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Research article

Modulating the AGE-RAGE Signaling Pathway in Degenerative Processes: Molecular Mechanisms and Therapeutic Prospect of Phytochemicals

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Abstract. The Receptor for Advanced Glycation End Products (RAGE) is a multi-functional cell-surface receptor capable of binding a broad range of ligands, including advanced glycation end products (AGEs). While RAGE is constitutively expressed in various tissues, AGEs arise from non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids. The AGE-RAGE interaction activates multiple redox-sensitive and pro-inflammatory signaling pathways, thereby contributing significantly to ageing, chronic inflammatory conditions, and metabolic degenerative diseases. Consequently, targeting the AGE-RAGE axis has become an important focus of contemporary biomedical research. Although substantial progress has been made in elucidating this pathway and developing synthetic AGE-RAGE inhibitors, many of these agents present limitations related to safety, bioavailability, or therapeutic efficacy. Phytochemicals such as polyphenols, alkaloids, and tannins have exhibited promising anti-glycation, antioxidant, and anti-inflammatory activities that may attenuate AGE-RAGE mediated cellular dysfunction. However, direct evidence of their capacity to inhibit RAGE at the receptor level remains limited. This review identifies critical knowledge gaps and demonstrates that structure-guided computational modeling combined with targeted experimental validation represents a promising strategy for the rational development of phytochemical-based RAGE modulators. These findings highlight the potential of natural products as safer and mechanistically informed therapeutic candidates for attenuating AGE-RAGE-mediated degenerative disease progression.

Keywords: AGE, RAGE, AGE-RAGE signaling, Ageing, Degenerative diseases, Phytochemicals

INTRODUCTION

Ageing is a progressive process characterized by the gradual accumulation of chemical modifications and structural damage to biological macromolecules such as DNA, proteins, and lipids, leading to an irreversible decline in cellular and physiological functions (Zhang et al., 2025). This decline is primarily driven

by molecular damage and imbalances in the body's homeostatic mechanisms, often influenced by endogenous and exogenous chemical factors (Choi et al., 2025). The chemistry of ageing is strongly associated with the free radical theory and the formation of advanced glycation end-products (AGEs) (Uceda et al., 2024a). Oxidative stress represents one of the most critical biochemical features of ageing. It results from the excessive production of reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals, and hydrogen peroxide by-products of normal cellular respiration (Dash et al., 2025). This process is further enhanced in the presence of transition metals like iron and copper through Fenton-type reactions (Song et al., 2024a). With advancing age, the body's natural antioxidant systems, including glutathione, superoxide dismutase, and catalase, become less efficient, thereby intensifying oxidative stress (Jomova et al., 2023). Consequently, oxidation of deoxyribonucleic acid (DNA) (e.g., formation of 8-oxo-dG), proteins, and lipids occurs, producing aldehydic by-products such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE), which can form covalent adducts with proteins and nucleic acids, leading to molecular dysfunction (Misra et al., 2025; Blouin and Saini, 2024).

The fundamental chemical interactions between ROS and biological macromolecules are central to cellular oxidative chemistry (Piras et al., 2016). During mitochondrial respiration, electrons escaping from the electron transport chain can react with oxygen to generate superoxide radicals (Napolitano et al., 2021). These radicals undergo dismutation to yield hydrogen peroxide, which in the presence of transition metals, produces highly reactive hydroxyl radicals via the Fenton reaction (Kanti Das., 2014). These radicals initiate lipid peroxidation by attacking polyunsaturated fatty acids in cell membranes, producing lipid radicals and hydroperoxides (Huang and Yang 2021). The subsequent decomposition of these hydroperoxides yields reactive aldehydes capable of cross-linking proteins and nucleic acids, thereby disrupting cellular integrity (Feng et al., 2024). Another major biochemical contributor to ageing is non-enzymatic glycation, a reaction between reducing sugars and free amino groups of lysine or arginine residues in proteins (Senatus and Schmidt, 2017). This process leads to the formation of unstable Schiff bases and Amadori intermediates that eventually rearrange into AGEs (Chen et al., 2024). AGEs impair biological function by inducing irreversible cross-links in long-lived structural proteins such as collagen, thereby decreasing tissue elasticity and resilience. Moreover, AGEs interact with the receptor for advanced glycation end-products (RAGE), a multi-ligand receptor that triggers oxidative stress and pro-inflammatory signaling cascades (Byun et al., 2017). RAGE activation also

stimulates matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix, accelerating tissue damage and skin ageing (Feng et al., 2024).

Although ROS generation and AGE formation originate from distinct biochemical processes, they are closely interconnected. ROS promote glycation by facilitating oxidative conversion of Amadori intermediates into AGEs, a process known as glycooxidation (Pathomthongtawechai and Chutipongtanate, 2020). Consequently, AGE formation, RAGE activation, and ROS generation form a self-propagating feedback loop that amplifies cellular and tissue ageing (Kinscherf and Pehar, 2022). The AGE-RAGE axis constitutes a crucial point of convergence through which chemical damage is converted into persistent biological signaling. A comprehensive synthesis of current knowledge on RAGE is therefore necessary to elucidate its role as a molecular amplifier of ageing-associated inflammation, oxidative stress, and tissue degeneration. Targeting the AGE-RAGE pathway has therefore become a central focus in anti-ageing research (Li et al., 2025). The accumulation of AGEs and their interaction with RAGE activate signaling pathways implicated in degenerative disorders such as diabetes, cardiovascular disease, and neurodegeneration (Wang et al., 2024). Inhibiting AGE formation, blocking RAGE activation, or interrupting downstream signaling could mitigate inflammation and tissue injury (Salazar et al., 2021). Importantly, these pathways can be modulated through pharmacological interventions as well as lifestyle factors such as dietary antioxidants, providing a practical framework for promoting healthy ageing (Chen, 2024).

Following the discovery of the pathogenesis associated with the Maillard reaction and the identification of the AGE-RAGE signaling axis, considerable research efforts have been directed toward inhibiting these processes (Al-Abbasy et al., 2024). The early 2000s witnessed the development of synthetic AGE inhibitors such as aminoguanidine and pyridoxamine, as well as RAGE-antagonistic peptides (RAPs) engineered to block AGE-RAGE binding. These synthetic inhibitors often contain functional groups designed to interact with the RAGE binding pocket, mimicking the physicochemical properties of AGEs (Kong et al., 2025). Although these agents show therapeutic promise in mitigating age-related diseases, limitations including low bioavailability, poor specificity, and safety concerns have constrained their clinical utility (Ngcobo, 2025). Consequently, attention has shifted toward natural or biochemical inhibitors, which tend to offer greater tolerability, multi-target activity, and holistic physiological benefits (Láng et al., 2024).

Naturally occurring compounds such as flavonoids, phenolic acids, and alkaloids, commonly found in dietary

sources are biodegradable, better tolerated for long-term use, and possess multiple functional groups (hydroxyl, methoxy, and carbonyl) that enable free radical scavenging and protection against protein and DNA modification (Rodríguez-Negrete et al., 2024). Their antioxidant, anti-inflammatory, and metal-chelating properties further underscore their therapeutic potential (Gulcin, 2025). Therefore, this review aims to synthesize current knowledge on the molecular mechanisms underlying the AGE-RAGE signaling pathway, evaluate existing inhibition strategies, and highlight emerging prospects for phytochemical modulation as potential therapeutic interventions in ageing and degenerative diseases. By consolidating emerging biochemical, molecular, and computational evidence on AGE-RAGE modulation, rational design of next-generation anti-ageing interventions might be engendered. Revelations from this study may guide future studies toward mechanism-driven therapeutic developments, thereby facilitating the identification of safer long-term modulators of age-related signaling as well as support the translation of phytochemical-based strategies into clinically relevant anti-ageing frameworks.

METHODS

Review Design and Reporting Framework

This review was conducted and reported using the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021). This framework was adopted to ensure transparency, reproducibility, and methodological rigor in the identification, screening, eligibility assessment, and inclusion of relevant literature. The PRISMA flow diagram illustrating the study selection process is provided in Figure 1.

Literature Search Strategy

A comprehensive and systematic literature search was performed across major academic databases, including PubMed, Scopus and the Web of Science as well as supplementary sources like Google Scholar and ResearchGate, to identify studies relevant to glycation chemistry, ageing, age-related diseases, advanced glycation end-products (AGEs), and their receptor (RAGE). Searches were conducted using Boolean operators and combinations of controlled and free-text keywords, including but not limited to: “advanced glycation end-products,” “AGE-RAGE signaling,” “glycation chemistry,” “oxidative stress,” “anti-glycation compounds,” “phytochemicals,” “natural inhibitors,” and “degenerative diseases.”

The search was restricted to peer-reviewed articles published in English between January 2005 to January 2026 to ensure inclusion of contemporary and methodologically sound research. To enhance coverage, manual reference screening of relevant review articles and primary studies was also undertaken.

Study Selection and Screening Process

All retrieved records were imported into the Zotero reference management system (version 7.0.32), where automated and manual duplicate removal was performed prior to title and abstract screening. Study selection followed a two-stage screening process consistent with PRISMA recommendations:

1. Title and abstract screening was conducted to exclude clearly irrelevant studies.
2. Full-text assessment was subsequently performed to evaluate eligibility based on predefined inclusion and exclusion criteria.

Screening and eligibility assessments were conducted independently by the authors, with discrepancies resolved through discussion and consensus. Only studies directly relevant to AGE-RAGE mechanisms and anti-ageing biochemical processes were retained.

Inclusion and Exclusion Criteria

Studies were included if they met one or more of the following:

- Provided mechanistic insight into the chemistry of ageing, AGE formation, or RAGE activation.
- Examined biochemical, molecular, pharmacological, or computational aspects of the AGE-RAGE axis.
- Investigated inhibitory or modulatory strategies targeting AGE formation or AGE-RAGE interaction.
- Reported structural, chemical, or biological properties of phytochemicals with antioxidant, anti-inflammatory, antiglycation, or metal-chelating activity relevant to AGE-RAGE modulation.

Studies were excluded if they were:

- Non-peer-reviewed sources (conference abstracts, editorials, commentaries).
- Not directly related to molecular, biochemical, or mechanistic aspects of the AGE-RAGE pathway.
- Lacking sufficient methodological detail or experimental validation.
- Purely descriptive without mechanistic or analytical relevance.

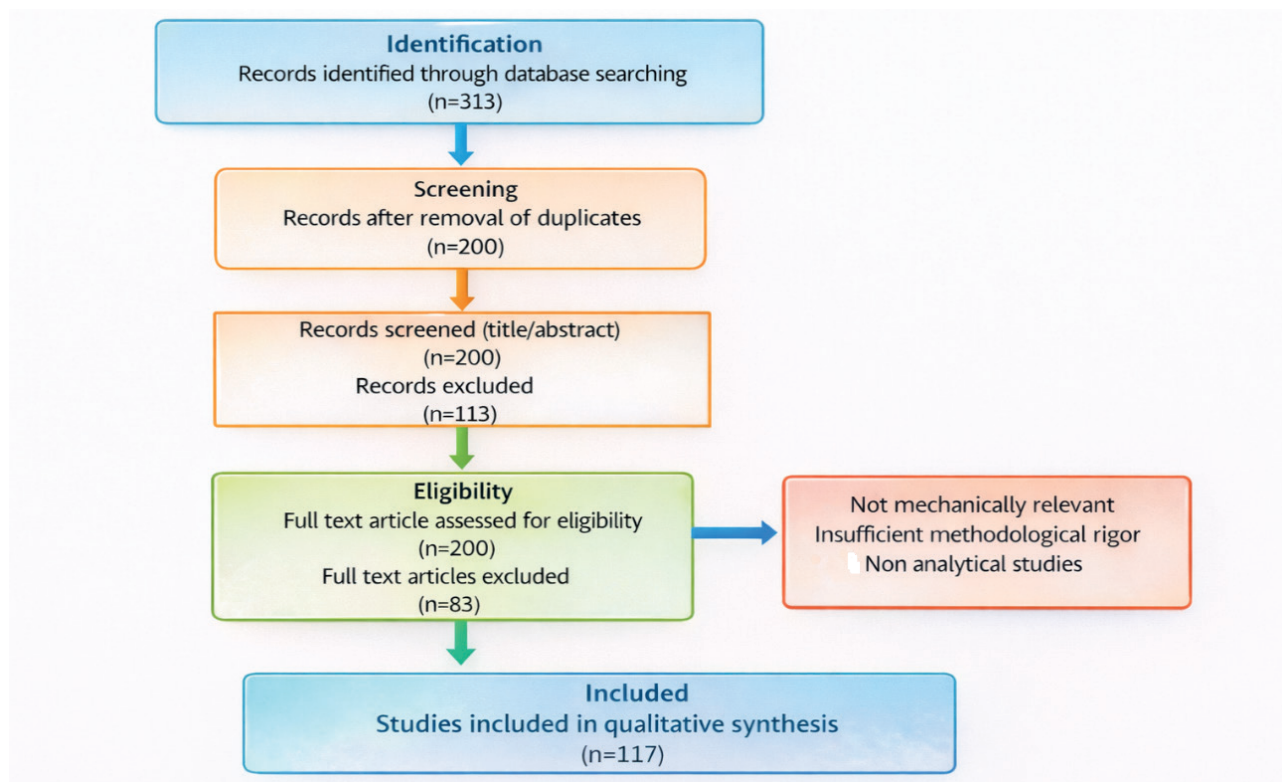


Figure 1: Model of article screening (PRISMA 2020)

Methodological Quality and Risk-of-Bias Assessment

All eligible studies were subjected to a structured qualitative appraisal in order to address methodological quality and potential bias. Experimental studies were evaluated based on criteria adapted from established risk-of-bias assessment tools, including:

- Clarity of experimental design and objectives
- Appropriateness of analytical or biochemical methods
- Adequacy of controls and reproducibility of results
- Consistency between reported data and conclusions

Computational and theoretical studies were assessed for:

- Validity of computational models and parameters
- Transparency and reproducibility of methodological workflows

Studies which failed to meet the minimum quality thresholds by our assessment were excluded during full-text screening. Given the mechanistic and qualitative nature of the review, quantitative risk-of-bias scoring and meta-analysis were not performed, consistent with PRISMA recommendations for non-interventional systematic reviews.

Data Extraction and Synthesis

Following PRISMA-guided screening, 313 records were initially identified. After duplicate removal and title/abstract screening, 200 articles were assessed at the full-text level. Out of these, 117 studies met the inclusion criteria and were retained for qualitative synthesis.

Data extraction focused on:

- Chemical pathways of AGE formation
- Structural and signaling features of RAGE
- Molecular mechanisms of AGE–RAGE inhibition
- Therapeutic and anti-ageing implications of phytochemical modulators

A narrative and thematic synthesis approach was employed to integrate findings across biochemical, pharmacological, and computational domains. Results were organized into thematic sections encompassing AGE chemistry, RAGE structure and signaling, inhibition mechanisms, and emerging phytochemical strategies, enabling identification of mechanistic trends and critical knowledge gaps.

CHEMISTRY OF AGES FORMATION

AGEs constitute a structurally heterogeneous group of biomolecules formed through complex non-enzymatic reactions involving reducing sugars and nucleophilic sites on proteins, lipids, or nucleic acids (Perrone et al., 2020). Their diversity arises from the wide range of precursors and reaction intermediates participating in their synthesis (Sharma et al., 2015). Chemically, AGEs are characterized by the presence of highly reactive carbonyl functional groups, which confer both their chemical reactivity and biological activity, including their propensity to cross-link biomolecules and alter cellular signaling (Nagai et al., 2014). Once formed, AGEs are chemically stable and essentially irreversible, leading to their progressive accumulation within tissues over time (Sadeghi et al., 2023). The formation of AGEs primarily occurs through three fundamental biochemical pathways: the Maillard reaction, the polyol pathway, and lipid peroxidation, each contributing distinct intermediates and structural variants to the overall AGE pool.

The Maillard Pathway

The Maillard reaction is a non-enzymatic chemical process involving a condensation reaction between reducing sugars and amino groups of biomolecules such as proteins, peptides, or amino acids (Twarda-Clapa et al., 2022). Reducing sugars possess highly reactive free aldehyde or ketone groups, which readily react with the nucleophilic amino group of amino acid residues, initiating the early stages of AGE formation (Al-Abbasy et al., 2024). This initial reaction yields an unstable Schiff base intermediate, which subsequently undergoes an Amadori rearrangement, producing more stable intermediates known as Amadori products (El Hosry et al., 2025). The Amadori rearrangement involves an intramolecular shift in bonding that converts the initial imine linkage into a ketoamine structure, thereby stabilizing the intermediate (Smita. Burhade et al., 2025). In glucose- and fructose-mediated reactions, the resulting rearrangements yield glucosamine and fructosamine derivatives, respectively (Takeuchi et al., 2010). The Amadori products formed during this process can undergo a cascade of dehydration, oxidation, and cross-linking reactions, leading to the generation of chemical complex and biologically active AGEs with pathogenic potential (Ho et al., 2024). Once formed, these AGEs are highly stable and irreversible, contributing to their persistence and accumulation in biological systems. Under oxidative conditions, Schiff bases may also bypass the Amadori stage entirely through the Namiki pathway,

directly yielding reactive dicarbonyl compounds that accelerate AGE formation (Thakor et al., 2024).

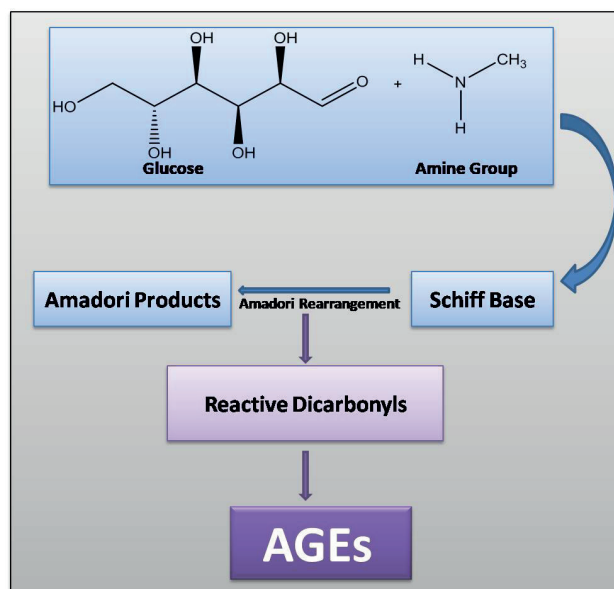


Figure 2: Formation of AGEs from the Maillard Pathway

The Polyol Pathway

The polyol pathway represents an alternative metabolic route for glucose utilization that significantly contributes to the formation of AGEs. In this pathway, glucose or other aldoses are first reduced to sorbitol through the catalytic action of the enzyme aldose reductase, and subsequently oxidized to fructose by sorbitol dehydrogenase (Delannoy et al., 2025). This two-step redox sequence not only alters carbohydrate metabolism but also enhances the generation of reactive carbonyl intermediates that promote glycation. The metabolic conversion of glucose to fructose via the polyol pathway increases AGE formation since fructose is a more potent glycating agent than glucose, reacting with amino residues at a markedly higher rate (Yamaguchi and Nagai, 2025). Furthermore, excessive sorbitol accumulation within tissues can induce osmotic stress, cellular swelling, and secondary oxidative damage, all of which potentiate inflammatory signaling and lipid peroxidation. These conditions create a biochemical environment that amplifies AGE production and accelerates tissue injury (Clarke et al., 2024). Thus, dysregulation of the polyol pathway not only contributes to AGE accumulation but also establishes a mechanistic link between hyperglycemia, oxidative stress, and inflammation, which are key processes underlying ageing and diabetic complications.

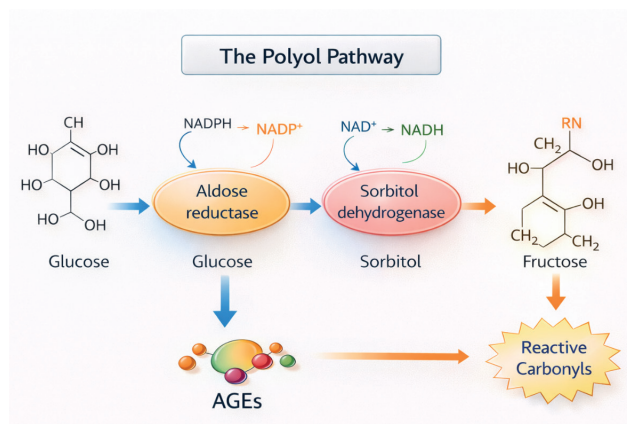


Figure 3: Formation of AGEs from the polyol pathway

The Lipid Peroxidation Pathway

The lipid peroxidation pathway refers to the oxidative degradation of lipids, primarily polyunsaturated fatty acids (PUFAs), resulting from the attack of ROS such as hydroxyl radicals, superoxide anions, and peroxides on cellular membranes (Valgimigli, 2023). This chain reaction leads to the generation of lipid radicals and hydroperoxides, which can propagate further oxidative damage across cell membranes. The process compromises membrane integrity, alters cellular signaling, and disrupts metabolic homeostasis, events that collectively contribute to the biochemical manifestations of ageing and degenerative diseases (Zheng et al., 2024). Although the body possesses endogenous defense mechanisms, including antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, as well as non-enzymatic antioxidants like vitamin E and coenzyme Q10, prolonged or excessive oxidative stress can overwhelm these protective systems (Pizzino et al., 2017). The resulting accumulation of lipid peroxidation by-products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) induces secondary modifications in proteins and nucleic acids, further amplifying oxidative injury (Yang et al., 2024). Consequently, chronic lipid peroxidation represents a major biochemical pathway linking oxidative stress, AGE formation, and cellular senescence, underscoring its pivotal role in the ageing process and the pathogenesis of various chronic diseases.

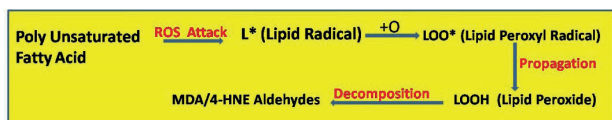


Figure 4: Formation of AGEs from the Lipid Peroxidation Pathway

MAJOR BIOLOGICALLY RELEVANT AGES IN HUMANS

Despite the extensive structural diversity of AGEs described in-vitro, pathological relevance in humans appears to be restricted to a limited subset that forms efficiently in-vivo, accumulates in tissues, and is reproducibly linked to disease. The pathogenic relevance of AGEs is determined less by their chemical diversity than by their ability to accumulate in tissues and engage RAGE-dependent signaling pathways implicated in chronic inflammation and metabolic disease (Ramasamy et al., 2005). This distinction is critical, as AGEs are not biologically interchangeable; their pathological relevance is governed by formation kinetics, chemical stability, resistance to proteolytic turnover, tissue persistence, abundance in long-lived proteins, and their ability to perturb protein structure, mechanical properties, or cellular signaling pathways (Bierhaus and Nawroth, 2009).

In human physiology and pathology, AGEs induce signaling effects through both receptor-independent mechanisms such as protein crosslinking, altered enzymatic activity, and matrix stiffening and receptor-dependent mechanisms, most notably via engagement of the receptor for advanced glycation end products (RAGE) (Ramasamy et al., 2005). The biological significance of AGEs extends beyond mere chemical detectability, encompassing their in-vivo persistence, accumulation in long-lived biomolecules, and capacity to drive functional impairment and pathology (Ramasamy et al., 2012). The AGEs discussed below are classified according to the strength of evidence supporting their accumulation, biological activity, and clinical relevance in humans.

AGEs with Established Clinical and Pathophysiological Relevance

Among the large number of chemically defined AGEs, N ϵ -(carboxymethyl)lysine (CML), N ϵ -(carboxyethyl)lysine (CEL), glucosepane, and pentosidine are the most consistently detected in human tissues and biological fluids. These species are regarded as major drivers of AGE-mediated pathology, preferentially accumulating in long-lived proteins such as collagen, elastin, lens crystallins, and basement membrane components, where limited turnover permits cumulative damage. Their formation is strongly accelerated by chronic hyperglycemia, oxidative stress, inflammation, and defective carbonyl detoxification (Sell et al., 2005). CML and CEL are non-crosslinking AGEs formed

predominantly through glycoxidative and dicarbonyl-driven pathways, respectively. CML arises from oxidative cleavage of early glycation intermediates as well as from reactions involving glyoxal, while CEL is formed primarily through modification of lysine residues by methylglyoxal (Sugawa et al., 2024). Although these AGEs do not directly crosslink proteins, they serve as robust molecular markers of carbonyl stress and are strongly associated with metabolic and degenerative disorders, including diabetes mellitus, cardiovascular disease, chronic kidney disease, and age-related tissue dysfunction. Importantly, both CML and CEL are recognized ligands for RAGE, enabling them to couple protein glycation to downstream pro-inflammatory, pro-oxidative, and pro-fibrotic signaling cascades (Khan et al., 2024).

In contrast, glucosepane and pentosidine are bifunctional crosslinking AGEs that exert profound effects on tissue biomechanics and structural integrity (Bronowicka-Szydełko et al., 2024). Glucosepane, the most abundant protein crosslink identified in human collagen, forms slowly through complex multistep reactions involving Amadori intermediates and reactive dicarbonyl species. Its exceptional chemical stability and resistance to enzymatic degradation lead to progressive accumulation with age, contributing to extracellular matrix stiffening, reduced vascular compliance, impaired cell-matrix interactions, and compromised tissue repair (Sell et al., 2005). Pentosidine, although less abundant than glucosepane, serves as a well-established fluorescent marker of cumulative glycation and oxidative stress and is frequently elevated in diabetic complications, renal failure, and inflammatory conditions (deRamon et al., 2022).

AGEs with Emerging or Context-Dependent Biological Relevance

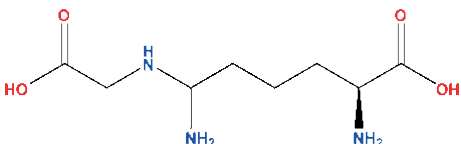
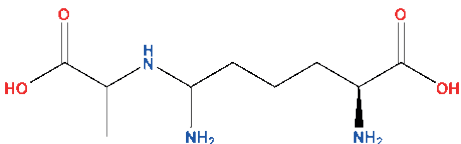
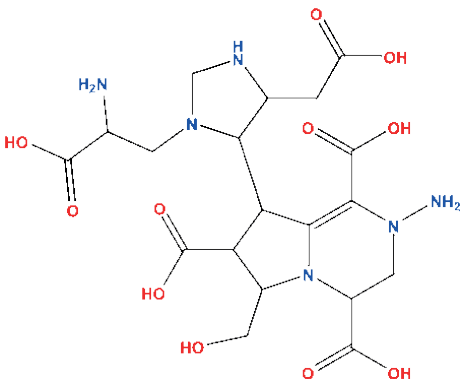
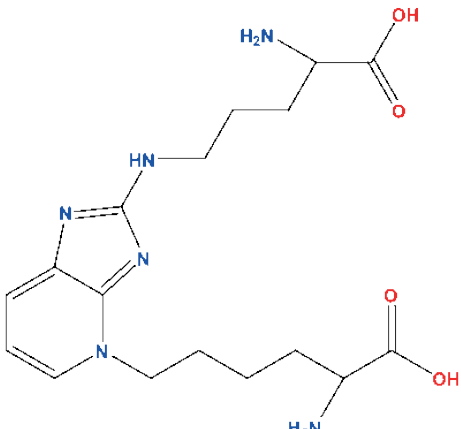
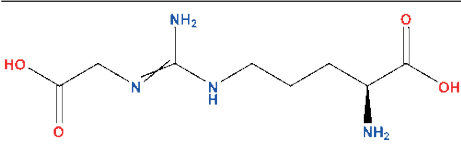
Several additional glycation products have been detected in human tissues and disease states beyond the dominant AGEs described above. These include N ϵ -(carboxymethyl)arginine (CMA), argpyrimidine, crossline, and vesperlysine. Many of these species arise preferentially under conditions of intense oxidative stress or elevated dicarbonyl flux and are often regarded as indicators of advanced glycoxidative damage rather than primary drivers of pathology (Ho et al., 2024; Lin et al., 2012). Argpyrimidine is generated through methylglyoxal-mediated modification of arginine residues and has been identified in diabetic tissues and sites of inflammation (Gomes et al., 2005). Although it can induce conformational alterations in

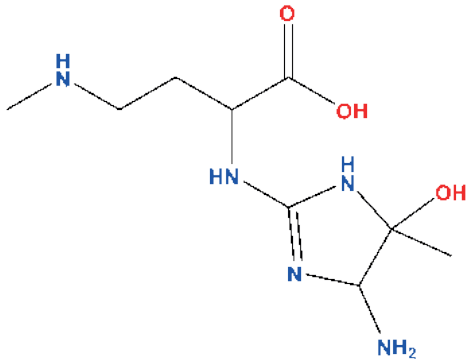
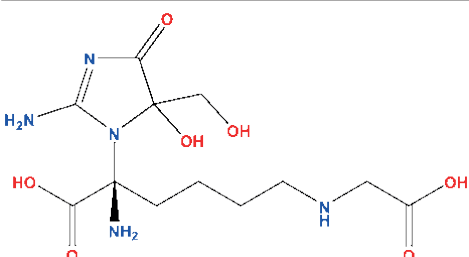
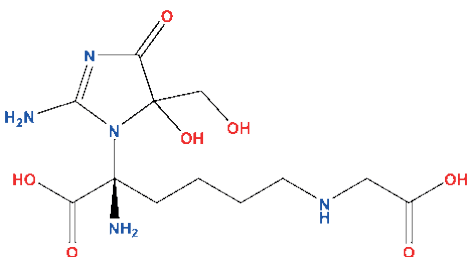
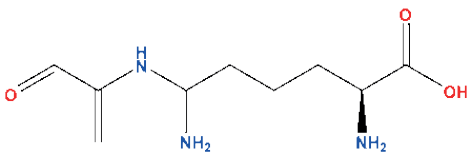
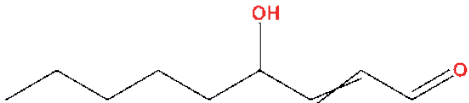
proteins and, under certain conditions, engage RAGE-dependent signaling, its comparatively low abundance suggests a limited contribution relative to dominant AGEs such as CML or glucosepane (Sadowska-Bartos and Bartosz, 2015). Likewise, crossline and vesperlysine constitute structurally elaborate crosslinking AGEs that, despite their chemical interest, occur at low levels in human tissues. Current evidence suggests that these AGEs may modulate disease processes in a context-dependent manner, potentially amplifying oxidative stress or inflammatory signaling under extreme metabolic dysregulation. However, their contribution to tissue dysfunction appears secondary to that of the dominant AGEs, and their precise roles remain incompletely defined. As such, they are best viewed as complementary markers and modulators of advanced glycation rather than central pathogenic entities (Santiago-Fernández et al., 2025).

Lipoxidation-Derived AGEs and Related Carbonyl Adducts

Reactive aldehyde-derived protein adducts, including malondialdehyde-lysine (MDA-Lys) and 4-hydroxynonenal (4-HNE) conjugates, are often discussed alongside AGEs because of their overlapping biological effects and shared roles in oxidative stress-associated pathologies. However, these adducts are generated primarily through lipid peroxidation rather than carbohydrate-mediated glycation and are therefore more appropriately classified as advanced lipoxidation end products (ALEs) (Yammine et al., 2024). ALEs contribute significantly to protein dysfunction, membrane damage, inflammation, and cellular stress responses and may interact with AGE-responsive receptors. Their formation chemistry, structural features, and biological behavior are distinct from classical sugar-derived AGEs. Conflating AGEs and ALEs risks obscuring mechanistic clarity, particularly in studies focused on carbonyl stress pathways and receptor-mediated signaling (Moldogazieva et al., 2019). Accordingly, ALEs should be regarded as parallel mediators of oxidative pathology that often coexist with AGEs in chronic disease states, rather than as core members of the AGE family in a strict biochemical sense.

Table 1: Major biologically relevant AGEs

AGE	Precursor compound(s)	Amino acids involved	Biological significance
 Nε-(Carboxymethyl)lysine (CML)	Glyoxal, Ascorbate oxidation products	Lysine	Most abundant AGE in human tissues; biomarker of oxidative stress, ageing, and diabetic complications; formed via glycoxidation and lipid peroxidation.
 Nε-(Carboxyethyl)lysine (CEL)	Methylglyoxal	Lysine	Non-crosslinking AGE; indicates methylglyoxal stress; associated with diabetes, atherosclerosis, and metabolic disorders.
 Glucosepane	3-Deoxyglucosone	Lysine + Arginine	Major protein crosslink in human collagen; accumulates in aged and diabetic tissues; increases tissue stiffness and reduces elasticity.
 Pentosidine	Ribose or Pentose sugars	Lysine + Arginine	Fluorescent crosslink AGE; biomarker for diabetic and renal complications; contributes to vascular stiffness and oxidative stress.
 Nε-(Carboxymethyl)arginine (CMA)	Glyoxylic acid	Arginine	Modifies the guanidino group of arginine; contributes to protein dysfunction and inflammatory signaling in oxidative stress conditions.

AGE	Precursor compound(s)	Amino acids involved	Biological significance
 Argpyrimidine	Methylglyoxal	Arginine	Fluorescent AGE modifying guanidino group; found in neural and vascular tissues; contributes to endothelial dysfunction and neurodegeneration.
 Crossline	Glucose	Lysine + Lysine	Fluorescent protein crosslink; promotes structural rigidity in long-lived proteins; associated with ageing and cataract formation.
 Vesperlysine A (VL-A)	Glucose or 3-deoxyglucosone	Lysine + Arginine	Fluorescent AGE isolated from aged skin collagen; contributes to tissue yellowing and oxidative damage.
 Malondialdehyde-lysine (MDA-Lys)	Malondialdehyde	Lysine	Lipid peroxidation product; forms adducts with lysine residues; marker of oxidative stress, atherosclerosis, and inflammation.
 4-hydroxynonenal (4-HNE)	PUFA oxidation	Cysteine, Lysine, Histidine	Highly reactive lipid-derived aldehyde; forms adducts with proteins; cytotoxic and pro-inflammatory; involved in neurodegeneration and chronic diseases.

RECEPTORS FOR ADVANCED GLYCATION END PRODUCTS (RAGE)

RAGE is a multifunctional cell-surface receptor belonging to the immunoglobulin superfamily, characterized by its ability to recognize and bind a wide range of structurally diverse ligands, including AGEs, S100 proteins, HMGB1, amyloid- β , and pathogen-associated molecules (Cross et al., 2024). This broad ligand recognition capacity gives RAGE a dual functional identity in both physiological and pathological contexts (Radziszewski et al., 2024). Under normal or acute conditions, ligand-induced RAGE activation supports host defense mechanisms, promotes cell survival, and facilitates tissue repair by triggering stress-response and immunomodulatory signaling pathways (Deepu et al., 2024). In contrast, chronic or dysregulated activation of RAGE sustains a persistent cycle of oxidative stress, inflammation, and metabolic imbalance, thereby contributing to the progression of metabolic disorders, vascular dysfunction, neurodegeneration, diabetes and cancer (Chandimali et al., 2025; Giridharan et al., 2021; Ramasamy et al., 2022).

RAGE exists primarily in two structural forms: the membrane-bound RAGE (mRAGE) and the soluble RAGE (sRAGE) (Adamu et al., 2024). mRAGE is the signaling-competent form responsible for mediating intracellular responses that promote cell survival, immune activation, and maintenance of tissue homeostasis during infection or injury (Watanabe and Son, 2021). Structurally, mRAGE comprises three extracellular immunoglobulin-like domains- the variable (V) domain and two constant domains (C1 and C2), followed by a single transmembrane helix and a short cytoplasmic tail essential for intracellular signal transduction (Radziszewski et al., 2024). Ligand recognition occurs predominantly in the V-domain, which contains conserved basic amino acid residues such as arginine and lysine that generate an electropositive surface, enabling strong interactions with negatively charged ligands (Ijaz et al., 2023; Olufunmilayo, et al., 2023). In contrast, sRAGE functions as a natural decoy receptor. Lacking the transmembrane and cytoplasmic domains, it consists solely of the three extracellular domains (V, C1, and C2). sRAGE binds circulating RAGE ligands, thereby preventing their interaction with mRAGE and attenuating excessive inflammation and oxidative signaling (Yue et al., 2022). It is generated through either alternative mRNA splicing or proteolytic shedding of the extracellular domain of mRAGE (Ho et al., 2024).

RAGE expression varies by cell type and developmental stage. It is highly expressed during embryogen-

esis, where it contributes to growth and differentiation, but its expression decreases significantly in adult tissues. Elevated RAGE levels in adults typically reflect pathological conditions characterized by heightened oxidative or inflammatory stress.

AGE-RAGE SIGNALING PATHWAY

The AGE-RAGE signaling pathway is initiated when AGEs interact with the RAGE, a process governed by a combination of electrostatic, hydrophobic, hydrogen-bonding, and aromatic interactions (Gutowska et al., 2023). RAGE's structural flexibility and the presence of multiple ligand-binding surfaces across its extracellular domains enable it to recognize chemically diverse ligands (Comajuncosa-Creus et al., 2024). The V-domain, in particular, provides specificity through its arrangement of basic residues while still accommodating a broad range of negatively charged or aromatic ligands (Dascalu et al., 2024). AGE-RAGE binding occurs mainly through three interaction types: (i) ionic interactions between the electropositive residues of RAGE and electronegative AGE functional groups such as carboxylates, sulfates, and phosphates; (ii) hydrogen bonding between amine or hydroxyl groups on RAGE and carbonyl groups on AGEs; and (iii) π - π and cation- π interactions involving aromatic amino acid side chains and the ring structures of AGE molecules (Stevenson et al., 2023). As AGEs accumulate with aging, particularly in long-lived macromolecules such as collagen, these carbonyl-rich structures increasingly engage RAGE and initiate downstream signaling (Wang et al., 2024). Central to this pathway are the activation of NADPH oxidase and the amplification of protein glycooxidation.

Upregulation of NADPH Oxidase

NADPH oxidase (NOX) is a membrane-associated enzyme complex responsible for controlled production of reactive oxygen species (ROS) in physiological signaling (Schröder, 2024). AGE-RAGE engagement activates NOX, triggering electron transfer from NADPH to molecular oxygen. Electrons released from the nicotinamide ring of NADPH as a hydride ion (H^-) are relayed through the NOX complex to oxygen, producing superoxide radicals ($O_2^{\bullet-}$) and subsequently other ROS such as hydroxyl radicals ($\bullet OH$) (Liu et al., 2025; Bastos et al., 2025). Iron ions in the labile iron pool further amplify ROS production via Fenton chemistry (Jomova et al., 2023). The resulting oxidative burst drives lipid peroxidation, protein oxidation, and DNA damage. Lipid per-

oxides weaken membrane integrity and decompose into toxic aldehydes including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which further propagate oxidative injury (Zhao et al., 2023). Oxidized proteins accumulate disulfides and sulfonic acids, leading to misfolding, aggregation, and loss of enzymatic function. DNA oxidation, particularly the formation of 8-oxo-2'-deoxyguanosine, promotes mutagenic mispairing, mitochondrial dysfunction, and impaired genomic repair which are hallmarks of aging and degenerative pathology (Zhao et al., 2023).

Protein Glycooxidation and Cross-Linking

AGE-RAGE activation also accelerates protein glycooxidation, promoting the formation of irreversible crosslinks in long-lived extracellular matrix proteins such as collagen and elastin. Major AGE-derived crosslinks including pentosidine, methylglyoxal-derived hydroimidazolone (MG-H1), and glucosepane, accumulate progressively and stiffen tissue structures (Meiliana et al., 2024). Binding of AGEs to RAGE induces conformational changes that trigger a redox-sensitive intracellular cascade (Nair et al., 2019). Elevated ROS levels enhance the formation of new AGEs, establishing a self-amplifying loop in which oxidative stress increases glycation, and glycation increases oxidative stress (Peng et al., 2024). Over time, this feedback cycle leads to persistent RAGE activation, extensive crosslinking of extracellular matrix proteins, reduced molecular mobility, and disruption of normal receptor-ligand dynamics. These processes contribute to the structural deterioration and functional decline characteristic of aging tissues (Benigni et al., 2024).

MECHANISM OF AGE-RAGE AXIS INHIBITION

Inhibition of the AGE-RAGE axis focuses on two complementary strategies: reducing the endogenous formation of AGEs and preventing the interaction of existing AGEs with the RAGE (Semchyshyn, 2024). The central goal is to either neutralize reactive glycation intermediates before they generate AGEs or to sequester AGEs in forms that render them incapable of binding to RAGE. Interventions targeting AGE formation generally act through carbonyl trapping, free radical scavenging, and metal chelation, three mechanistic pathways that collectively limit glycooxidative stress in biological systems (Yadav et al., 2023). From an anti-ageing perspective, these strategies tackle a key upstream knowledge gap by showing that AGE accumulation is not an una-

voidable outcome of ageing, but a process amenable to chemical modulation. Elucidating the molecular mechanisms by which AGE formation can be suppressed establishes a rational basis for interventions aimed at decelerating the underlying biochemical drivers of ageing, rather than simply managing its downstream manifestations.

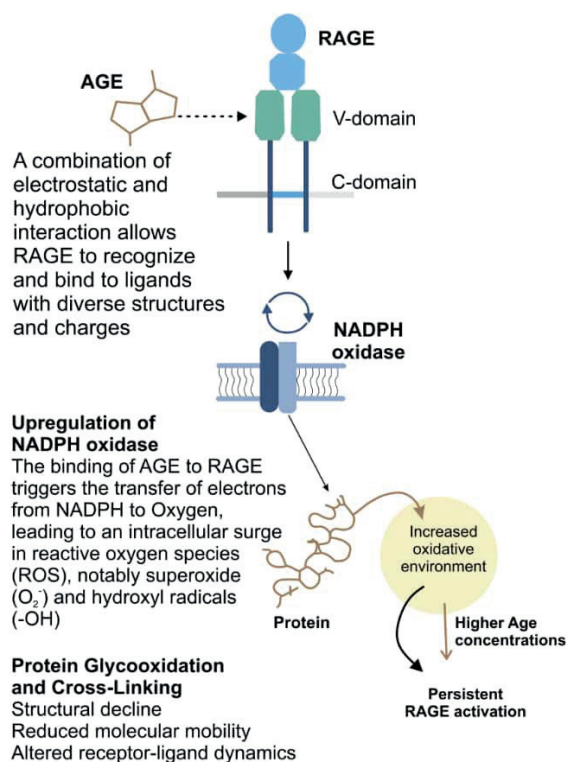


Figure 5: The AGE-RAGE axis describes the interaction between accumulated advanced glycation end products and their cellular receptor, RAGE, triggering oxidative stress and pro-inflammatory signaling. This interaction creates a self-amplifying loop that promotes chronic inflammation, vascular dysfunction, and tissue degeneration

Carbonyl Trapping

Carbonyl trapping is a frontline defense against AGE formation because it directly intercepts the highly reactive carbonyl electrophiles particularly dicarbonyl compounds and methylglyoxal that drive early Maillard chemistry. These carbonyl species readily attack nucleophilic amino acid residues such as lysine and arginine, initiating irreversible AGE formation. Carbonyl trapping agents contain nucleophilic functional groups that rapidly react with these dicarbonyl intermediates to form chemically stable, non-toxic adducts, effectively neutral-

izing the glycation potential of the intermediates (Uceda et al., 2024b). By preventing carbonyl–protein interactions, this mechanism interrupts the Maillard reaction at its early stages, maintaining the integrity of free amino groups and substantially reducing downstream AGE accumulation (Hidalgo and Zamora, 2023). This mechanistic insight addresses a critical research gap by demonstrating that early chemical interception of glycation intermediates can preserve protein integrity and retard the progressive structural deterioration of long-lived biomolecules that drive tissue ageing.

Free Radical Scavenging

Oxidative stress accelerates glycoxidation reactions and amplifies AGE production. Antioxidants counteract this process by donating electrons or hydrogen atoms to neutralize reactive oxygen species (ROS), thereby suppressing oxidative pathways that promote AGE formation. Polyphenols, particularly those enriched with hydroxyl-substituted aromatic rings, serve as highly effective free radical scavengers due to their ability to stabilize unpaired electrons and terminate radical propagation chains (Andrés et al., 2023). By reducing ROS levels, antioxidants lower glycoxidative pressure on proteins and lipids, creating a biochemical environment less conducive to AGE generation and RAGE activation. Importantly, this reinforces the concept that oxidative stress is not only a parallel ageing pathway but a catalytic accelerator of AGE–RAGE signaling, thereby positioning antioxidant modulation as a strategic lever in slowing ageing-related molecular damage.

Metal Chelation

Transition metals such as Fe^{2+} and Cu^{2+} catalyze oxidative steps in the Maillard reaction through Fenton-type reactions that generate hydroxyl radicals. Metal chelators inhibit AGE formation by binding these catalytic metal ions through electron-donating atoms especially oxygen or nitrogen, forming stable, inert complexes that prevent metal-mediated oxidation (Ohiagu et al., 2025). Compounds with ortho-dihydroxy ($-\text{OH}$) functional groups or phenolic structures bearing carboxylic acid substituents exhibit strong chelating capacity and effectively suppress metal-induced glycation (Lee et al., 2023). This mechanism complements antioxidant and carbonyl-trapping pathways by targeting a different but critical driver of glycoxidative stress.

MODULATING THE AGE–RAGE SIGNALING

Blocking the AGE–RAGE axis focuses on preventing the physical interaction between AGEs and their cellular receptor, RAGE, thereby suppressing downstream oxidative and inflammatory signaling. This strategy primarily involves the use of molecules that competitively occupy the ligand-binding pocket of RAGE, mimicking structural or chemical features of AGE ligands. Binding occurs through a combination of hydrogen bonding, ionic interactions, van der Waals forces, and hydrophobic effects that stabilize inhibitor–receptor interactions within the RAGE V-domain (Khateri et al., 2024). Among promising inhibitors, sulfonated flavonoid derivatives such as sulfoquercetin demonstrate significantly enhanced affinity for RAGE. Their negatively charged sulfonate and carboxylate groups form strong ionic interactions with conserved cationic residues (e.g., Arg and Lys) within the electropositive binding surface of the V-domain. These electrostatic interactions (Table 2) are complemented by the ability of flavonoid aromatic rings to engage in π – π stacking and cation– π interactions with the aromatic amino acids in RAGE, further stabilizing the ligand–receptor complex (Arellanes-Lozada et al., 2023).

In addition to ionic and aromatic interactions, many synthetic inhibitors are specifically designed to fit into the non-polar hydrophobic pockets of the receptor. Occupation of these pockets enhances binding affinity by reducing solvent exposure and maximizing van der Waals contacts. Because the V-domain possesses several hydrophobic and aromatic residues, these inhibitors can effectively outcompete endogenous AGEs for binding, thereby preventing receptor activation. Another important strategy for modulating AGE–RAGE signaling is the use of soluble RAGE (sRAGE) as a circulating decoy receptor. Although sRAGE does not inhibit the binding of AGEs to membrane-bound RAGE (mRAGE) directly, it reduces AGE–RAGE signaling by sequestering AGEs in the extracellular environment (Reddy et al., 2023). Unlike mRAGE, sRAGE lacks the transmembrane segment and the intracellular cytoplasmic tail required for signal transduction, meaning that AGE binding to sRAGE does not initiate downstream inflammatory or oxidative pathways (Rojas et al., 2024). Therefore, elevated levels of sRAGE serve a protective role by limiting the availability of AGEs for interaction with mRAGE. This underscores the fact that ageing-related inflammation and oxidative stress are not passive consequences of molecular damage but are actively sustained by ligand–receptor signaling, which is amenable to pharmacological modulation.

Table 2: Reactive Groups Involved in AGE–RAGE Complex Formation

RAGE (V-domain)	Functional Groups	Properties
Arginine	Guanidinium group	Strongly basic, cationic at pH 7.4
Lysine	ε-Amino group	Basic, cationic at pH 7.4
Serine, Threonine	–OH groups	H-bond donors/acceptors
Tyrosine, Phe	Aromatic rings	π–π stacking sites
AGEs	Functional Groups	Properties
Carboxymethyllysine	–COOH	Negatively charged
Pyrraline, MG-H1	Imidazole, carbonyls	H-bonding, polar
Crosslinked AGEs	Dicarbonyl bridges	Reactive, electrophilic

PHYTOCHEMICAL MODULATION OF THE AGE–RAGE PATHWAY

The interaction between AGEs and their cognate receptor (RAGE) constitutes a pivotal molecular nexus that amplifies oxidative stress, inflammation, and cumulative tissue injury across numerous metabolic, vascular, and age-associated pathologies. Engagement of RAGE by structurally diverse AGEs triggers a cascade of intracellular events including ROS overproduction, NF-κB activation, cytokine release, and sustained feedback upregulation of RAGE itself that perpetuate a chronic pro-oxidant and pro-inflammatory milieu. This self-reinforcing loop is now recognized as a central driver of diabetic complications, neurodegeneration, renal fibrosis, endothelial dysfunction, and accelerated biological ageing. Despite growing recognition of this axis, a critical gap remains in translating chemical insights into safe, long-term anti-ageing interventions capable of modulating AGE–RAGE signaling without adverse effects.

Amid growing global interest in safer, naturally derived therapeutic candidates, phytochemicals especially polyphenols, alkaloids, and tannins have gained prominence for their capacity to modulate key biochemical determinants of glycoxidative stress (Montserrat Corona-España et al., 2024). These plant-derived metabolites operate through multilayered and complementary mechanisms, making them uniquely suited for targeting the complex molecular architecture of the AGE–RAGE axis.

Polyphenols

Chemically, polyphenols are defined by aromatic ring systems bearing multiple hydroxyl (–OH) substituents, a structural arrangement that confers pronounced redox activity through facile electron and hydrogen atom donation. Representative compounds such as quercetin, catechin, and resveratrol possess conjugated π-electron systems and phenolic hydroxyl groups making them able to stabilize radical intermediates, thus underpinning their widely reported antioxidant effects. In in-vitro chemical and cell-free assays, these polyphenols efficiently scavenge reactive oxygen species and inhibit lipid peroxidation at low micromolar concentrations (typically 1–50 μM), while ortho- and para-dihydroxyl motifs enable chelation of redox-active transition metals (e.g., Fe²⁺, Cu²⁺), limiting Fenton-type radical generation (Láng et al., 2024).

In cellular models, polyphenols demonstrate additional redox-dependent modulation of signaling pathways, though these effects are concentration-sensitive and context-dependent. Quercetin and catechin have been reported to suppress activation of redox-sensitive transcription factors such as NF-κB and AP-1 in inflammatory cell lines, typically at concentrations ≥10 μM, while resveratrol modulates AMPK- and sirtuin-associated pathways involved in metabolic stress responses (Lee et al., 2023; Ravindranath and Ravindranath, 2011; Wu et al., 2011). Importantly, these cellular responses are frequently accompanied by demonstrable decreases in intracellular oxidative stress, indicating that the observed modulation of signaling pathways is largely a downstream consequence of antioxidant action rather than the result of specific high-affinity receptor–ligand interactions (Terao, 2023). Evidence from in-vivo animal models supports a broader biological impact of polyphenols but also highlights pharmacokinetic constraints. Oral administration of quercetin, catechin, or resveratrol in rodents (commonly 10–100 mg/kg/day) reduces systemic markers of oxidative stress, inflammation, and microbial burden in disease models characterized by redox imbalance (Alharbi et al., 2025; Navarro-Cruz et al., 2024). These effects likely arise from the combined contribution of the parent compounds and their circulating metabolites, some of which may preserve residual antioxidant or metal-chelating activity. However, extensive biotransformation, rapid systemic elimination, and restricted tissue distribution substantially hinder straightforward translation of animal dosing outcomes to human therapeutic settings. Human data remain comparatively limited and largely indirect. While epidemiological and short-term intervention studies asso-

ciate polyphenol-rich diets with reduced oxidative and inflammatory biomarkers, plasma concentrations of unmetabolized polyphenols typically remain in the low nanomolar to submicromolar range. At these levels, direct radical scavenging is unlikely to be the dominant mechanism, implying that long-term modulation of redox homeostasis may arise from cumulative, metabolite-driven, or adaptive biological responses rather than acute antioxidant chemistry.

Alkaloids

Alkaloids characterized by the presence of nitrogen-containing heterocyclic rings, a feature that imparts basicity, electronic density, and a strong propensity for interaction with biological macromolecules. This chemical architecture distinguishes alkaloids from polyphenols and underlies their characteristic high-affinity binding to enzymes, nucleic acids, and neurotransmitter receptors. Representative compounds such as berberine, morphine, and caffeine illustrate the functional diversity of this class, spanning planar aromatic cations, rigid polycyclic scaffolds, and methylxanthine systems. These structural features enable alkaloids to engage biological targets primarily through π - π stacking, hydrogen bonding, electrostatic interactions, and intercalation-like behavior, rather than through direct redox chemistry (Srivastava and Singh, 2020). In *in-vitro* systems, alkaloids act as potent enzyme and receptor modulators, often at low micromolar or submicromolar concentrations. Berberine inhibits a range of enzymes involved in glucose metabolism, oxidative stress regulation, and inflammatory signaling, while also demonstrating affinity for DNA through groove binding and partial intercalation, leading to altered transcriptional activity (Zych et al., 2020). Caffeine, in contrast, exerts weaker direct enzyme inhibition but efficiently antagonizes adenosine receptors and modulates phosphodiesterase activity at higher micromolar concentrations (Pohanka and Dobes, 2013). Morphine shows limited enzyme inhibition but exhibits strong, selective binding to opioid receptors, highlighting that alkaloid bioactivity is dictated more by target specificity than by shared chemical reactivity. Antimicrobial effects observed in cell-free and microbial assays are frequently linked to enzyme inhibition or disruption of nucleic acid function rather than nonspecific cytotoxicity.

In cellular models, alkaloids predominantly exert indirect biological effects mediated by enzyme inhibition and receptor engagement, rather than direct scavenging of reactive species (García-Muñoz et al., 2024). Berberine suppresses inflammatory and metabolic signaling cascades by inhibiting kinases and transcriptional

regulators downstream of enzyme-controlled pathways, while caffeine alters intracellular signaling by modulating cyclic nucleotide turnover and neurotransmitter receptor activity. These effects are typically observed at concentrations ranging from 5–50 μ M, although sensitivity varies widely depending on cell type and target expression. Importantly, alkaloids often influence multiple signaling nodes simultaneously, reflecting their ability to interact with conserved structural motifs across different proteins (Jiang et al., 2024). Evidence from *in-vivo* studies confirm that alkaloids function as systemic modulators of metabolic and neural signaling with attendant pharmacokinetic constraints. Berberine administration in rodents (commonly 50–150 mg/kg/day) improves metabolic parameters, reduces inflammatory mediators, and indirectly attenuates oxidative and glycoxidative stress, effects attributed to enzyme inhibition and altered signaling rather than direct antioxidant activity (Ai et al., 2021). Caffeine, at physiologically relevant doses, exerts well-characterized neurostimulatory and metabolic effects through central and peripheral receptor modulation (Song et al., 2024b). Human data reinforce the view that alkaloids are pharmacologically potent but mechanistically selective agents.

Tannins

Tannins represent a structurally distinct subgroup of polyphenols defined by highly polymeric phenolic frameworks bearing dense arrays of hydroxyl (–OH) groups, thus making them excellent candidates for metal ion coordination and macromolecular binding. Representative compounds include tannic acid, gallotannins, and ellagitannins, whose multiple galloyl or hexahydroxydiphenoyl units generate multidentate binding sites unavailable to low-molecular-weight phenolics. This chemical architecture underlies the characteristic astringency of tannins and distinguishes their mode of action from monomeric antioxidants (Cosme et al., 2025). In *in-vitro* chemical and cell-free systems, tannins exhibit the strongest metal-chelating and protein-binding capacity among plant phenolics, forming stable complexes with transition metals such as Fe^{2+} and Cu^{2+} at low micromolar concentrations. Through this mechanism, tannins effectively suppress metal-catalyzed redox cycling and hydroxyl radical generation, providing potent protection against oxidative damage. Concurrently, their ability to precipitate proteins through hydrogen bonding and hydrophobic interactions disrupts enzyme activity and structural protein function. These effects are robust and reproducible in simplified systems and are directly attributable to tannin polymer size and hydroxyl density rather than to specific receptor interactions (Karamać, 2009).

In cellular and microbial models, tannins demonstrate broad antioxidant, antimicrobial, and anti-inflammatory activity, though these effects are largely indirect and context-dependent. Antioxidant activity in cells is primarily linked to extracellular or membrane-proximal metal sequestration rather than intracellular radical scavenging, as the large molecular size of tannins limits passive cellular uptake (Camarda et al., 2026). Antimicrobial effects are consistently observed *in-vitro*, and are mediated through protein complexation at the microbial cell surface, enzyme inhibition, and disruption of membrane-associated processes. However, these same protein-binding properties can reduce selectivity and complicate mechanistic interpretation in complex biological systems. Studies on animals support a protective role of tannins against oxidative and microbial damage, particularly in gastrointestinal and inflammatory models. Dietary tannins and tannin-rich extracts reduce oxidative stress markers, inflammatory cytokines, and microbial burden in rodents, effects often attributed to local actions within the gut lumen and mucosal interface (Huang et al., 2018). Importantly, intact tannins show limited systemic bioavailability due to poor absorption and extensive interaction with dietary proteins and gut microbiota. As a result, biological effects observed *in-vivo* are increasingly understood to involve microbial metabolites (e.g., urolithins from ellagitannins) rather than the parent polymers (Cosme et al., 2025). Accordingly, while tannins display strong mechanistic potential as modulators of glycoxidative stress, direct extrapolation to human AGE-RAGE inhibition remains unclear. Their contribution is more plausibly interpreted as indirect modulation of oxidative and inflammatory tone rather than as direct systemic AGE inhibitors, further highlighting the need for metabolite-focused and tissue-level investigations.

Table 3: Bioactive attributes of polyphenols, alkaloids, and tannins in oxidative/glycoxidative stress

Feature	Polyphenols	Alkaloids	Tannins
Basic Structure	Aromatic rings with multiple hydroxyl (-OH) groups	Nitrogen-containing heterocyclic rings	Polymeric phenolic structures with multiple hydroxyl groups
Representative Compounds	Quercetin, Catechin, Resveratrol	Berberine, Morphine, Caffeine	Tannic acid, Gallotannins, Ellagitannins
Major Mechanism of Action	Electron/hydrogen donation; free radical scavenging; metal chelation	Enzyme and receptor binding; interference with DNA and proteins	Metal ion complexation; protein precipitation; ROS suppression

Feature	Polyphenols	Alkaloids	Tannins
Primary Biological Activities	Antioxidant, anti-inflammatory, antimicrobial	Neuroactive, antimicrobial, enzyme inhibitory	Antioxidant, antimicrobial, anti-inflammatory, anticarcinogenic
Dominant Molecular Target	ROS/RNS; transition metals	Enzymes, DNA, neurotransmitter receptors	Transition metals (Fe ²⁺ , Cu ²⁺); microbial proteins
Mode of Antioxidant Defense	Radical scavenging and redox cycling	Indirect modulation via enzyme inhibition	Metal sequestration and protein complexation
Comparative Strength	Strong direct antioxidant and redox modulator	Potent enzyme/receptor modulator	Strongest chelating and protein-binding capacity
Biological Niche	Protection against oxidative stress and inflammation	Regulation of metabolic and neural signaling	Prevention of oxidative and microbial damage

MECHANISTIC GAPS IN AGE-RAGE INTERACTIONS AND COMPUTATIONAL PERSPECTIVES IN DRUG DISCOVERY

Although diverse mechanisms have been elucidated regarding the indirect modulation of AGE toxicity, no phytochemical has yet been conclusively demonstrated to directly block the interaction between AGEs and RAGE. Existing evidence suggests that these compounds primarily modulate upstream processes (e.g., inhibition of AGE formation, carbonyl scavenging) or downstream signaling pathways (e.g., suppression of ROS generation and inflammatory cytokines) rather than interacting at the receptor binding interface itself (Ceramella et al., 2024). This represents a notable gap in our pharmacological understanding, underscoring the need for targeted receptor-level investigations. Current computational approaches can provide a powerful strategy for exploring the potential of phytochemicals as direct RAGE antagonists. In-silico tools such as molecular docking, molecular dynamics (MD) simulations, and pharmacophore modeling can offer detailed insights into ligand-receptor interactions at the atomic scale. Docking studies focusing on the VC1 domain of RAGE, the principal region involved in AGE recognition can reveal, binding affinities of phytochemicals, hydrogen bonding patterns, π - π and cation- π interactions with aromatic and basic residues, as well as structural compatibility and stability within the RAGE binding pocket. Such computational explorations have been implemented to assess phytochemicals and synthetic ligands (Ouamnina et al.,

2024; (Ouamnina et al., 2024; Ikezu et al., 2025; Nwofor et al., 2025). Incorporating MD simulations further enables the evaluation of complex stability, ligand-induced conformational changes, and solvent dynamics over time.

For computational predictions to achieve biological relevance, they must be validated through complementary experimental assays such as fluorescence quenching to measure RAGE–ligand interactions, surface plasmon resonance (SPR) for real-time affinity quantification, and isothermal titration calorimetry (ITC) to determine thermodynamic parameters. Such integrated validation would substantially advance the search for natural AGE–RAGE antagonists.

CONCLUSION

A growing body of evidence underscores the AGE–RAGE axis as a central biochemical driver of oxidative stress, chronic inflammation, and degenerative pathology across multiple organ systems. Its involvement in metabolic dysfunction, vascular remodeling, neurodegeneration, and tissue ageing highlights the pathway as a critical, modifiable node in disease progression. Despite significant advances in elucidating AGE formation routes, RAGE structural biology, and downstream redox-sensitive signaling, substantial mechanistic gaps remain particularly regarding ligand specificity, receptor dynamics, and the interplay between glycooxidation, lipid peroxidation, and cellular stress responses. Addressing these gaps will require integrated chemical, biochemical, and computational approaches capable of resolving molecular events with higher precision. Continued exploration of both endogenous defense mechanisms and exogenous modulators will be essential for developing safe, effective therapeutic strategies that interrupt AGE accumulation, dampen RAGE-mediated signaling, and ultimately mitigate the molecular processes that underpin ageing and degenerative disease.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

All authors have read and agreed to the published version of the manuscript.

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Ikechukwu Obinna Achinihu: Investigation, Writing original draft, Editing.

Chidi Edbert Duru: Conceptualization, Methodology, Data curation, Review.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

- Adamu, A., Li, S., Gao, F., & Xue, G. (2024). The role of neuroinflammation in neurodegenerative diseases: Current understanding and future therapeutic targets. *Frontiers in Aging Neuroscience*, 16, 1347987. <https://doi.org/10.3389/fnagi.2024.1347987>
- Ai, X., Yu, P., Peng, L., Luo, L., Liu, J., Li, S., Lai, X., Luan, F., & Meng, X. (2021). Berberine: A review of its pharmacokinetics properties and therapeutic potentials in diverse vascular diseases. *Frontiers in Pharmacology*, 12, 762654. <https://doi.org/10.3389/fphar.2021.762654>
- Al-Abbasy, O. Y., Younus, S. A., Rashan, A. I., & Sheej Ahmad, O. A. (2024). Maillard reaction: Formation, advantage, disadvantage and control. A review. *Food Science and Applied Biotechnology*, 7(1), 145. <https://doi.org/10.30721/fsab2024.v7.i1.333>
- Alharbi, H. O. A., Alshebremi, M., Babiker, A. Y., & Rahmani, A. H. (2025). The role of quercetin, a flavonoid in the management of pathogenesis through regulation of oxidative stress, inflammation, and biological activities. *Biomolecules*, 15(1), 151. <https://doi.org/10.3390/biom15010151>
- Andrés, C. M. C., Pérez De La Lastra, J. M., Andrés Juan, C., Plou, F. J., & Pérez-Lebeña, E. (2023). Polyphenols as antioxidant/pro-oxidant compounds and donors of reducing species: Relationship with human antioxidant metabolism. *Processes*, 11(9), 2771. <https://doi.org/10.3390/pr11092771>
- Arellanes-Lozada, P., Hernández-Cocoletzi, H., Lijanová, I. V., Olivares-Cuapa, J. C., Olivares-Cuapa, J. M., Calvillo-Muñoz, E. Y., & Likhanova, N. V. (2023). Effect of sulfonate anions on the performance of triethylmethylammonium-derived ionic liquids as corrosion inhibitors. *Journal of Adhesion Science and*

- Technology*, 37(18), 2642–2666. <https://doi.org/10.1080/01694243.2022.2163843>
- Bastos, K. V. L. da S., De Souza, A. B., Tomé, A. C., & De Moura Souza, F. (2025). New strategies for the extraction of antioxidants from fruits and their by-products: A systematic review. *Plants*, 14(5), 755. <https://doi.org/10.3390/plants14050755>
- Bennici, G., Almahasheer, H., Alghrably, M., Valensin, D., Kola, A., Kokotidou, C., Lachowicz, J., & Jaremko, M. (2024). Mitigating diabetes associated with reactive oxygen species (ROS) and protein aggregation through pharmacological interventions. *RSC Advances*, 14(25), 17448–17460. <https://doi.org/10.1039/D4RA02349H>
- Bierhaus, A., & Nawroth, P. P. (2009). Multiple levels of regulation determine the role of the receptor for AGE (RAGE) as common soil in inflammation, immune responses and diabetes mellitus and its complications. *Diabetologia*, 52(11), 2251–2263. <https://doi.org/10.1007/s00125-009-1458-9>
- Blouin, T., & Saini, N. (2024). Aldehyde-induced DNA-protein crosslinks—DNA damage, repair and mutagenesis. *Frontiers in Oncology*, 14, 1478373. <https://doi.org/10.3389/fonc.2024.1478373>
- Bronowicka-Szydelko, A., Gostomska-Pampuch, K., Kuzan, A., Pietkiewicz, J., Krzystek-Korpacka, M., & Gamian, A. (2024). Effect of advanced glycation end-products in a wide range of medical problems including COVID-19. *Advances in Medical Sciences*, 69(1), 36–50. <https://doi.org/10.1016/j.advms.2024.01.003>
- Byun, K., Yoo, Y., Son, M., Lee, J., Jeong, G.-B., Park, Y. M., Salekdeh, G. H., & Lee, B. (2017). Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases. *Pharmacology & Therapeutics*, 177, 44–55. <https://doi.org/10.1016/j.pharmthera.2017.02.030>
- Camarda, L., Budriesi, R., Corazza, I., Frosini, M., Marzetti, C., & Mattioli, L. B. (2026). Antioxidant and health-related effects of tannins: From agri-food by-products to human and animal health. *Antioxidants*, 15(1), 104. <https://doi.org/10.3390/antiox15010104>
- Ceramella, J., De Maio, A. C., Basile, G., Facente, A., Scali, E., Andreu, I., Sinicropi, M. S., Iacopetta, D., & Catalano, A. (2024). Phytochemicals involved in mitigating silent toxicity induced by heavy metals. *Foods*, 13(7), 978. <https://doi.org/10.3390/foods13070978>
- Chandimali, N., Bak, S. G., Park, E. H., Lim, H.-J., Won, Y.-S., Kim, E.-K., Park, S.-I., & Lee, S. J. (2025). Free radicals and their impact on health and antioxidant defenses: A review. *Cell Death Discovery*, 11(1), 19. <https://doi.org/10.1038/s41420-024-02278-8>
- Chen, Q. (2024). Neurobiological and anti-aging benefits of yoga: A comprehensive review of recent advances in non-pharmacological therapy. *Experimental Gerontology*, 196, 112550. <https://doi.org/10.1016/j.exger.2024.112550>
- Chen, Y., Meng, Z., Li, Y., Liu, S., Hu, P., & Luo, E. (2024). Advanced glycation end products and reactive oxygen species: Uncovering the potential role of ferroptosis in diabetic complications. *Molecular Medicine*, 30(1), 141. <https://doi.org/10.1186/s10020-024-00905-9>
- Choi, J. Y., Ha, N. G., Lee, W. J., & Boo, Y. C. (2025). Synthetic and natural agents targeting advanced glycation end-products for skin anti-aging: A comprehensive review of experimental and clinical studies. *Antioxidants*, 14(4), 498. <https://doi.org/10.3390/antiox14040498>
- Clarke, D. M., Koutnik, A. P., Johnson, R. J., DeBlasi, J. M., Bikman, B. T., Arroyo, J. A., & Reynolds, P. R. (2024). Differential rates of glycation following exposure to unique monosaccharides. *International Journal of Molecular Sciences*, 25(13), 6921. <https://doi.org/10.3390/ijms25136921>
- Comajuncosa-Creus, A., Jorba, G., Barril, X., & Aloy, P. (2024). Comprehensive detection and characterization of human druggable pockets through binding site descriptors. *Nature Communications*, 15(1), 7917. <https://doi.org/10.1038/s41467-024-52146-3>
- Cosme, F., Aires, A., Pinto, T., Oliveira, I., Vilela, A., & Gonçalves, B. (2025). A comprehensive review of bioactive tannins in foods and beverages: Functional properties, health benefits, and sensory qualities. *Molecules*, 30(4), 800. <https://doi.org/10.3390/molecules30040800>
- Cross, K., Vetter, S. W., Alam, Y., Hasan, M. Z., Nath, A. D., & Leclerc, E. (2024). Role of the receptor for advanced glycation end products (RAGE) and its ligands in inflammatory responses. *Biomolecules*, 14(12), 1550. <https://doi.org/10.3390/biom14121550>
- Dascalu, A.-E., Furman, C., Landrieu, I., Cantrelle, F.-X., Morteletque, J., Grolaux, G., Gillery, P., Tessier, F., Lipka, E., Billamboz, M., Boulanger, E., & Ghinet, A. (2024). Development of receptor for advanced glycation end products (RAGE) ligands through target directed dynamic combinatorial chemistry: A novel class of possible antagonists. *Chemistry – A European Journal*, 30(20), e202303255. <https://doi.org/10.1002/chem.202303255>
- Dash, U. C., Bhol, N. K., Swain, S. K., Samal, R. R., Nayak, P. K., Raina, V., Panda, S. K., Kerry, R. G., Duttaroy, A. K., & Jena, A. B. (2025). Oxidative stress and inflammation in the pathogenesis of neurologi-

- cal disorders: Mechanisms and implications. *Acta Pharmaceutica Sinica B*, 15(1), 15–34. <https://doi.org/10.1016/j.apsb.2024.10.004>
- Deepu, V., Rai, V., & Agrawal, D. K. (2024). Quantitative assessment of intracellular effectors and cellular response in RAGE activation. *Archives of Internal Medicine Research*, 07(02). <https://doi.org/10.26502/aimr.0168>
- Delannoy, Peter, Dean R. Tolan, Miguel A. Lanaspá, Iñigo San Millán, So Young Bae, and Richard J. Johnson. 2025. “Aldose Reductase, Fructose and Fat Production in the Liver.” *Biochemical Journal* 482(05):295–307. doi:10.1042/BCJ20240748.
- deRamon, Edward A., Venkata R. Sabbasani, Matthew D. Streeter, Yannan Liu, Timothy R. Newhouse, David M. McDonald, and David A. Spiegel. 2022. “Pentosinane, a Post-Translational Modification of Human Proteins with Underappreciated Stability.” *Journal of the American Chemical Society* 144(48):21843–47. doi:10.1021/jacs.2c09626.
- El Hosry, Leina, Vanessa Elias, Vanessa Chamoun, Malda Halawi, Philippe Cayot, Anthony Nehme, and Elias Bou-Maroun. 2025. “Maillard Reaction: Mechanism, Influencing Parameters, Advantages, Disadvantages, and Food Industrial Applications: A Review.” *Foods* 14(11):1881. doi:10.3390/foods14111881.
- Feng, Chao, Xianglong Chen, Xiuqing Yin, Yanfei Jiang, and Chunyue Zhao. 2024. “Matrix Metalloproteinases on Skin Photoaging.” *Journal of Cosmetic Dermatology* 23(12):3847–62. doi:10.1111/jocd.16558.
- García-Muñoz, Ana María, Desirée Victoria-Montesinos, Pura Ballester, Begoña Cerdá, and Pilar Zafrilla. 2024. “A Descriptive Review of the Antioxidant Effects and Mechanisms of Action of Berberine and Silymarin.” *Molecules* 29(19):4576. doi:10.3390/molecules29194576.
- Giridharan, Vijayasree V., Jaqueline S. Generoso, Allan Collodel, Diogo Domingui, Cristiano Julio Faller, Flavio Tardin, Gursimrat S. Bhatti, Fabricia Petronilho, Felipe Dal-Pizzol, and Tatiana Barichello. 2021. “Receptor for Advanced Glycation End Products (RAGE) Mediates Cognitive Impairment Triggered by Pneumococcal Meningitis.” *Neurotherapeutics* 18(1):640–53. doi:10.1007/s13311-020-00917-3.
- Gomes, Ricardo, Marta Sousa Silva, Alexandre Quintas, Carlos Cordeiro, António Freire, Paulino Pereira, Américo Martins, Estela Monteiro, Eduardo Barroso, and Ana Ponces Freire. 2005. “Argpyrimidine, a Methylglyoxal-Derived Advanced Glycation End-Product in Familial Amyloidotic Polyneuropathy.” *Biochemical Journal* 385(2):339–45. doi:10.1042/BJ20040833.
- Gulcin, İlhami. 2025. “Antioxidants: A Comprehensive Review.” *Archives of Toxicology* 99(5):1893–1997. doi:10.1007/s00204-025-03997-2.
- Gutowska, Klaudia, Krzysztof Czajkowski, and Alina Kuryłowicz. 2023. “Receptor for the Advanced Glycation End Products (RAGE) Pathway in Adipose Tissue Metabolism.” *International Journal of Molecular Sciences* 24(13):10982. doi:10.3390/ijms241310982.
- Hidalgo, Francisco J., and Rosario Zamora. 2023. “Carbonyl-Trapping by Phenolics and the Inhibition of the Formation of Carcinogenic Heterocyclic Aromatic Amines with the Structure of Aminoimidazoazaarene in Beef Patties.” *Food Chemistry* 425:136505. doi:10.1016/j.foodchem.2023.136505.
- Ho, Keat Lam, Phaik Har Yong, Chee Woon Wang, Siew Huah Lim, Umah Rani Kuppasamy, Bavani Arumugam, Chek Tung Ngo, and Zhi Xiang Ng. 2024. “In Vitro Anti-Inflammatory Activity and Molecular Docking of *Peperomia pellucida* (L.) Kunth Extract via the NF-κB and PPAR-γ Signalling in Human Retinal Pigment Epithelial Cells.” *Bioorganic Chemistry* 153:107969. doi:10.1016/j.bioorg.2024.107969.
- Huang, Qianqian, Xiuli Liu, Guoqi Zhao, Tianming Hu, and Yuxi Wang. 2018. “Potential and Challenges of Tannins as an Alternative to In-Feed Antibiotics for Farm Animal Production.” *Animal Nutrition* 4(2):137–50. doi:10.1016/j.aninu.2017.09.004.
- Huang, Yu, and Jiewen Yang. 2021. “Degradation of Sulfamethoxazole by the Heterogeneous Fenton-like Reaction between Gallic Acid and Ferrihydrite.” *Ecotoxicology and Environmental Safety* 226:112847. doi:10.1016/j.ecoenv.2021.112847.
- Ijaz, Siddra, Imran Ul Haq, Riffat Malik, Ghalia Nadeem, Hayssam M. Ali, and Sukhwinder Kaur. 2023. “In Silico Characterization of Differentially Expressed Short-Read Nucleotide Sequences Identified in Dieback Stress-Induced Transcriptomic Analysis Reveals Their Role as Antimicrobial Peptides.” *Frontiers in Plant Science* 14:1168221. doi:10.3389/fpls.2023.1168221.
- Ikezu, U. M., Duru, C. E., Ikpa, C. B., and Ibe, F. C. (2025). In silico discovery of dual-targeting molecules from *Acalypha wilkesiana* against hypertension and hyperglycemia. *Discover Chemistry*, 2, 86. doi:10.1007/s44371-025-00175-2
- Jiang, Chunjie, Guojuan Lao, Jianmin Ran, and Ping Zhu. 2024. “Berberine Alleviates AGEs-Induced Ferroptosis by Activating NRF2 in the Skin of Diabetic Mice.” *Experimental Biology and Medicine* 249:10280. doi:10.3389/ebm.2024.10280.
- Jomova, Klaudia, Renata Raptova, Suliman Y. Alomar, Saleh H. Alwasel, Eugenie Nepovimova, Kamil Kuca, and Marian Valko. 2023a. “Reactive Oxygen Spe-

- cies, Toxicity, Oxidative Stress, and Antioxidants: Chronic Diseases and Aging.” *Archives of Toxicology* 97(10):2499–2574. doi:10.1007/s00204-023-03562-9.
- Jomova, Klaudia, Renata Raptova, Suliman Y. Alomar, Saleh H. Alwasel, Eugenie Nepovimova, Kamil Kuca, and Marian Valko. 2023b. “Reactive Oxygen Species, Toxicity, Oxidative Stress, and Antioxidants: Chronic Diseases and Aging.” *Archives of Toxicology* 97(10):2499–2574. doi:10.1007/s00204-023-03562-9.
- Kanti Das, Tushar, Mas Rina Wati, and Kaneez Fatima-Shad. 2014. “Oxidative Stress Gated by Fenton and Haber Weiss Reactions and Its Association With Alzheimer’s Disease.” *Archives of Neuroscience* 2(3). doi:10.5812/archneurosci.20078.
- Karamać, Magdalena. 2009. “Chelation of Cu(II), Zn(II), and Fe(II) by Tannin Constituents of Selected Edible Nuts.” *International Journal of Molecular Sciences* 10(12):5485–97. doi:10.3390/ijms10125485.
- Khan, Sameer Ullah, Kaneez Fatima, Shariqa Aisha, and Fayaz Malik. 2024. “Unveiling the Mechanisms and Challenges of Cancer Drug Resistance.” *Cell Communication and Signaling* 22(1):109. doi:10.1186/s12964-023-01302-1.
- Khateri, Somayeh, Maryam Mehrabi, and Reza Khodarahmi. 2024. “Inhibitory Effects of Quercetin and Resveratrol and Their Sulfonamide Derivatives on the Carbonic Anhydrase Activity: Spectroscopic Studies of the Binding Process.” *Chemical Papers* 78(1):151–63. doi:10.1007/s11696-023-03048-z.
- Kinscherf, Noah Alexander, and Mariana Pehar. 2022. “Role and Therapeutic Potential of RAGE Signaling in Neurodegeneration.” *Current Drug Targets* 23(12):1191–1209. doi:10.2174/1389450123666220610171005.
- Kong, Linghong, Hui Wang, Weiwei Jiang, Yun Chen, Zhuoling Du, Qiong Zhang, Jianyue Dong, Changchun Zeng, and Hanping Liu. 2025. “Network Pharmacology-Based Study in Polymetformin’s New Function of Blocking AGEs/RAGE Pathway Curing Diabetic Complications.” *Scientific Reports* 15(1):19632. doi:10.1038/s41598-025-00956-w.
- Láng, Léonie, Simon McArthur, Alpar S. Lazar, Line Pourtau, David Gaudout, Matthew G. Pontifex, Michael Müller, and David Vauzour. 2024. “Dietary (Poly)Phenols and the Gut–Brain Axis in Ageing.” *Nutrients* 16(10):1500. doi:10.3390/nu16101500.
- Lee, Jeongmin, Jae-Seung Yun, and Seung-Hyun Ko. 2022. “Advanced Glycation End Products and Their Effect on Vascular Complications in Type 2 Diabetes Mellitus.” *Nutrients* 14(15):3086. doi:10.3390/nu14153086.
- Lee, Vanessa J., Samuel E. Janisse, and Marie C. Hefern. 2023. “Plant-Derived Chelators and Ionophores as Potential Therapeutics for Metabolic Diseases.” *Chemical Society Reviews* 52(11):3927–45. doi:10.1039/D3CS00167A.
- Li, Wen, Qiuping Chen, Chengjie Peng, Dan Yang, Si Liu, Yanwen Lv, Langqi Jiang, Shijun Xu, and Lihua Huang. 2025. “Roles of the Receptor for Advanced Glycation End Products and Its Ligands in the Pathogenesis of Alzheimer’s Disease.” *International Journal of Molecular Sciences* 26(1):403. doi:10.3390/ijms26010403.
- Lin, Jianguo, Youcai Tang, Qiaohua Kang, Yunfeng Feng, and Anping Chen. 2012. “Curcumin Inhibits Gene Expression of Receptor for Advanced Glycation End-Products (RAGE) in Hepatic Stellate Cells In Vitro by Elevating PPAR γ Activity and Attenuating Oxidative Stress.” *British Journal of Pharmacology* 166(8):2212–27. doi:10.1111/j.1476-5381.2012.01910.x.
- Liu, Sixuan, Jiachen Liu, Yinhuai Wang, Fei Deng, and Zebin Deng. 2025. “Oxidative Stress: Signaling Pathways, Biological Functions, and Disease.” *MedComm* 6(7):e70268. doi:10.1002/mco2.70268.
- Meiliana, Anna, Nurrani Mustika Dewi, and Andi Wijaya. 2024. “Molecular Mechanisms of Methylglyoxal in Diabetes-Related Macrovascular Complications.” *The Indonesian Biomedical Journal* 16(5):411–26. doi:10.18585/inabj.v16i5.3242.
- Misra, Radhika, Emily Deehan, Kelly Frasier, Esther Nwozo, Renee Chang, Travis Jackson, and Bailey Patrick. 2025. “Advanced Glycation End Products (AGEs) in Non-Alcoholic Fatty Liver Disease (NAFLD) and Their Contribution to Skin Aging.”
- Moldogazieva, Nurbubu T., Innokenty M. Mokhosoev, Tatiana I. Mel’nikova, Yuri B. Porozov, and Alexander A. Terentiev. 2019. “Oxidative Stress and Advanced Lipoxidation and Glycation End Products (ALEs and AGEs) in Aging and Age-Related Diseases.” *Oxidative Medicine and Cellular Longevity* 2019:1–14. doi:10.1155/2019/3085756.
- Montserrat Corona-España, Ana, Mario Alberto Garcia-Ramirez, Regina Romo-Gonzalez, Ingrid Mayanin Rodriguez-Buenfil, and Orfil González Reynoso. 2024. “Phytochemicals from Secondary Metabolism and Their Role as Antioxidant and Anti-Inflammatory Molecules.” In *Biochemistry*, vol. 64, edited by M. Kamran Khan. IntechOpen.
- Nagai, Ryoji, Jun-ichi Shirakawa, Rei-ichi Ohno, Narumi Moroishi, and Mime Nagai. 2014. “Inhibition of AGEs Formation by Natural Products.” *Amino Acids* 46(2):261–66. doi:10.1007/s00726-013-1487-z.
- Nair, Arathi, Prashant Chauhan, Bhaskar Saha, and Katharina F. Kubatzky. 2019. “Conceptual Evolution of Cell Signaling.” *International Journal of Molecular Sciences* 20(13):3292. doi:10.3390/ijms20133292.

- Napolitano, Gaetana, Gianluca Fasciolo, and Paola Venditti. 2021. "Mitochondrial Management of Reactive Oxygen Species." *Antioxidants* 10(11):1824. doi:10.3390/antiox10111824.
- Navarro-Cruz, Addí Rhode, Daniel Juárez-Serrano, Ivan Cesar-Arteaga, Ashuin Kammar-García, Jorge Alberto Guevara-Díaz, Obdulia Vera-López, Martin Lazcano-Hernández, Ivonne Pérez-Xochipa, and Orietta Segura-Badilla. 2024. "Oral Administration of Resveratrol Reduces Oxidative Stress Generated in the Hippocampus of Wistar Rats in Response to Consumption of Ethanol." *Frontiers in Behavioral Neuroscience* 17:1304006. doi:10.3389/fnbeh.2023.1304006.
- Ngcobo, Nokwanda N. 2025. "Influence of Ageing on the Pharmacodynamics and Pharmacokinetics of Chronically Administered Medicines in Geriatric Patients: A Review." *Clinical Pharmacokinetics*. doi:10.1007/s40262-024-01466-0.
- Nwofor, O. K., Duru, C. E., and Nwofor, C. N. (2025). In-vitro, bioinformatics and computational biophysical analyses of antifungal phytochemicals from *Acalypha wilkesiana* variants targeting *Malassezia* lipase. *Tropical Journal of Drug Research*, 2(9), 231–244. doi:10.26538/tjdr/v2i9.3
- Ohiagu, Franklyn Ikechukwu, Paul Chidoka Chikezie, Tochukwu Oluwatosin Maduka, Chinwendu Mauren Chikezie, Ogueri Nwaiwu, and Keshav Raj Paudel. 2025. "Antioxidants, Radical Scavengers, and Their Impact on Oxidative Stress." *Free Radicals and Antioxidants* 14(2):62–85. doi:10.5530/fra.2024.2.7.
- Olufunmilayo, Edward O., Michelle B. Gerke-Duncan, and R. M. Damian Holsinger. 2023. "Oxidative Stress and Antioxidants in Neurodegenerative Disorders." *Antioxidants* 12(2):517. doi:10.3390/antiox12020517.
- Ouamnina, Abdoussadeq, Abderrahim Alahyane, Imane Elateri, Mourad Ouhammou, and Mohamed Abderazik. 2024. "In Vitro and Molecular Docking Studies of Antiglycation Potential of Phenolic Compounds in Date Palm (*Phoenix dactylifera* L.) Fruit: Exploring Local Varieties in the Food Industry." *Horticulturae* 10(6):657. doi:10.3390/horticulturae10060657.
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P., and Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, 372, n71. doi:10.1136/bmj.n71
- Pathomthongtaweethai, Nutthapoom, and Somchai Chutipongtanate. 2020. "AGE/RAGE Signaling-Mediated Endoplasmic Reticulum Stress and Future Prospects in Non-Coding RNA Therapeutics for Diabetic Nephropathy." *Biomedicine & Pharmacotherapy* 131:110655. doi:10.1016/j.biopha.2020.110655.
- Peng, Huan, Yuqi Gao, Chenye Zeng, Rui Hua, Yan-nan Guo, Yida Wang, and Zhao Wang. 2024. "Effects of Maillard Reaction and Its Product AGEs on Aging and Age-Related Diseases." *Food Science and Human Wellness* 13(3):1118–34. doi:10.26599/FSHW.2022.9250094.
- Perrone, Anna, Antonio Giovino, Jubina Benny, and Federico Martinelli. 2020. "Advanced Glycation End Products (AGEs): Biochemistry, Signaling, Analytical Methods, and Epigenetic Effects." *Oxidative Medicine and Cellular Longevity* 2020:1–18. doi:10.1155/2020/3818196.
- Piras, S., A. L. Furfaro, C. Domenicotti, N. Traverso, U. M. Marinari, M. A. Pronzato, and M. Nitti. 2016. "RAGE Expression and ROS Generation in Neurons: Differentiation versus Damage." Edited by K. V. Ramana. *Oxidative Medicine and Cellular Longevity* 2016(1):9348651. doi:10.1155/2016/934865
- Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D., & Bitto, A. (2017). Oxidative stress: Harms and benefits for human health. In V. M. Victor (Ed.), *Oxidative Medicine and Cellular Longevity*, 2017(1), 8416763. <https://doi.org/10.1155/2017/8416763>
- Pohanka, M., & Dobes, P. (2013). Caffeine inhibits acetylcholinesterase, but not butyrylcholinesterase. *International Journal of Molecular Sciences*, 14(5), 9873–9882. <https://doi.org/10.3390/ijms14059873>
- Radziszewski, M., Galus, R., Łuszczynski, K., Winiarski, S., Wąsowski, D., Malejczyk, J., Włodarski, P., & Ścieżyńska, A. (2024). The RAGE pathway in skin pathology development: A comprehensive review of its role and therapeutic potential. *International Journal of Molecular Sciences*, 25(24), 13570. <https://doi.org/10.3390/ijms252413570>
- Ramasamy, R., Yan, S. F., and Schmidt, A. M. (2012). The diverse ligand repertoire of the receptor for advanced glycation endproducts and pathways to the complications of diabetes. *Vascular Pharmacology*, 57(5–6), 160–167. doi:10.1016/j.vph.2012.06.004
- Ramasamy, R., Shekhtman, A., & Schmidt, A. M. (2022). The RAGE/DIAPH1 signaling axis & implications for the pathogenesis of diabetic complications. *International Journal of Molecular Sciences*, 23(9), 4579. <https://doi.org/10.3390/ijms23094579>
- Ramasamy, R., Vannucci, S. J., Shi Du Yan, S., Herold, K.,

- Yan, S. F., & Schmidt, A. M. (2005). Advanced glycation end products and RAGE: A common thread in aging, diabetes, neurodegeneration, and inflammation. *Glycobiology*, 15(7), 16R–28R. <https://doi.org/10.1093/glycob/cwi053>
- Ravindranath, N. H., & Ravindranath, M. H. (2011). Green tea catechins suppress NF- κ B-mediated inflammatory responses: Relevance to nutritional management of inflammation. *British Journal of Nutrition*, 105(12), 1715–1717. <https://doi.org/10.1017/S0007114510005611>
- Reddy, V. P., Aryal, P., & Soni, P. (2023). RAGE inhibitors in neurodegenerative diseases. *Biomedicines*, 11(4), 1131. <https://doi.org/10.3390/biomedicines11041131>
- Rodríguez-Negrete, E. V., Morales-González, Á., Madrigal-Santillán, E. O., Sánchez-Reyes, K., Álvarez-González, I., Madrigal-Bujaidar, E., Valadez-Vega, C., Chamorro-Cevallos, G., Garcia-Melo, L. F., & Morales-González, J. A. (2024). Phytochemicals and their usefulness in the maintenance of health. *Plants*, 13(4), 523. <https://doi.org/10.3390/plants13040523>
- Rojas, A., Lindner, C., Schneider, I., Gonzalez, I., & Uribe-arri, J. (2024). The RAGE axis: A relevant inflammatory hub in human diseases. *Biomolecules*, 14(4), 412. <https://doi.org/10.3390/biom14040412>
- Sadeghi, M., Miroliaei, M., Kamyabiamineh, A., Taslimi, P., & Ghanadian, M. (2023). The impact of AGEs on human health and the development of their inhibitors based on natural compounds. *Arabian Journal of Chemistry*, 16(10), 105143. <https://doi.org/10.1016/j.arabjc.2023.105143>
- Sadowska-Bartosch, I., & Bartosz, G. (2015). Prevention of protein glycation by natural compounds. *Molecules*, 20(2), 3309–3334. <https://doi.org/10.3390/molecules20023309>
- Salazar, J., Navarro, C., Ortega, Á., Nava, M., Morillo, D., Torres, W., Hernández, M., Cabrera, M., Angarita, L., Ortiz, R., Chacín, M., D'Marco, L., & Bermúdez, V. (2021). Advanced glycation end products: New clinical and molecular perspectives. *International Journal of Environmental Research and Public Health*, 18(14), 7236. <https://doi.org/10.3390/ijerph18147236>
- Santiago-Fernández, O., Coletto, L., Tasset, I., Kaushik, S., Concepcion, A. R., Qaisar, R., Macho-González, A., Lindenau, K., Diaz, A., Khawaja, R. R., Donega, S., Banskota, N., Ubaida-Mohien, C., Pharaoh, G., Ahn, B., Hartnell, L. M., Ramírez-Pardo, I., Chavda, B., Gazteluiturri, A., Kinter, M., Ferrucci, L., Reisz, J. A., D'Alessandro, A., Van Remmen, H., Muñoz-Cánoves, P., Feske, S., & Cuervo, A. M. (2025). Age-related decline of chaperone-mediated autophagy in skeletal muscle leads to progressive myopathy. *Nature Metabolism*, 7(12), 2589–2611. <https://doi.org/10.1038/s42255-025-01412-9>
- Schröder, K. (2024). Specific signaling by nicotinamide adenine dinucleotide oxidases – Role of their site of action. *Current Opinion in Chemical Biology*, 81, 102461. <https://doi.org/10.1016/j.cbpa.2024.102461>
- Sell, D. R., Biemel, K. M., Reihl, O., Lederer, M. O., Strauch, C. M., & Monnier, V. M. (2005). Glucosepane is a major protein cross-link of the senescent human extracellular matrix. *Journal of Biological Chemistry*, 280(13), 12310–12315. <https://doi.org/10.1074/jbc.M500733200>
- Semchyshyn, H. (2024). Fructose-mediated AGE-RAGE axis: Approaches for mild modulation. *Frontiers in Nutrition*, 11, 1500375. <https://doi.org/10.3389/fnut.2024.1500375>
- Senatus, L. M., & Schmidt, A. M. (2017). The AGE-RAGE axis: Implications for age-associated arterial diseases. *Frontiers in Genetics*, 8, 187. <https://doi.org/10.3389/fgene.2017.00187>
- Sharma, C., Kaur, A., Thind, S. S., Singh, B., and Raina, S. (2015). Advanced glycation end-products (AGEs): An emerging concern for processed food industries. *Journal of Food Science and Technology*, 52(12), 7561–7576. doi:10.1007/s13197-015-1851-y
- Smita, B., Jain, P., Saini, L., & Modi, Y. (2025). Distinguish between reducing and non-reducing sugars V1.
- Song, J., Zhu, L., Yu, S., Li, G., & Wang, D. (2024a). The synergistic effect of adsorption and Fenton oxidation for organic pollutants in water remediation: An overview. *RSC Advances*, 14(45), 33489–33511. <https://doi.org/10.1039/D4RA03050H>
- Song, X., Singh, M., Lee, K. E., Vinayagam, R., & Kang, S. G. (2024b). Caffeine: A multifunctional efficacious molecule with diverse health implications and emerging delivery systems. *International Journal of Molecular Sciences*, 25(22), 12003. <https://doi.org/10.3390/ijms252212003>
- Srivastava, A. K., & Singh, V. K. (2020). Physiological role of some alkaloids.
- Stevenson, B. C., Berden, G., Martens, J., Oomens, J., & Armentrout, P. B. (2023). Spectroscopic investigation of the metal coordination of the aromatic amino acids with zinc and cadmium. *The Journal of Physical Chemistry A*, 127(16), 3560–3569. <https://doi.org/10.1021/acs.jpca.2c08940>
- Sugawa, H., Ikeda, T., Tominaga, Y., Katsuta, N., & Nagai, R. (2024). Rapid formation of N ϵ -(carboxymethyl) lysine (CML) from ribose depends on glyoxal production by oxidation. *RSC Chemical Biology*, 5(11), 1140–1146. <https://doi.org/10.1039/D4CB00183D>
- Takeuchi, M., Takino, J., and Yamagishi, S. (2010).

- Involvement of the toxic AGEs (TAGE)-RAGE system in the pathogenesis of diabetic vascular complications: A novel therapeutic strategy. *Current Drug Targets*, 11(11), 1468–1482. doi:10.2174/1389450111009011468
- Terao, J. (2023). Potential role of quercetin glycosides as anti-atherosclerotic food-derived factors for human health. *Antioxidants*, 12(2), 258. <https://doi.org/10.3390/antiox12020258>
- Thakor, P. M., Patel, J. D., Patel, R. J., Chaki, S. H., Khimani, A. J., Vaidya, Y. H., Chauhan, A. P., Dholakia, A. B., Patel, V. C., Patel, A. J., Bhavsar, N. H., & Patel, H. V. (2024). Exploring new Schiff bases: Synthesis, characterization, and multifaceted analysis for biomedical applications. *ACS Omega*, 9(33), 35431–35448. <https://doi.org/10.1021/acsomega.4c02007>
- Twarda-Clapa, A., Olczak, A., Białkowska, A. M., & Koziolkiewicz, M. (2022). Advanced glycation end-products (AGEs): Formation, chemistry, classification, receptors, and diseases related to AGEs. *Cells*, 11(8), 1312. <https://doi.org/10.3390/cells11081312>
- Uceda, Ana Belén, Laura Mariño, Rodrigo Casasnovas, and Miquel Adrover. 2024a. “An Overview on Glycation: Molecular Mechanisms, Impact on Proteins, Pathogenesis, and Inhibition.” *Biophysical Reviews* 16(2):189–218. doi:10.1007/s12551-024-01188-4.
- Uceda, Ana Belén, Laura Mariño, Rodrigo Casasnovas, and Miquel Adrover. 2024b. “An Overview on Glycation: Molecular Mechanisms, Impact on Proteins, Pathogenesis, and Inhibition.” *Biophysical Reviews* 16(2):189–218. doi:10.1007/s12551-024-01188-4.
- Valgimigli, L. (2023). Lipid peroxidation and antioxidant protection. *Biomolecules*, 13(9), 1291. doi:10.3390/biom13091291
- Wang, Bijian, Taidou Jiang, Yaoyu Qi, Sha Luo, Ying Xia, Binyan Lang, Bolan Zhang, and Shuzhan Zheng. 2024. “AGE-RAGE Axis and Cardiovascular Diseases: Pathophysiologic Mechanisms and Prospects for Clinical Applications.” *Cardiovascular Drugs and Therapy*. doi:10.1007/s10557-024-07639-0.
- Watanabe, Haruki, and Myoungsun Son. 2021. “The Immune Tolerance Role of the HMGB1-RAGE Axis.” *Cells* 10(3):564. doi:10.3390/cells10030564.
- Wu, Yuncheng, Xinqun Li, Julie Xiaohong Zhu, Wenjie Xie, Weidong Le, Zhen Fan, Joseph Jankovic, and Tianhong Pan. 2011. “Resveratrol-Activated AMPK/SIRT1/Autophagy in Cellular Models of Parkinson’s Disease.” *Neurosignals* 19(3):163–74. doi:10.1159/000328516.
- Yadav, Neera, Jyoti Dnyaneshwar Palkhede, and Sun-Yeou Kim. 2023. “Anti-Glucotoxicity Effect of Phytoconstituents via Inhibiting MGO-AGEs Formation and Breaking MGO-AGEs.” *International Journal of Molecular Sciences* 24(8):7672. doi:10.3390/ijms24087672.
- Yamaguchi, Hiroko, and Ryoji Nagai. 2025. “Insights from the Fructose-derived Product Glucoselysine: Revisiting the Polyol Pathway in Diabetic Complications.” *Journal of Diabetes Investigation* 16(4):569–77. doi:10.1111/jdi.70000.
- Yammine, Aline, Imen Ghzaïel, Vivien Pires, Amira Zarrouk, Omar Kharoubi, Hélène Greige-Gerges, Lizette Auezova, Gérard Lizard, and Anne Vejux. 2024. “Cytoprotective Effects of α -Linolenic Acid, Eicosapentaenoic Acid, Docosahexaenoic Acid, Oleic Acid and α -Tocopherol on 7-Ketocholesterol – Induced Oxidative Stress: Major Roles of PI3-K / PDK-1 / Akt Signaling Pathway and Glutathione Peroxidase Activity in Cell Rescue.” *Current Research in Toxicology* 6:100153. doi:10.1016/j.crtox.2024.100153.
- Yang, Jianying, Juyue Luo, Xutong Tian, Yaping Zhao, Yumeng Li, and Xin Wu. 2024. “Progress in Understanding Oxidative Stress, Aging, and Aging-Related Diseases.” *Antioxidants* 13(4):394. doi:10.3390/antiox13040394.
- Yue, Qing, Yu Song, Zi Liu, Lin Zhang, Ling Yang, and Jinlong Li. 2022. “Receptor for Advanced Glycation End Products (RAGE): A Pivotal Hub in Immune Diseases.” *Molecules* 27(15):4922. doi:10.3390/molecules27154922.
- Zhang, Yihan, Zhen Zhang, Chuyue Tu, Xu Chen, and Ruikun He. 2025. “Advanced Glycation End Products in Disease Development and Potential Interventions.” *Antioxidants* 14(4):492. doi:10.3390/antiox14040492.
- Zhao, Yang, Matthew Simon, Andrei Seluanov, and Vera Gorbunova. 2023. “DNA Damage and Repair in Age-Related Inflammation.” *Nature Reviews Immunology* 23(2):75–89. doi:10.1038/s41577-022-00751-y.
- Zheng, Yongxin, Junlu Sun, Zhiting Luo, Yimin Li, and Yongbo Huang. 2024. “Emerging Mechanisms of Lipid Peroxidation in Regulated Cell Death and Its Physiological Implications.” *Cell Death & Disease* 15(11):859. doi:10.1038/s41419-024-07244-x.
- Zych, Maria, Weronika Wojnar, Magdalena Kielanowska, Joanna Folwarczna, and Ilona Kaczmarczyk-Sedlak. 2020. “Effect of Berberine on Glycation, Aldose Reductase Activity, and Oxidative Stress in the Lenses of Streptozotocin-Induced Diabetic Rats In Vivo—A Preliminary Study.” *International Journal of Molecular Sciences* 21(12):4278. doi:10.3390/ijms21124278.

