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**Review Article**

# AGE-RAGE Pathway as a Potential Therapeutic Target

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**Abstract**

The advanced glycation end products (AGEs) are created by reactions involving a nonenzymatic glycation of lysine or arginine of proteins, and then additional glycoxidation due to oxidative stress occurs. They are part of the secondary stages of traumatic brain injury and the initiation and aggravation of several conditions, such as diabetes mellitus, Alzheimer's disease, and atherosclerosis. Receptor for AGE, also known as receptor for advanced glycation end product (RAGE), interacts with AGEs and produces intra- and interprotein cross-linkages that deactivate different enzymes and accelerate the course of illness. There is rising interest in targeting the AGE-RAGE pathway as a potential therapeutic intervention by developing AGE inhibitors, AGE-breaker compounds, RAGE antagonists, and exogenous sRAGE administration to treat AGE-related diseases, including diabetes mellitus and various neurodegenerative diseases. This implies that AGEs play a substantial part in the etiology of many diseases, and addressing the AGE-RAGE pathway might bring about new therapeutic options.

***Keywords***: AGE-RAGE pathway, Advanced glycation end products, Therapeutic target.

**مسار AGE-RAGE كهدف علاجي محتمل**

**الخلاصة**

يتم إنشاء المنتجات النهائية المتقدمة للجليكاسيون (AGEs) عن طريق التفاعلات التي تنطوي على غليكأيشن غير إنزيمي لليسين أو الأرجينين في لبروتينات، ثم يحدث أكسدة جليكولوجية إضافية بسبب الإجهاد التأكسدي. إنها جزء من المراحل الثانوية لإصابات الدماغ الرضحية وبدء وتفاقم العديد من الحالات، مثل داء السكري ومرض الزهايمر وتصلب الشرايين. يتفاعل مستقبل AGE، المعروف أيضا باسم مستقبلات المنتج النهائي المتقدم للجليكاسيون (RAGE)، مع AGEs وينتج روابط متقاطعة داخل وبين البروتينات تعمل على تعطيل الإنزيمات المختلفة وتسريع مسار المرض. هناك اهتمام متزايد باستهداف مسار AGE-RAGE كتدخل علاجي محتمل من خلال تطوير مثبطات AGE، ومركبات كسر AGE، ومضادات RAGE، وإعطاء sRAGE الخارجية لعلاج الأمراض المرتبطة بالعمر، بما في ذلك داء السكري والأمراض التنكسية العصبية المختلفة. هذا يعني أن AGEs تلعب دورا كبيرا في مسببات العديد من الأمراض، وقد تؤدي معالجة مسار AGE-RAGE إلى خيارات علاجية جديدة.

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## INTRODUCTION

Advanced glycation end products (AGEs) are receiving a lot of interest as one of the several theories put out to explain aging, which is the gradual buildup of damage that results in illness and death [1]. In both normal and pathological circumstances, glycation—a nonenzymatic reaction of glucose with proteins, lipids, or nucleic acids—occurs [2]. By stimulating oxidative stress, AGEs trigger the activation of several transcription factors that are induced by stress, which results in the production of inflammatory and proinflammatory mediators such as acute-phase proteins and cytokines [3]. As a result, AGEs disrupt human health by interfering with hormones and contributing to age-related, chronic inflammatory diseases [1].

### Formation and Types of Advanced Glycation End Products

In the early 1900s, the classic Maillard reaction, a variety of glycation reactions involving various biomolecules including proteins, lipids, and nucleic acids, led to the recognition of AGEs, which are heterogeneous molecules generated as a nonenzymatic end result of reactions of glucose or other saccharides with proteins and lipids [1–5]. Under physiological conditions, long-lived proteins like collagen are the

main target of endogenous AGE development, which might take weeks or years [6]. This process accelerates under stressful circumstances like oxidative or glycative stress, and it can also impact short-lived substrates (such as hormones and enzymes), causing structural modifications [4,7]. Aside from their natural development, smoking and a diet high in AGEs can also accumulate in the human body. Human circulating AGEs and ingested AGEs are significantly correlated [7].

## The Receptor for Advanced Glycation End Products (RAGE)

The AGEs have negative impacts through both receptor- and non-receptor-mediated pathways. Non-receptor-mediated processes include increased extracellular matrix formation, collagen cross-binding, and sub-endothelial low-density lipoprotein (LDL) trapping. In a receptor-mediated mechanism, AGEs interact with RAGE to modify intracellular signaling, gene expression, and oxygen radical production. This results in triggering nuclear factor kappa B (NF-κB), as well as growing expression of adhesion molecules and proinflammatory cytokines [8,9]. Many conditions, including hypertension, atherosclerosis, coronary artery and cerebral vascular disease, end-stage renal disease, hyperthyroidism, Alzheimer's disease, and diabetes, have been linked to the AGEs and their cell receptor, receptor for RAGE [8]. The capacity of RAGE, which is a member of the multiple ligand immunoglobulin superfamily, to bind AGEs led to its discovery. These processes occur slowly in normal health and aging but more promptly in diabetes. [10]. There are four receptor subclasses for AGEs; these include the full-length RAGE, which is a multiligand member of the immunoglobulin superfamily cell surface receptor, N-truncated RAGE, and C-truncated RAGE, which possess two isoforms, which are the endogenous secretory RAGE (esRAGE) and total soluble RAGE (sRAGE) [9]. The interaction that occurs between RAGE and AGEs has a negative impact on cell function and both causes and participates in the development of pathological conditions. The role of N-truncated RAGE, which is present in the plasma membrane, is not fully interpreted. C-truncated isoforms are blood-circulating and lack cytosolic and transmembrane domains. The two C-truncated RAGE isoforms, sRAGE and esRAGE, have cytoprotective effects against AGEs because they either sequester RAGE ligands or compete with intact RAGE for ligand binding [9]. To oppose the impacts of stressors (AGE and RAGE), the body has anti-AGE-RAGE defensive mechanisms, such as sRAGE, which competes for AGE with RAGE, and enzymes that degrade AGEs [8]. AGE-RAGE stress would result from elevated AGE and RAGE levels brought on by increased AGE intake, a lack of AGE-degradative enzymes, a reduction in sRAGE, and a rise in RAGE expression [8]. According to reports, one of the key risk biomarkers for diseases and a predictor of AGE-RAGE pathway stress is the ratio of AGEs to sRAGE [9].

## RAGE Polymorphism

Multiple diseases have been linked to functional mutations in the RAGE gene [11]. The *RAGE* gene is localized on chromosome 6p21.3 of class III major histocompatibility complex locus (MHC). Numerous cell types, namely T-lymphocytes, endothelial cells, macrophages, monocytes, dendritic cells, and smooth muscles, express RAGE. RAGE can bind to a variety of ligands, such as AGEs, and has been connected to several diseases, including vascular disease, Alzheimer's disease, cancer, atherosclerosis, diabetic nephropathy, and retinopathy [12]. Gene expression and ligand binding affinity are impacted by genetic differences in the *RAGE* gene. Additionally, by controlling alternative splicing or altering the protein's susceptibility to proteolytic cleavage, polymorphisms within RAGE may be able to control the individual amounts of sRAGE [13]. About 30 polymorphisms have been found in the RAGE gene, according to genetic research. One mutation, known as rs2070600, is found in the second motif and stimulates RAGE to be glycosylated. This alters the receptor protein structure, influences its split by certain proteases (reducing proteolysis of RAGE), and alters blood AGEs and sRAGE levels [14]. It has been demonstrated that two functional polymorphisms in the exon 1 of the *RAGE* gene promoter region, specifically rs1800624 and rs1800625 variants, enhance transcription activity *in vitro* [12,15]. Other polymorphisms include the 2184A/G polymorphism, which is found on the *RAGE* gene's intron 8 and has been linked to antioxidant status and microvascular dermatoses [16], and rs184003 in intron 7, which was linked to increased RAGE expression levels [17]. Moreover, a study conducted in Iraq has shown that RAGE polymorphisms (rs1800624), (rs2070600), and (rs184003) are significantly associated with colorectal cancer [18].

## Advanced Glycation End Products and Disease

An imbalance between AGEs and the effective AGE detoxification system mechanism occurs when AGEs are created in excess. AGE buildup causes oxidative stress, inflammation, and cumulative metabolic distress (hyperglycemia and hyperlipidemia) in addition to increasing the glycation process for long-lived proteins [3]. Through both endogenous production and external intake, AGEs play a substantial role in human disorders related to aging and diabetes. Glycation disrupts the normal biological functions of proteins, lipids, DNA, and extracellular matrix (ECM) components by causing them to crosslink covalently. Immunogenic DNA-AGEs

are caused by DNA glycation in diseases including diabetes, cancer, and neurodegeneration [1].

### *The AGEs in diabetes mellitus*

Since AGEs are created and deposited permanently in the body based on blood sugar control and duration, they can play a significant role in establishing metabolic memory in diabetes-related complications. There has been direct evidence of a link between the development of diabetic cardiovascular disease and the buildup of AGEs [19]. Numerous studies have demonstrated that impaired signaling of insulin, disturbance of metabolic balance, and interference with the function of the intestinal barrier are the negative consequences of the AGE-RAGE axis [20,21]. Due to hyperglycemia in diabetic nephropathy, direct glycation of cell proteins occurs. and AGE deposits mostly build up in the tubular and glomerular basement membranes, as well as the mesangium. The RAGE signaling cascade mediates a greater synthesis of growth factors, hence facilitating glomerulosclerosis. Furthermore, a greater number of pro-inflammatory molecules are produced, and permeability is raised, leading to hyperfiltration and albuminuria [22]. AGEs additionally trigger the release of growth factors. This leads to increased plaque development, fibrosis, endothelial dysfunction, and vascular wall proliferation. Patients with DM may have AGE deposits in their atherosclerotic plaques. In addition to general endothelial dysfunction and wall thickening, increasing ROS generation can oxidize more low-density lipoprotein (LDL) along the AGE/RAGE axis [23]. Diabetic retinopathy and neuropathy also include changes to tissue-specific cells and small blood vessels. Growth factors that promote angiogenesis and proliferative retinopathy are upregulated by AGEs, which build up in the retinal vessel wall [22]. Glycation of the lens α-crystallin also results in the crosslinking of protein, which reduces lens transparency and promotes diabetes and age-related cataracts [24]. The pathophysiology of neuropathy is also influenced by AGE deposits. Schwann cells, the perineurium, axoplasm, and endoneural blood vessels have all been shown to have AGE accumulation [22].

### *The AGEs in cardiovascular diseases*

Elevated AGE concentrations and the prevalence of cardiovascular diseases in diabetes patients are associated with increasing arterial resistance, systolic and diastolic dysfunction, arrhythmias, heart failure, in-stent restenosis, and coronary artery disorders [25,26]. Protein cross-linking caused by AGE modification contributes to systolic hypertension and diastolic heart failure by increasing vascular and cardiac stiffness as well as impairing physiological function of several organs [23]. The mechanisms that underline the abnormalities brought on by AGE-modified myosin, F-actin, and ryanodine receptor type 2 (RyR2) have been addressed [27]. Moreover, AGE-RAGE pathway signaling stimulates oxidative stress, deactivating nitric oxide (NO) and promoting the development of peroxynitrite. Asymmetric dimethylarginine (ADMA), which inhibits NO synthase and has been correlated to endothelial dysfunction in high-risk coronary artery disease patients, can also be produced by AGEs [28]. Additionally, reactive oxygen species (ROS) and pro-inflammatory cytokines tumor necrosis factor alpha, TNF-α; interleukin (IL)-6 in addition to various growth and adhesion factors such as transforming growth factor beta, TGF-β; intracellular cell adhesion molecule-1, ICAM-1; endothelin-1, ET-1; and vascular adhesion molecules (vascular cell adhesion molecule-1, VCAM-1) are produced as a result of AGE-RAGE signaling activating numerous intracellular pathways, further establishing vascular inflammation [29].

### *The AGEs in cancer*

Numerous risk factors linked to cancer, including obesity, poor nutrition, and inactivity, are also linked to an elevated buildup of AGEs. Research revealed the presence of AGE in human cancers in the larynx, breast, and colon; it has now been proven that prostate tumors also have high levels of AGE [30]. Additionally, brain, lung, oral squamous cell, and ovarian cancers, lymphoma, and melanoma have been shown to express RAGE [31]. AGEs were shown to be more prevalent in late stages of cancer than in localized phases and to be greater in cancer patients than in healthy individuals [32]. Collagen cross-linking in prostate tumors caused by AGE-modified basement membranes encourages the invasive characteristics of prostate epithelial cells and is associated with a low survival rate. Serum from patients with high-grade prostate cancer had much greater amounts of the AGE metabolite carboxymethyl-lysine. Additionally, tumor tissue had the greatest amounts of RAGEs when compared to non-cancer tissue [33]. A number of AGE-modified proteins with known functional importance to breast cancer were discovered by mass spectrometry investigation of the AGE level in tumors [30]. RAGE expression levels were markedly elevated in high-stage breast tumors, both at the mRNA and protein levels. The relationship between RAGE expression and tumor growth was statistically significant [34,35]. RAGE protects pancreatic tumor cells from oxidative damage by promoting autophagy and preventing apoptosis. The inflammatory stress of the pancreatic tumor microenvironment is increased when a ligand binds to RAGE and triggers downstream NF-κB-mediated signaling [36]. The ability of RAGE ligand HMGB1 to promote melanoma cell migration revealed signaling function in melanoma. Further research revealed that RAGE's interactions with its

ligands, especially AGEs, may be crucial in promoting the progression and invasion of melanoma [37].

### *The AGEs in neurodegenerative diseases*

Neurodegeneration is the outcome of several abnormal biological and physiological processes caused by dysregulation of the AGE-RAGE axis [38]. The pathophysiology of Alzheimer's disease (AD) is linked to AGEs because they interact with RAGE to cause neurodegeneration [39]. RAGE causes the production of proinflammatory cytokines at the blood-brain barrier (BBB) and is increased in patients with Alzheimer's brains [40]. When AGE interacts with RAGE, it activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which triggers NF-kB, producing ROS. Many cytokine genes, including TNF-α, IL-1, IL-6, and IL-8, are activated by NF-kB. Proinflammatory cytokines increase ROS and NADPH oxidase [41]. Patients with AD had higher levels of neuronal and astroglial AGE-positive cells [41]. Additionally, RAGE molecules are known to help transport amyloid β (Aβ) into and across the BBB during AD, suggesting that RAGE plays a role in mediating the elevated ligand concentration levels detected as the disease progresses [42,43]. Despite being clearly involved in regulating neuroinflammation in cases with Parkinson's disease (PD), RAGE's cell distribution and its newly identified capacity to bind α-syn fibrils suggest that it can also be involved in other cell processes that are essential for the development of dopamine neuron degeneration [44].

### *AGEs in kidney diseases*

In addition to hyperglycemia, AGEs can also occur in conditions linked to elevated oxidative stress, such as chronic kidney disease (CKD), in which elevated AGE levels are caused by increased AGE generation and impaired renal clearance [45]. By increasing oxidative stress in the body through a variety of mechanisms and inducing an inflammatory response, AGEs may be one of the main causes of kidney diseases [46]. Advanced oxidation protein products (AOPP), AGE, and AGE-oxidized LDL develop quickly in diabetes, and they all play a role in early cell stress and signaling, which are thought to be associated with the onset of renal disease [47]. Pro-inflammatory RAGE ligands (S100A12, HMGB1) are released when renal disease is establishing, resulting in attraction and activation of inflammatory cells in the nephron. The uncontrolled cycle of inflammatory signaling and oxidative stress produces additional AGE, causes local extracellular matrix to crosslink, and results in the development of amyloid fibrils, all of which further impair kidney function [47].

### *AGEs in irritable bowel disease (IBD)*

Inflammatory bowel diseases (IBD) include Crohn's disease (CD) and ulcerative colitis (UC) that involve the small intestine and colon. RAGE was increased during inflammation in the small intestine and colon. RAGE activation may impact intestinal inflammation through a number of mechanisms, including increased production of inflammatory mediators and adhesion molecules that facilitate leukocyte recruitment [48]. RAGE and its ligands, such as S100A12 and HMGB1, have been shown to be upregulated in CD patients, and by stimulating oxidative stress and endothelium activation, RAGE may cause intestinal inflammation [48].

### *AGEs in other diseases*

Through risen oxidative stress levels and inflammatory events, RAGE may contribute to the pathophysiology of several liver disorders. Particularly in older adults or patients with metabolic disorders, RAGE ligands cause harmful effects on hepatic insulin resistance, fibrosis and steatosis, ischemic and nonischemic liver disease, and hepatocellular carcinoma growth and metastasis by upregulating RAGE expression in the liver [49]. In addition to being highly expressed in the lung, RAGE has been linked to acute alveolar epithelial cell damage and fibrotic transformation in a number of organs, including pulmonary fibrosis [50]. In patients with COPD, the RAGE–sRAGE pathway seems to have a significant role, especially in emphysema; it implies that sRAGE in the circulation may be a helpful biomarker of emphysema and its progression; and it suggests that RAGE may be a prospective therapeutic target [51].

## Therapeutic Agents Targeting the AGE-RAGE Pathway

Reducing AGE accumulation and RAGE signaling can prevent the harmful consequences of AGEs. Drugs, lifestyle changes, and nutraceutical therapies can all target the AGE production pathway at different levels [4].

## AGE Inhibitors

The development of AGEs and the oxidative stress they cause in a number of diseases has led to the development of several AGE inhibitors, many of which are now undergoing progressed clinical trials. Aminoguanidine, metformin, carnosine, homocarnosine, pyridoxamine, and N-phenacylthiazolium bromide are a few interesting medication options. Aspirin and tenilsetam, two anti-inflammatory medications, also have AGE-inhibiting characteristics. The antioxidants function as

AGE inhibitors, most likely via sequestering free radicals and metal-ion chelation [7].

### *Aminoguanidine*

As an AGE inhibitor, aminoguanidine (pimagedine) scavenges AGE precursors to halt AGE production [52]. By forming the corresponding adducts, which are comparatively non-toxic molecules, aminoguanidine sequesters harmful 1,2-dicarbonyl compounds. It also possesses additional favorable characteristics for reducing oxidative stress, namely transition-metal-ion chelation and peroxynitrite scavenging. All of these mechanisms worked together to greatly reduce the production of AGE [7,53]. Aminoguanidine prevented AGE accumulation or abrogation of AGE synthesis in diabetic animal models, affecting the progression of diabetes and its related complications [54]. It has also been shown that aminoguanidine's scavenging action may reverse diabetic nephropathy by lowering albuminuria and renal vascular damage [52]. In patients with type 1 diabetes, it lowers glomerular filtration and proteinuria and prevents the retinopathy from worsening [41]. However, due to the adverse effects that were noted in diabetic patients during Phase III clinical trials, the medication is not being developed any further, in part due to pyridoxal sequestration, which led to a vitamin B6 deficiency [7,55].

### *Metformin*

The glucose-lowering drug metformin has been shown to have positive effects on glycation indicators, including a decrease in AGEs and oxidative stress in T2DM patients [4]. Through the phosphorylation and activation of adenosine monophosphate-activated protein kinase by a serine-threonine protein kinase called LKB1, metformin can lower blood glucose levels [7]. Metformin also acts as a dicarbonyl scavenger in addition to its insulin-sensitizing action. It's possible that the two bioactivities working together are what produced the notable drop in the amount of AGE in the blood. However, metformin did not reduce AGEs more effectively than other glucose-lowering medications like pioglitazone and repaglinide. This indicates that glycemic control is more important for inhibiting the AGE-RAGE axis than dicarbonyl scavenging [52].

### *Carnosine*

As a dipeptide that consists of β-alanine and histidine, carnosine acts by inhibiting AGEs via three mechanisms. It exhibits metal chelator characteristics, combines with the carbonyl group on proteins that have already undergone modification to form protein-carbonyl-carnosine adducts (antiglycating agents), and functions as an antioxidant by capturing reactive oxygen species [7,22]. This procedure, known as "carnosinylation," stops additional cross-linking with other glycated proteins. Furthermore, there is no further interaction between these carnosine-modified AGEs and RAGE [22]. As a naturally occurring dipeptide that is non-toxic, it may be used therapeutically as an AGE inhibitor, maybe in conjunction with other AGE inhibitors such as aminoguanidine. Under the brand name Can-C1, N-acetylcarnosine, a prodrug for carnosine, is beneficial in the treatment and prevention of age-related cataracts [7].

### *Tenilsetam*

Tenilsetam is categorized as a nootropic and is an AGE inhibitor. By covalently attaching itself to the reactive carbonyl groups and preventing the production of AGE, tenilsetam appears to function as a carbonyl scavenger. Tenilsetam was used in a clinical trial on Alzheimer's disease that showed improvements in psychomotor activity, cognition, and attention but not enhanced psychological shifts or reaction time. Tenilsetam's effectiveness as an AGE inhibitor was unknown at that time, though. Therefore, it is uncertain how strongly tenilsetam altered the AGE/RAGE axis, and no parameters related to AGEs were examined [22].

### *Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARB)*

AGEs may rise due to oxidative stress, which is facilitated by renin-angiotensin system activation. *In vitro* research has revealed that AGE production is inhibited by ACE-I and ARBs. Instead of trapping reactive carbonyls, these compounds strongly chelate metal ions and sequester ROS, which prevents the glycoxidation that causes AGE formation. Due to their AGE-lowering characteristics, ACE-I and ARB may reduce the risk of atherosclerosis and diabetic nephropathy, along with other AGE-related conditions [7]. ACE-I and ARB combined therapy have potential in the prevention and treatment of diabetic nephropathy by slowing down the progression of microalbuminuria to clinically significant albuminuria [4,7].

### *Statins*

Because lipid-lowering medications include anti-oxidative properties that partially diminish lipid peroxidation, they may also limit the production of AGE. After a year of treatment, atorvastatin reduced serum AGEs in patients with dyslipidemia and nonalcoholic steatohepatitis (NASH). Following a year of atorvastatin treatment, serum AGEs were also decreased in patients with dyslipidemia and non-diabetic chronic renal disease. Patients with diabetes who were given cerivastatin for three months also

experienced this effect. Simvastatin inhibited the development of AGEs, which in turn reduced the expression of RAGE in carotid artery plaques in addition to lowering serum AGEs [4].

### *OPB-9195*

OPB-9195 uses carbonyl trapping and metal-ion chelation to prevent the formation of AGE, particularly those of pentosidine and CML. OPB-9195 has been demonstrated to decrease glycated albumin levels, blood pressure, and oxidative damage in stroke-prone spontaneously hypertensive rats. But because it depleted vitamin B6, it has been discontinued [7].

### *Pyridoxamine*

Thiamine pyrophosphate and pyridoxamine (vitamin B6) may be just as successful at inhibiting AGE as aminoguanidine. By cleaving (or trapping) 1,2-dicarbonyl intermediates produced by glycoxidation and lipoxidation, pyridoxamine has been demonstrated to inhibit the synthesis of CML and Ne-(carboxyethyl) lysine (CEL), the main products of these processes. Additionally, it traps ROS, which prevents the oxidative breakdown of the Amadori intermediates in Maillard reactions and AGE production [7,53]. Pyridoxamine was used in a phase II clinical trial to lower AGE plasma levels and halt the progression of renal damage in patients with type 1 and type 2 diabetes [41]. Argpyrimidine and other AGEs mediated by methylglyoxal are suppressed by pyridoxamine, which also stops methylglyoxal-treated human lens epithelial cell apoptosis, and thus it reduces the complications associated with diabetes [56].

### *Vitamin B12*

Cobalamin, often known as vitamin B12, is a water-soluble vitamin that is vital for sustaining hematopoiesis and brain function. Because B12 may have antioxidant properties, oxidative stress and the development of diseases related to aging may be exacerbated by subclinical B12 deficiency [57]. Direct scavenging of ROS, especially superoxide; indirect stimulation of ROS scavenging by maintaining glutathione; modulation of cytokine and growth factor production to provide protection against immune response-induced oxidative stress; suppression of homocysteine-induced oxidative stress; and suppression of oxidative stress resulting from AGEs are some of the possible antioxidant mechanisms of B12 [57,58].

### *Benfotiamine*

A soluble derivative of vitamin B1 is responsible for activating the transketolase. The AGE pathway produces monosaccharides that transketolase transform into ribulose-5-phosphate, which is then broken down by the pentose phosphate route. By activating transketolase, benfotiamine is depleted, leading to an increase in AGE pathway metabolites. Neuropathy ratings indicated that benfotiamine significantly improved neuropathy, and it was well tolerated [22,41].

### *HMGB1 inhibitors*

The RAGE ligand High Mobility Group Box 1 (HMGB1) is yet another potential therapeutic target. HMGB1 box A, which counteracts HMGB1's function, anti-HMGB1 antibodies, and chemical inhibitors of HMGB1 are examples of these inhibitors. HMGB1 box A and anti-HMGB1 antibodies have been effectively used in a number of preclinical studies of arthritis, sepsis, and pancreatitis. Ethacrynic acid, ethyl pyruvate, sulforaphane, oltipraz, thrombomodulin, antithrombin III, and polymyxin B are examples of small molecule inhibitors of HMGB1. Numerous preliminary studies have been utilized to administer these small compounds [55].

### *AGE cross-link breakers*

By breaking the carbon-carbon bond in the middle of carbonyls, AGE cross-link breaker breaks apart α-carbonyl complexes [8]. Therapies that break down established AGE-protein crosslinks include N-phenacyl-thiazolium bromide (PTB) and alagebrium chloride (ALT-711) [22,55].

### *N-Phenacyl-thiazolium bromide (PTB)*

The salts of phenacyl-thiazolium have been evaluated in Phase II clinical trials for systolic hypertension; however, limited efficacy in a number of *in vivo* studies has been found. Protein crosslink breakers like these could serve as effective treatments for diabetes and its complications. Additionally, it functions as a transition-metal-ion chelator, reducing the oxidative stress that causes AGEs to develop. Thiazolium salts are among the strongest ascorbate oxidation inhibitors, demonstrating that their antioxidant activity might at least partially explain their AGE-inhibiting capabilities via reducing glycoxidation [7].

### *Alagebrium*

Alagebrium lowers AGE levels by non-enzymatically breaking the established cross-linking between AGE and adjacent long-lived collagen and elastin. Additionally, it has been demonstrated to decrease arterial stiffness; however, the improvement of other measures, such as cardiac output and diastolic and

systolic blood pressure, was not sufficiently significant [8]. Alagebrium effectiveness in renal diseases when given as delayed intervention has also been documented [59], with no serious adverse effect like aminoguanidine, but unfortunately, alagebrium development has been discontinued [52].

## RAGE Antagonists

Targeting RAGE directly by preventing the signal cascade that is initiated by RAGE binding to its ligands is another approach. RAGE can be directly targeted with RAGE inhibitors, RAGE peptides, anti-RAGE antibodies, DNA aptamers, sRAGE, or the intracellular domain of RAGE [55].

### *Azeliragon*

One of the RAGE inhibitors is azeliragon, an immunoglobulin G containing a RAGE-binding domain. While TTP4000 causes RAGE to become inactive because a preferred ligand binds with itself rather than RAGE, azeliragon prevents the ligand from attaching to RAGE. Both drugs are categorized as antidementives and are being studied in relation to Alzheimer's disease [22,41]. Unfortunately, a phase 3 clinical trial in 2019 did not fulfill its co-primary aim, despite modest improvements in cognition shown in the diabetic patient group [55].

### *RAGE peptides*

RAGE peptides, like the mutant RAGE peptide S391A-RAGE362-404, also prevent RAGE from dimerizing with G-protein-coupled receptors and from being transactivated. This peptide reduced angiotensin II-dependent inflammation and atherogenesis in an animal model of atherosclerosis. *In vivo* cancer models have also employed novel RAGE antagonistic peptides to prevent RAGE activation. These substances have not yet advanced beyond preliminary studies [60,61].

### *Aptamers*

Single-stranded DNA or RNA molecules known as aptamers have a high affinity and selectivity for binding to a variety of target proteins. Their non-immunogenicity and small size make them highly promising therapeutic options. Notably, in an animal model of type 2 diabetes, high-affinity AGE-aptamer prevents the development of nephropathy. Additionally, they inhibited adipocyte remodeling and enhanced glycemic control in fructose-fed rats, in part by inhibiting the production of oxidative stress mediated by AGE-RAGE [5]. Even though DNA aptamers work similarly to antibodies, they offer several advantages, including easier production, faster tissue absorption, lower immunogenicity, higher stability, no within-batch variability, and shorter generation times. Shorter circulation periods, high production costs, and a lack of safety and toxicological data are some of the issues with DNA aptamers [55].

### *Exogenous sRAGE*

Another way to target RAGE signaling is with its antagonist soluble isoform, sRAGE [55]. By interacting with RAGE ligands, sRAGE functions as a decoy for RAGE and protects against the harmful consequences of AGE-RAGE interaction. Patients might benefit from higher sRAGE levels by exogenous sRAGE administration [41]. According to preclinical findings, sRAGE has anti-atherosclerotic properties and, when used, considerably reduces the severity of the developed atherosclerotic plaques [22]. Additionally, blocking RAGE by sRAGE is helpful in several animal disease models, such as vascular dysfunction, diabetic nephropathy, nephritis, and wound healing in diabetes [55].

## Conclusion

Evidence that RAGE contributes to the development of several diseases is growing. The most important factor in determining how these diseases develop involves the AGE-RAGE axis. RAGE is associated with several inflammatory pathological events, such as diabetes, cancer, autoimmunity, cardiovascular disease, and neurodegenerative disorders. For many diseases, RAGE inhibition, whether by ligands or signal transduction, is a promising new therapeutic target. Antioxidants, RAGE ligand binding inhibition, RAGE expression suppression, AGE consumption and production decline, and sRAGE elevation might all be new therapeutic approaches for disease prevention, reversal, and delaying. Additional preclinical and clinical studies are needed.


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