1218–20. https://doi.org/10.2337/dc09-0053.
58. Jabaudon M, Blondonnet R, Roszyk L, et al. Soluble forms and ligands of the receptor for advanced glycation end-products in patients with acute respiratory distress syndrome: an observational prospective study. PLoS ONE. 2015;10(8): e0135857. https://doi.org/10.1371/journal.pone.0135857.
59. Scavello F, Zeni F, Milano G, et al. soluble receptor for advanced glycation end-products regulates age-associated cardiac fibrosis. Int J Biol Sci. 2021;17(10):2399–416. https://doi.org/10.7150/ijbs.56379.
60. Dang M, Zeng X, Chen B, et al. Soluble receptor for advance glycation end-products inhibits ischemia/reperfusion-induced myocardial autophagy via the STAT3 pathway. Free Radical Biol Med. 2019;130:107–19. https://doi.org/10.1016/j.freeradbiomed.2018.10.437.
61. Liu Y, Yu M, Zhang Z, et al. Blockade of receptor for advanced glycation end products protects against systolic overload-induced heart failure after transverse aortic constriction in mice. Eur J Pharmacol. 2016;791:535–43. https://doi.org/10.1016/j.ejphar.2016.07.008.
62. Bayarsaikhan D, Bayarsaikhan G, Lee J, Lee B. A study on the protective effect of sRAGE-MSCs in a rodent reperfusion model of myocardial infarction. Int J Mole Sci. 2022;23(24):15630. https://doi.org/10.3390/ijms232415630.
63. Kong X, Wang GD, Ma MZ, et al. Sesamin ameliorates advanced glycation end products-induced pancreatic β-cell dysfunction

and apoptosis. Nutrients. 2015;7(6):4689–704. https://doi.org/10.3390/nu7064689.
64. Sakasai-Sakai A, Takata T, Takino JI, Takeuchi M. Impact of intracellular glyceraldehyde-derived advanced glycation end-products on human hepatocyte cell death. Sci Rep. 2017;7(1):14282. https://doi.org/10.1038/s41598-017-14711-3.
65. Rüster C, Bondeva T, Franke S, Förster M, Wolf G. Advanced glycation end-products induce cell cycle arrest and hypertrophy in podocytes. Nephrol, Dialysis, Transp. 2008;23(7):2179–91. https://doi.org/10.1093/ndt/gfn085.
66. Yang L, Liang B, Li J, et al. Dapagliflozin alleviates advanced glycation end product induced podocyte injury through AMPK/mTOR mediated autophagy pathway. Cell Signal. 2022;90:110206. https://doi.org/10.1016/j.cellsig.2021.110206.
67. Jeong SR, Lee KW. Methylglyoxal-derived advanced glycation end product (AGE4)-induced apoptosis leads to mitochondrial dysfunction and endoplasmic reticulum stress through the RAGE/JNK pathway in kidney cells. Int J Mole Sci. 2021;22(12):6530. https://doi.org/10.3390/ijms22126530.
68. Chambers A, Bury JJ, Minett T, et al. Advanced glycation end product formation in human cerebral cortex increases with alzheimer-type neuropathologic changes but is not independently associated with dementia in a population-derived aging brain cohort. J Neuropathol Exp Neurol. 2020;79(9):950–8. https://doi.org/10.1093/jnen/nlaa064.
69. Dai Y, Zhou S, Qiao L, et al. Non-apoptotic programmed cell deaths in diabetic pulmonary dysfunction: the new side of advanced glycation end products. Front Endocrinol. 2023;14:1126661. https://doi.org/10.3389/fendo.2023.1126661.
70. Huo S, Wang Q, Shi W, et al. ATF3/SPI1/SLC31A1 Signaling Promotes Cuproptosis Induced by Advanced Glycosylation End Products in Diabetic Myocardial Injury. Int J Mole Sci. 2023;24(2):1667. https://doi.org/10.3390/ijms24021667.
71. Kierdorf K, Fritz G. RAGE regulation and signaling in inflammation and beyond. J Leukoc Biol. 2013;94(1):55–68. https://doi.org/10.1189/jlb.1012519.
72. Xue J, Manigrasso M, Scalabrin M, et al. Change in the molecular dimension of a RAGE-ligand complex triggers RAGE signaling. Structure (London, England : 1993). 2016;24(9):1509–22. https://doi.org/10.1016/j.str.2016.06.021.
73. Xu Y, Toure F, Qu W, et al. Advanced glycation end product (AGE)-receptor for AGE (RAGE) signaling and up-regulation of Egr-1 in hypoxic macrophages. J Biol Chem. 2010;285(30):23233–40. https://doi.org/10.1074/jbc.M110.117457.
74. Jangde N, Ray R, Rai V. RAGE and its ligands: from pathogenesis to therapeutics. Crit Rev Biochem Mol Biol. 2020;55(6):555–75. https://doi.org/10.1080/10409238.2020.1819194.
75. Jiang JM, Wang Z, Li DD. Effects of AGEs on oxidation stress and antioxidation abilities in cultured astrocytes. Biomed Environ Sci: BES. 2004;17(1):79–86.
76. Poznyak A, Grechko AV, Poggio P, et al. The diabetes mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. Int J Mole Sci. 2020;21(5):1835. https://doi.org/10.3390/ijms21051835.
77. Wei Q, Ren X, Jiang Y, et al. Advanced glycation end products accelerate rat vascular calcification through RAGE/oxidative stress. BMC Cardiovasc Disord. 2013;13:13. https://doi.org/10.1186/1471-2261-13-13.
78. Moldogazieva NT, Mokhosoev IM, Mel'nikova TI, Porozov YB, Terentiev AA. oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in aging and age-related diseases. Oxid Med Cell Longev. 2019;2019:3085756. https://doi.org/10.1155/2019/3085756.
79. Liu Y, Qu Y, Wang R, et al. The alternative crosstalk between RAGE and nitrative thioredoxin inactivation during diabetic myocardial ischemia-reperfusion injury. Am J Physiol Endocrinol Metab. 2012;303(7):E841–52. https://doi.org/10.1152/ajpendo.00075.2012.
80. Grimm S, Ott C, Hörlacher M, et al. Advanced-glycation-end-product-induced formation of immunoproteasomes: involvement of RAGE and Jak2/STAT1. Biochem J. 2012;448(1):127–39. https://doi.org/10.1042/bj20120298.
81. Shen CY, Lu CH, Wu CH, et al. The development of Maillard reaction, and advanced glycation end product (AGE)-receptor for age (RAGE) signaling inhibitors as novel therapeutic strategies for patients with AGE-related diseases. Molecules (Basel, Switzerland). 2020;25(23):5591. https://doi.org/10.3390/molecules25235591.
82. Shen CY, Wu CH, Lu CH, et al. Advanced glycation end products of bovine serum albumin suppressed Th1/Th2 cytokine but enhanced monocyte IL-6 gene expression via MAPK-ERK and MyD88 transduced NF-κB p50 signaling pathways. Molecules (Basel, Switzerland). 2019;24(13):2461. https://doi.org/10.3390/molecules24132461.
83. Ziegler T, Horstkotte M, Lange P, et al. Endothelial RAGE exacerbates acute postischaemic cardiac inflammation. Thromb Haemost. 2016;116(2):300–8. https://doi.org/10.1160/th15-11-0898.
84. Bucciarelli LG, Wendt T, Qu W, et al. RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. Circulation. 2002;106(22):2827–35. https://doi.org/10.1161/01.cir.0000039325.03698.36.
85. Han C, Zhai L, Shen H, Wang J, Guan Q. Advanced glycation end-products (AGEs) promote endothelial cell pyroptosis under cerebral ischemia and hypoxia via HIF-1α-RAGE-NLRP3. Mol Neurobiol. 2023;60(5):2355–66. https://doi.org/10.1007/s12035-023-03228-8.
86. Guo Y, Lin C, Xu P, et al. AGEs induced autophagy impairs cutaneous wound healing via stimulating macrophage polarization to M1 in diabetes. Sci Rep. 2016;6:36416. https://doi.org/10.1038/srep36416.
87. Su LY, Li H, Lv L, et al. Melatonin attenuates MPTP-induced neurotoxicity via preventing CDK5-mediated autophagy and SNCA/α-synuclein aggregation. Autophagy. 2015;11(10):1745–59. https://doi.org/10.1080/15548627.2015.1082020.
88. Takata T, Sakasai-Sakai A, Ueda T, Takeuchi M. Intracellular toxic advanced glycation end-products in cardiomyocytes may cause cardiovascular disease. Sci Rep. 2019;9(1):2121. https://doi.org/10.1038/s41598-019-39202-5.
89. Liu Y, Li J, Han Y, et al. Advanced glycation end-products suppress autophagy by AMPK/mTOR signaling pathway to promote vascular calcification. Mol Cell Biochem. 2020;471(1–2):91–100. https://doi.org/10.1007/s11010-020-03769-9.
90. Takahashi A, Takabatake Y, Kimura T, et al. Autophagy inhibits the accumulation of advanced glycation end products by promoting lysosomal biogenesis and function in the kidney proximal tubules. Diabetes. 2017;66(5):1359–72. https://doi.org/10.2337/db16-0397.
91. Piperi C, Adamopoulos C, Dalagiorgou G, Diamanti-Kandarakis E, Papavassiliou AG. Crosstalk between advanced glycation and endoplasmic reticulum stress: emerging therapeutic targeting for metabolic diseases. J Clin Endocrinol Metab. 2012;97(7):2231–42. https://doi.org/10.1210/jc.2011-3408.
92. Ren J, Bi Y, Sowers JR, Hetz C, Zhang Y. Endoplasmic reticulum stress and unfolded protein response in cardiovascular diseases. Nat Rev Cardiol. 2021;18(7):499–521. https://doi.org/10.1038/s41569-021-00511-w.
93. Passarelli M, Machado UFF. AGEs-induced and endoplasmic reticulum stress/inflammation-mediated regulation of GLUT4 expression and atherogenesis in diabetes mellitus. Cells. 2021;11(1):104. https://doi.org/10.3390/cells11010104.

94. Belali OM, Ahmed MM, Mohany M, et al. LCZ696 protects against diabetic cardiomyopathy-induced myocardial inflammation, ER stress, and apoptosis through inhibiting AGEs/NF-κB and PERK/CHOP signaling pathways. Int J Mole Sci. 2022;23(3):1288. https://doi.org/10.3390/ijms23031288.
95. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circ Res. 2018;122(4):624–38. https://doi.org/10.1161/circresaha.117.311586.
96. Ward MS, Fortheringham AK, Cooper ME, Forbes JM. Targeting advanced glycation endproducts and mitochondrial dysfunction in cardiovascular disease. Curr Opin Pharmacol. 2013;13(4):654–61. https://doi.org/10.1016/j.coph.2013.06.009.
97. Lin KH, Ng SC, Paul CR, et al. MicroRNA-210 repression facilitates advanced glycation end-product (AGE)-induced cardiac mitochondrial dysfunction and apoptosis via JNK activation. J Cell Biochem. 2021;122(12):1873–85. https://doi.org/10.1002/jcb.30146.
98. Yang Q, Shi Y, Jin T, Duan B, Wu S. Advanced glycation end products induced mitochondrial dysfunction of chondrocytes through repression of AMPKα-SIRT1-PGC-1α pathway. Pharmacology. 2022;107(5–6):298–307. https://doi.org/10.1159/000521720.
99. Singh S, Siva BV, Ravichandiran V. Advanced glycation end products: key player of the pathogenesis of atherosclerosis. Glycoconj J. 2022;39(4):547–63. https://doi.org/10.1007/s10719-022-10063-x.
100. Yamagishi SI, Matsui T. Role of hyperglycemia-induced advanced glycation end product (AGE) accumulation in atherosclerosis. Ann Vasc Dis. 2018;11(3):253–8. https://doi.org/10.3400/avd.ra.18-00070.
101. Xing Y, Pan S, Zhu L, et al. Advanced glycation end products induce atherosclerosis via RAGE/TLR4 signaling mediated-M1 macrophage polarization-dependent vascular smooth muscle cell phenotypic conversion. Oxid Med Cell Longev. 2022;2022:9763377. https://doi.org/10.1155/2022/9763377.
102. Pan J, Bao X, Gonçalves I, Jujić A, Engström G. Skin autofluorescence, a measure of tissue accumulation of advanced glycation end products, is associated with subclinical atherosclerosis in coronary and carotid arteries. Atherosclerosis. 2022;345:26–32. https://doi.org/10.1016/j.atherosclerosis.2022.02.014.
103. Fishman SL, Sonmez H, Basman C, Singh V, Poretsky L. The role of advanced glycation end-products in the development of coronary artery disease in patients with and without diabetes mellitus: a review. Mole Med (Cambridge, Mass). 2018;24(1):59. https://doi.org/10.1186/s10020-018-0060-3.
104. Ying L, Shen Y, Zhang Y, et al. Advanced glycation end products via skin autofluorescence as potential marker of carotid atherosclerosis in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2021;31(12):3449–56. https://doi.org/10.1016/j.numecd.2021.09.005.
105. Zhang L, He J, Wang J, et al. Knockout RAGE alleviates cardiac fibrosis through repressing endothelial-to-mesenchymal transition (EndMT) mediated by autophagy. Cell Death Dis. 2021;12(5):470. https://doi.org/10.1038/s41419-021-03750-4.
106. Fang M, Wang J, Li S, Guo Y. Advanced glycation end-products accelerate the cardiac aging process through the receptor for advanced glycation end-products/transforming growth factor-β-Smad signaling pathway in cardiac fibroblasts. Geriatr Gerontol Int. 2016;16(4):522–7. https://doi.org/10.1111/ggi.12499.
107. Blackburn NJR, Vulesevic B, McNeill B, et al. Methylglyoxal-derived advanced glycation end products contribute to negative cardiac remodeling and dysfunction post-myocardial infarction. Basic Res Cardiol. 2017;112(5):57. https://doi.org/10.1007/s00395-017-0646-x.
108. Ku SH, Hong J, Moon HH, et al. Deoxycholic acid-modified polyethylenimine based nanocarriers for RAGE siRNA therapy in acute myocardial infarction. Arch Pharmacal Res. 2015;38(7):1317–24. https://doi.org/10.1007/s12272-014-0527-x.
109. Zhu Z, Zhu J, Zhao X, et al. All-trans retinoic acid ameliorates myocardial ischemia/reperfusion injury by reducing cardiomyocyte apoptosis. PLoS ONE. 2015;10(7):e0133414. https://doi.org/10.1371/journal.pone.0133414.
110. O'Shea KM, Ananthakrishnan R, Li Q, et al. The Formin, DIAPH1, is a key modulator of myocardial ischemia/reperfusion injury. EBioMedicine. 2017;26:165–74. https://doi.org/10.1016/j.ebiom.2017.11.012.
111. Zhu W, Tsang S, Browe DM, et al. Interaction of β1-adrenoceptor with RAGE mediates cardiomyopathy via CaMKII signaling. JCI insight. 2016;1(1): e84969. https://doi.org/10.1172/jci.insight.84969.
112. Fuhr JC, Ramos MEK, Piovesan F, Renner LO, Siqueira LO. Relationship of advanced glycation end-products in hypertension in diabetic patients: a systematic review. J Bras Nefrol. 2022;44(4):557–72. https://doi.org/10.1590/2175-8239-JBN-2022-0006en.
113. Akasaka J, Naruse K, Sado T, et al. Involvement of receptor for advanced glycation endproducts in hypertensive disorders of pregnancy. Int J Mole Sci. 2019;20(21):5462. https://doi.org/10.3390/ijms20215462.
114. Selejan SR, Linz D, Tatu AM, et al. Sympathoadrenergic suppression improves heart function by upregulating the ratio of sRAGE/RAGE in hypertension with metabolic syndrome. J Mol Cell Cardiol. 2018;122:34–46. https://doi.org/10.1016/j.yjmcc.2018.08.003.
115. Bangert A, Andrassy M, Müller AM, et al. Critical role of RAGE and HMGB1 in inflammatory heart disease. Proc Natl Acad Sci USA. 2016;113(2):E155–64. https://doi.org/10.1073/pnas.1522288113.
116. Selejan SR, Linz D, Mauz M, et al. Renal denervation reduces atrial remodeling in hypertensive rats with metabolic syndrome. Basic Res Cardiol. 2022;117(1):36. https://doi.org/10.1007/s00395-022-00943-6.
117. Bohm A, Urban L, Tothova L, et al. Advanced glycation end products predict long-term outcome of catheter ablation in paroxysmal atrial fibrillation. J Interv Cardiac Electrophysiol. 2022;64(1):17–25. https://doi.org/10.1007/s10840-021-00972-6.
118. Hatano M. Potential of receptor for advanced glycation end-products (RAGE) as an eligible biomarker for therapy evaluation in patients with pulmonary hypertension. Int Heart J. 2016;57(2):132–3. https://doi.org/10.1536/ihj.16-073.
119. Jia D, He Y, Zhu Q, et al. RAGE-mediated extracellular matrix proteins accumulation exacerbates HySu-induced pulmonary hypertension. Cardiovasc Res. 2017;113(6):586–97. https://doi.org/10.1093/cvr/cvx051.
120. Rabbani N, Thornalley PJ. Advanced glycation end products in the pathogenesis of chronic kidney disease. Kidney Int. 2018;93(4):803–13. https://doi.org/10.1016/j.kint.2017.11.034.
121. Genuth S, Sun W, Cleary P, et al. Skin advanced glycation end products glucosepane and methylglyoxal hydroimidazolone are independently associated with long-term microvascular complication progression of type 1 diabetes. Diabetes. 2015;64(1):266–78. https://doi.org/10.2337/db14-0215.
122. Legrand C, Ahmed U, Anwar A, et al. Glycation marker glucosepane increases with the progression of osteoarthritis and correlates with morphological and functional changes of cartilage in vivo. Arthritis Res Ther. 2018;20(1):131. https://doi.org/10.1186/s13075-018-1636-6.

123. Sell DR, Biemel KM, Reihl O, et al. Glucosepane is a major protein cross-link of the senescent human extracellular matrix Relationship with diabetes. J Biol Chem. 2005;280(13):12310–5. https://doi.org/10.1074/jbc.M500733200.
124. Monnier VM, Sun W, Sell DR, et al. Glucosepane: a poorly understood advanced glycation end product of growing importance for diabetes and its complications. Clin Chem Lab Med. 2014;52(1):21–32. https://doi.org/10.1515/cclm-2013-0174.
125. Fotheringham AK, Gallo LA, Borg DJ, Forbes JM. Advanced glycation end products (AGEs) and chronic kidney disease: does the modern diet AGE the kidney? Nutrients. 2022;14(13):2675. https://doi.org/10.3390/nu14132675.
126. Sebastian SA, Padda I, Johal G. Cardiovascular-kidney-metabolic (CKM) syndrome: a state-of-the-art review. Curr Probl Cardiol. 2024;49(2):102344. https://doi.org/10.1016/j.cpcardiol.2023.102344.
127. Kadowaki T, Maegawa H, Watada H, et al. Interconnection between cardiovascular, renal and metabolic disorders: a narrative review with a focus on Japan. Diabetes Obes Metab. 2022;24(12):2283–96. https://doi.org/10.1111/dom.14829.
128. Ciobanu DM, Olar LE, Stefan R, et al. Fluorophores advanced glycation end products (AGEs)-to-NADH ratio is predictor for diabetic chronic kidney and cardiovascular disease. J Diabetes Complications. 2015;29(7):893–7. https://doi.org/10.1016/j.jdiacomp.2015.06.006.
129. Janda K, Krzanowski M, Gajda M, et al. Vascular effects of advanced glycation end-products: content of immunohistochemically detected AGEs in radial artery samples as a predictor for arterial calcification and cardiovascular risk in asymptomatic patients with chronic kidney disease. Dis Markers. 2015;2015:153978. https://doi.org/10.1155/2015/153978.
130. Amaya-Garrido A, Brunet M, Buffin-Meyer B, et al. Calprotectin is a contributor to and potential therapeutic target for vascular calcification in chronic kidney disease. Sci Transl Med. 2023;15(712):eabn5939. https://doi.org/10.1126/scitranslmed.abn5939.
131. Belmokhtar K, Ortillon J, Jaisson S, et al. Receptor for advanced glycation end products: a key molecule in the genesis of chronic kidney disease vascular calcification and a potential modulator of sodium phosphate co-transporter PIT-1 expression. Nephrol, Dialysis, Transp. 2019;34(12):2018–30. https://doi.org/10.1093/ndt/gfz012.
132. Dozio E, Caldiroli L, Molinari P, et al. Accelerated AGEing: the impact of advanced glycation end products on the prognosis of chronic kidney disease. Antioxidants (Basel, Switzerland). 2023;12(3):584. https://doi.org/10.3390/antiox12030584.
133. Saum K, Campos B, Celdran-Bonafonte D, et al. Uremic advanced glycation end products and protein-bound solutes induce endothelial dysfunction through suppression of Krüppel-Like Factor 2. J Am Heart Assoc. 2018;7(1):e007566. https://doi.org/10.1161/jaha.117.007566.
134. Cavero-Redondo I, Soriano-Cano A, Álvarez-Bueno C, et al. Skin autofluorescence-indicated advanced glycation end products as predictors of cardiovascular and all-cause mortality in high-risk subjects: a systematic review and meta-analysis. J Am Heart Assoc. 2018;7(18):e009833. https://doi.org/10.1161/jaha.118.009833.
135. Zeng C, Li Y, Ma J, Niu L, Tay FR. Clinical/translational aspects of advanced glycation end-products. Trends Endocrinol Metab. 2019;30(12):959–73. https://doi.org/10.1016/j.tem.2019.08.005.
136. Nie C, Li Y, Qian H, Ying H, Wang L. Advanced glycation end products in food and their effects on intestinal tract. Crit Rev Food Sci Nutr. 2022;62(11):3103–15. https://doi.org/10.1080/10408398.2020.1863904.
137. Chen M, Li H, Wang G, et al. Atorvastatin prevents advanced glycation end products (AGEs)-induced cardiac fibrosis via activating peroxisome proliferator-activated receptor gamma (PPAR-γ). Metabolism: Clin Exp. 2016;65(4):441–53. https://doi.org/10.1016/j.metabol.2015.11.007.
138. Ihm SH, Chang K, Kim HY, et al. Peroxisome proliferator-activated receptor-gamma activation attenuates cardiac fibrosis in type 2 diabetic rats: the effect of rosiglitazone on myocardial expression of receptor for advanced glycation end products and of connective tissue growth factor. Basic Res Cardiol. 2010;105(3):399–407. https://doi.org/10.1007/s00395-009-0071-x.
139. Gao H, Li H, Li W, Shen X, Di B. Pioglitazone attenuates atherosclerosis in diabetic mice by inhibition of receptor for advanced glycation end-product (RAGE) signaling. Medical Sci Monit. 2017;23:6121–31. https://doi.org/10.12659/msm.907401.
140. Seferović PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(5):853–72. https://doi.org/10.1002/ejhf.1170.
141. Han J, Hou J, Liu Y, et al. Using network pharmacology to explore the mechanism of panax notoginseng in the treatment of myocardial fibrosis. J Diabetes Res. 2022;2022:8895950. https://doi.org/10.1155/2022/8895950.
142. Hongwei Y, Ruiping C, Yingyan F, et al. Effect of Irbesartan on AGEs-RAGE and MMPs systems in rat type 2 diabetes myocardial-fibrosis model. Exp Biol Med (Maywood). 2019;244(7):612–20. https://doi.org/10.1177/1535370219840981.
143. Suchal K, Malik S, Khan SI, et al. Protective effect of mangiferin on myocardial ischemia-reperfusion injury in streptozotocin-induced diabetic rats: role of AGE-RAGE/MAPK pathways. Sci Rep. 2017;7:42027. https://doi.org/10.1038/srep42027.
144. Lu L, Zhang Q, Xu Y, et al. Intra-coronary administration of soluble receptor for advanced glycation end-products attenuates cardiac remodeling with decreased myocardial transforming growth factor-beta1 expression and fibrosis in minipigs with ischemia-reperfusion injury. Chin Med J. 2010;123(5):594–8.
145. Liu Y, Yu M, Zhang L, et al. Soluble receptor for advanced glycation end products mitigates vascular dysfunction in spontaneously hypertensive rats. Mol Cell Biochem. 2016;419(1–2):165–76. https://doi.org/10.1007/s11010-016-2763-5.
146. Liang Q, Li F, Li Y, et al. Self-assisted membrane-penetrating helical polypeptides mediate anti-inflammatory RNAi against myocardial ischemic reperfusion (IR) injury. Biomater Sci. 2019;7(9):3717–28. https://doi.org/10.1039/c9bm00719a.
147. Hong J, Ku SH, Lee MS, et al. Cardiac RNAi therapy using RAGE siRNA/deoxycholic acid-modified polyethylenimine complexes for myocardial infarction. Biomaterials. 2014;35(26):7562–73. https://doi.org/10.1016/j.biomaterials.2014.05.025.
148. Park H, Ku SH, Park H, et al. RAGE siRNA-mediated gene silencing provides cardioprotection against ventricular arrhythmias in acute ischemia and reperfusion. J Controlled Release. 2015;217:315–26. https://doi.org/10.1016/j.jconrel.2015.09.006.
149. Wright KJ, Thomas MM, Betik AC, Belke D, Hepple RT. Exercise training initiated in late middle age attenuates cardiac fibrosis and advanced glycation end-product accumulation in senescent rats. Exp Gerontol. 2014;50:9–18. https://doi.org/10.1016/j.exger.2013.11.006.