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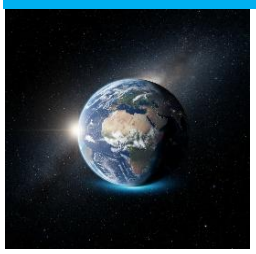

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Natural Inhibitors of Advanced Glycation End Products in the Prevention of Oxidative Stress and Inflammation

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Abstract

Background:

Advanced glycation end products (AGEs) are formed as a result of non-enzymatic reactions between reducing sugars and proteins, lipids, and nucleic acids. Their excessive accumulation promotes oxidative stress, chronic inflammation, and the development of metabolic, neurodegenerative, and cardiovascular diseases. Natural bioactive compounds may limit the formation of AGEs and mitigate their harmful effects on the body.

Aim:

The aim of this study is to review current literature data on natural compounds that inhibit the formation of AGEs and their effects on oxidative stress and inflammatory processes.

Material and Methods:

A narrative literature review was conducted using the PubMed, Web of Science, and Google Scholar databases, including systematic reviews as well as experimental and clinical studies published between 2010 and 2026. The effects of polyphenols, anthocyanins, and vitamins C, E, and B1 were analyzed in the context of reducing glycation, oxidative stress, and inflammatory responses.

Results:

The analysis of the literature demonstrated that polyphenols, anthocyanins, and vitamins C, E, and B1 effectively reduce the formation of major glycation products (CML, CEL) both *in vitro* and *in vivo*. These compounds increase the activity of antioxidant enzymes, decrease the levels of reactive oxygen species and pro-inflammatory cytokines, and modulate the NF-κB and RAGE signaling pathways. The combination of several compounds, such as resveratrol and curcumin, shows a synergistic effect, further reducing AGE formation and oxidative stress.

Conclusions:

Natural bioactive compounds, including polyphenols, anthocyanins, and vitamins, demonstrate significant potential in reducing the formation of AGEs, oxidative stress, and chronic

inflammation. Their use may support the protection of tissues susceptible to glycation and oxidative damage.

Keywords:
AGEs, polyphenols, resveratrol, curcumin, quercetin, anthocyanins, oxidative stress, vitamin C, vitamin E, chronic inflammation, natural glycation inhibitors.

1. Introduction

In recent years, increasing attention has been paid to the role of oxidative stress and chronic inflammation in the pathogenesis of many civilization-related diseases. Disturbances in the oxidative–antioxidant balance lead to damage to proteins, lipids, and nucleic acids, thereby contributing to the development of metabolic, cardiovascular, and neurodegenerative diseases. (Pomroy et al., 2025; Shiraga et al., 2026) One of the key mechanisms leading to these disturbances is the formation of advanced glycation end products (AGEs), which may accumulate in tissues and intensify inflammatory processes as well as oxidative stress. (Shen et al., 2020; van Dongen et al., 2022) The aim of this study is to review current literature data concerning natural compounds that inhibit the formation of AGEs and their effects on oxidative stress and inflammatory processes.

2. Research materials and methods

A comprehensive literature search was conducted in the PubMed, Web of Science, and Google Scholar databases to identify relevant studies examining the effects of natural bioactive compounds on the formation of advanced glycation end-products (AGEs), oxidative stress, and chronic inflammation. The search included publications from 2010 to 2026. The following keywords and their combinations were used: “AGEs,” “polyphenols,” “resveratrol,” “curcumin,” “quercetin,” “anthocyanins,” “vitamin C,” “vitamin E,” “vitamin B1,” “oxidative stress,” and “chronic inflammation.” The inclusion criteria comprised original research articles, systematic reviews, and meta-analyses published in English that addressed the influence of natural compounds on AGEs, oxidative stress markers, and inflammatory mediators. Both clinical and experimental studies were considered. Articles not written in English, opinion pieces, conference abstracts, and studies with insufficient methodological information or without

available full text were excluded from the analysis.

3. Research results

3.1 AGEs and Oxidative Stress

Advanced Glycation End Products (AGEs)

AGEs constitute a heterogeneous group of compounds formed as a result of non-enzymatic reactions between reducing sugars and macromolecules such as proteins, lipids, and nucleic acids.(Pomroy et al., 2025; Shiraga et al., 2026) This process, known as the Maillard reaction, involves several stages: the formation of a reversible Schiff base, its transformation into stable Amadori or Heyns products, and the generation of stable and irreversible AGEs. (Pomroy et al., 2025; Sadeghi et al., 2025) Dicarbonyl compounds, such as methylglyoxal (MGO) and glyoxal (GO), play a key role in their formation, and their excessive accumulation promotes intensified glycation processes and the development of oxidative stress. Among the best-characterized AGEs are Nε-carboxymethyllysine (CML), Nε-carboxyethyllysine (CEL), pentosidine, and pyrraline. (Alouffi & Khan, 2020; Yumnam, Subedi, & Kim, 2020) Advanced glycation end products and their precursors represent a diverse group of compounds whose levels in the body increase with age and are associated with negative health effects. (van Dongen et al., 2022) These compounds are formed endogenously during metabolic processes, but they may also originate from dietary sources. (Garay-Sevilla, Rojas, Portero-Otin, & Uribarri, 2021) Endogenous AGEs are mainly produced through the multi-stage Maillard reaction, the progression of which is accelerated by hyperglycemia and oxidative stress. In food products, these compounds occur naturally in raw meat and other animal-derived products, and their levels increase during thermal processing such as grilling, baking, and frying. (Pomroy et al., 2025; Twarda-Clapa, Olczak, Białkowska, & Koziołkiewicz, 2022)

Role of AGE Receptors

AGEs interact with cells through binding to various surface receptors that initiate numerous signaling pathways associated with oxidative stress and inflammatory responses. The best-characterized receptor involved in these processes is the receptor for advanced glycation end products (RAGE). It is a multiligand receptor belonging to the immunoglobulin superfamily and is capable of binding various ligands, including AGEs. (Taguchi & Fukami, 2023; Twarda-Clapa et al., 2022) Activation of RAGE leads to the initiation of multiple intracellular signaling

pathways, including the mitogen-activated protein kinase (MAPK) pathway and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. As a result, there is an increased expression of inflammatory mediators, such as pro-inflammatory cytokines, as well as an enhanced production of reactive oxygen species. (Liu, Pan, Wang, Liu, & Zhang, 2023; Wasilewska, Mazur, Kordas, Mizia, & Juranek, 2026)

Excessive activation of AGE-dependent pathways and their receptors leads to further structural modifications of biological macromolecules. Consequently, their normal function becomes impaired. In tissues, this process is associated with intensified oxidative stress and activation of inflammatory processes, which may contribute to the development of many chronic diseases, including obesity, cancer, cognitive dysfunction, and respiratory diseases. (Shen et al., 2020)

Oxidative Stress and Disease Complications

Oxidative stress is a biological process in which excessive accumulation of reactive oxygen species (ROS) occurs, exceeding the capacity of the body's antioxidant defense systems. As a consequence, damage to proteins, lipids, and nucleic acids occurs, which may lead to impaired cellular function and, in extreme cases, to cell death. (Jin et al., 2023) One of the factors that intensifies oxidative stress is the activation of RAGE receptors, which increases ROS production and weakens antioxidant mechanisms. As a result, a vicious cycle is formed - accumulation of AGEs promotes further glycation and the progression of oxidative damage. (Boccardi, Mancinetti, & Mecocci, 2025) AGEs also play an important role in the development of diabetic complications, such as neuropathy and nephropathy, as well as in neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Increased levels of AGEs are also observed in older individuals and in many disorders associated with the aging process. For this reason, increasing attention is being paid to strategies aimed at limiting their formation or neutralizing their harmful effects. (Fotheringham, Gallo, Borg, & Forbes, 2022; Haddad et al., 2019; Stratmann, 2022)

3.2 Inhibitors of AGE Formation

Inhibitors of AGE formation can be divided into two main groups depending on their source: synthetic molecules and naturally occurring compounds. In recent years, particular attention has been paid to natural substances present in foods that exhibit antioxidant and anti-

inflammatory properties and are capable of inhibiting glycation processes. Among the most frequently studied natural inhibitors of AGEs are resveratrol, curcumin, antioxidant vitamins (C and E), and anthocyanins. (Y. Zhang, Zhang, Tu, Chen, & He, 2025)

Polyphenols

Polyphenols constitute a large group of organic compounds commonly found in plants. They exhibit numerous biological properties, including antioxidant, anti-inflammatory, and immunomodulatory effects. These compounds play an important role in protecting the body against oxidative damage, chronic inflammation, and the formation of AGEs. Four main groups of polyphenols can be distinguished: flavonoids, stilbenes, phenolic acids, and lignans. Among the best-known polyphenols are resveratrol, curcumin, quercetin, and catechins. The mechanism of action of polyphenols primarily involves the neutralization of reactive oxygen species, chelation of metal ions, and inhibition of enzymes that generate free radicals, thereby reducing oxidative stress. In addition, these compounds modulate signaling pathways associated with inflammatory responses, including NF-κB and TLR4 (Toll-like receptor 4), which leads to decreased production of pro-inflammatory cytokines and enhancement of endogenous antioxidant mechanisms. As a result, polyphenols protect cells against oxidative damage, reduce inflammation, and inhibit the formation of AGEs. (Jin et al., 2023; Y. Zhang et al., 2025)

Resveratrol

Resveratrol is a natural polyphenolic compound found primarily in cereals, fruits, vegetables, dried legumes, peanuts, and red wine. It exhibits a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antidiabetic, and cardioprotective properties. Resveratrol activates signaling pathways involved in cellular antioxidant defense, such as nuclear factor erythroid 2–related factor 2 (Nrf2), AMP-activated protein kinase (AMPK), and sirtuin 1 (SIRT1). Activation of these pathways leads to increased activity of antioxidant enzymes and decreased production of reactive oxygen species and pro-inflammatory mediators. (Jin et al., 2023; Zhou et al., 2021) Studies have shown that resveratrol can reduce oxidative stress and influence pathways related to AGE formation. In a study conducted on diabetic rats, the effects of resveratrol on oxidative stress and renal RAGE expression were evaluated. Rats were administered resveratrol at doses of 1, 5, or 10 mg/kg body weight for 30 days. The study observed a decrease in the levels of the oxidative stress marker malondialdehyde (MDA),

plasma glucose, and RAGE expression, along with an increase in total antioxidant capacity and insulin levels. Another study demonstrated that resveratrol inhibits excessive ROS production, reduces cell apoptosis, and improves mitochondrial function by increasing the activity of respiratory chain complexes and mitochondrial membrane potential. This mechanism is associated with activation of the SIRT1/PGC-1α (sirtuin 1/peroxisome proliferator-activated receptor γ coactivator 1α) signaling pathway, which plays a key role in the regulation of cellular energy metabolism. (Moridi et al., 2015; T. Zhang et al., 2019) In a 2023 clinical study involving older adults with type 2 diabetes, supplementation with resveratrol at 1000 mg/day for six months significantly increased total antioxidant capacity and SIRT1 levels compared with a dose of 500 mg/day and placebo. The results suggest that higher doses of resveratrol more effectively reduce oxidative stress, protect cells from oxidative damage, and may provide a safe supportive strategy in preventing micro- and macrovascular complications of type 2 diabetes. (García-Martínez, Ruiz-Ramos, Pedraza-Chaverri, Santiago-Osorio, & Mendoza-Núñez, 2023) Resveratrol also exhibits anti-inflammatory effects by reducing levels of certain pro-inflammatory cytokines, such as interleukin 1β (IL-1β). (Hu, Lei, Zhang, & Luo, 2022) In summary, resveratrol is an effective antioxidant and antiglycation compound that can protect cells and tissues from oxidative stress and diabetes-induced damage.

Curcumin

Curcumin is a natural compound present in turmeric. It exhibits multifunctional biological activities, including anti-inflammatory, antioxidant, antidiabetic, and analgesic properties. (Roney, Huq, Rullah, Zamri, & Mohd Aluwi, 2025) In patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes, supplementation with curcumin for 12 months led to a significant reduction in pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-6, as well as oxidative stress markers, including malondialdehyde (MDA). At the same time, an increase in antioxidant enzyme activity, such as glutathione peroxidase and superoxide dismutase, was observed. These effects were associated with improvements in metabolic parameters, including reduced levels of non-esterified fatty acids (NEFA), total body fat, liver steatosis and stiffness, and better glycemic control. (Yaikwawong, Jansarikit, Jirawatnotai, & Chuengsamarn, 2025) Curcumin may also positively influence the gut microbiota. In a study conducted in patients with chronic kidney disease, supplementation with curcumin phytosomes for six months reduced inflammatory mediators and lipid peroxidation. Simultaneously, changes in gut microbiota composition were observed, including a decrease in Escherichia-Shigella bacteria and an increase in bacteria from

the Lachnoclostridium and Lactobacillaceae families. (Pivari et al., 2022) In healthy, physically active athletes following a Mediterranean diet, three months of supplementation with curcumin combined with Boswellia serrata extract (BSE) significantly reduced AGE accumulation and lipid peroxidation. Levels of soluble RAGE (sRAGE) and NEFA decreased in both groups, while inflammatory markers remained stable, likely due to their low baseline levels in healthy athletes. These results suggest that curcumin combined with BSE effectively limits AGE accumulation and lipid oxidative stress, potentially supporting tissue protection against the effects of chronic physical exertion. (Chilelli et al., 2016) Studies have also shown that the combination of resveratrol and curcumin can inhibit AGE cross-linking in cartilage, limiting aging-related processes and reduced chondrocyte metabolism, suggesting a potential role in slowing the progression of osteoarthritis associated with aging and diabetes. (Mehta et al., 2021) In summary, curcumin exhibits strong anti-inflammatory, antioxidant, and antiglycation properties, supporting tissue protection and metabolic health. Both clinical and experimental studies confirm its good tolerance and lack of significant side effects.

Quercetin

Quercetin is a flavonoid found in vegetables and fruits, primarily in onions, lettuce, asparagus, apples, and cherries. It has strong antioxidant properties due to the presence of multiple hydroxyl groups in its chemical structure. This compound enhances the body's antioxidant capacity by regulating glutathione levels, neutralizing ROS, influencing antioxidant enzyme activity, and modulating oxidative stress-related signaling pathways such as MAPK and NF-κB. (Qi, Qi, Xiong, & Long, 2022) A 2025 study demonstrated that flavonoids such as quercetin and catechins possess strong antioxidant properties and the ability to inhibit inflammatory processes and platelet aggregation. Moreover, their co-administration with vitamin C can produce a synergistic effect, increasing total antioxidant potential and enhancing cellular protection against oxidative stress. (Chrysikopoulou et al., 2025) Quercetin may also protect podocytes from damage in diabetic nephropathy by regulating the AGE-RAGE pathway and interacting with key molecular targets such as TNF and vascular endothelial growth factor A (VEGF-A). These mechanisms reduce inflammation, limit vascular permeability, and inhibit cell apoptosis. (Ma et al., 2022)

Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG) is the primary catechin in green tea and one of its most important bioactive components. It exhibits antioxidant, anti-inflammatory, cardioprotective, and anticancer properties, protecting the body against numerous chronic diseases, including diabetes, cardiovascular diseases, cancer, and neurodegenerative disorders. EGCG acts at the cellular level by reducing oxidative stress, regulating NF-κB and SIRT1 signaling pathways, and supporting autophagy processes, which enhance cellular resilience to damage. Due to its limited bioavailability, EGCG is most commonly consumed as a tea infusion or dietary supplement. (Capasso et al., 2025; Dong, Fang, Li, & Chai, 2025) A clinical study demonstrated that 12 weeks of consumption of a beverage containing green tea catechins (400 mg/day) and inulin (2.3 g/day) in individuals with visceral obesity improved insulin sensitivity, although it did not significantly affect visceral fat mass. Gut microbiota analyses suggested that an increase in Coprococcus abundance may have contributed to improved insulin sensitivity. These findings highlight the potential of catechins as natural agents supporting glucose metabolism, reducing oxidative stress, and modulating inflammation, which is relevant for the prevention of chronic diseases associated with AGE formation. (Iino et al., 2026)

Vitamins

Vitamins C (ascorbic acid) and E (α-tocopherol) are important natural antioxidants that can reduce oxidative stress and inflammatory processes in the body. Vitamin C, a water-soluble compound, neutralizes ROS and protects cells from oxidative damage, and may also limit AGE accumulation. Vitamin E, a fat-soluble antioxidant, protects cell membranes from lipid peroxidation. In a clinical study, eight weeks of supplementation with vitamin C (1000 mg/day) and vitamin E (800 IU/day) led to a significant reduction in oxidative stress markers, such as ROS and MDA. The combined action of vitamins C and E exhibits a synergistic effect, enhancing the body's antioxidant potential and limiting the activation of inflammatory pathways, such as NF-κB. (Amini et al., 2021; Y. Zhang et al., 2025) Similarly, in a study involving patients with type 2 diabetes, supplementation with vitamin C at 500 mg/day for eight weeks resulted in a significant decrease in AGE and MDA levels, without changes in inflammatory markers, confirming its beneficial effect on reducing systemic oxidative stress. (Rabizadeh et al., 2023) In addition to vitamins C and E, vitamin B1 (thiamine) plays an

important role in protection against oxidative stress. This compound scavenges hydroxyl radicals, supports macrophage phagocytic activity, inhibits NF-κB activation, and regulates the production of pro-inflammatory cytokines. Clinical studies have shown that combined administration of vitamins C and B1 can reduce markers of cardiac muscle damage, early inflammatory responses, and the incidence of postoperative arrhythmias, indicating a synergistic protective effect of these vitamins. (Saetang et al., 2025)

Anthocyanins

Anthocyanins are natural polyphenolic compounds primarily found in berries such as blueberries, bilberries, and blackcurrants. These compounds exhibit strong antioxidant properties and the ability to inhibit glycation processes. Anthocyanins, including cyanidin and delphinidin glycosides, can limit AGE formation by scavenging and neutralizing reactive carbonyl species, such as methylglyoxal (MGO), which is a major precursor of glycation reactions.(Hsiao, Hsia, Pan, Ho, & Hung, 2024; Peng et al., 2024) Experimental studies have also confirmed the activity of anthocyanins *in vivo*. In an animal model, a blueberry extract rich in anthocyanins reduced the accumulation of two major glycation products, CML and CEL, in animals fed a diet high in AGEs. The reduction of these compounds was observed in multiple tissues, including serum, kidneys, skin, brain, and the gastrointestinal tract, suggesting a potential protective effect of anthocyanins on tissues particularly susceptible to glycation stress. (Mo et al., 2024) Furthermore, blueberry anthocyanin extract has been shown to inhibit glycation by reducing intermediate glycation products such as Schiff bases, fructosamine, and α-dicarbonyl compounds. Additionally, anti-inflammatory effects were observed, associated with inhibition of the NF-κB signaling pathway and decreased production of inflammatory mediators, including IL-6 and TNF-α. (Peng et al., 2024) These findings indicate that anthocyanins may represent a promising group of natural inhibitors of AGE formation and factors that mitigate oxidative stress and chronic inflammation.

Phenolic Acids

Phenolic acids, such as chlorogenic acid and caffeic acid, naturally occur in many fruits and vegetables and exhibit protective effects at the cellular level. Animal studies have shown that a diet enriched with caffeic acid can reduce glycation stress and limit AGE formation. The antiglycation mechanism of this compound involves inhibition of the polyol pathway through decreased activity and expression of renal enzymes such as aldose reductase and sorbitol

dehydrogenase, thereby limiting the accumulation of sorbitol and fructose, which promote AGE formation. (Chao, Mong, Chan, & Yin, 2010) These polyphenols also exhibit anti-inflammatory effects in the gut. In a human colonic myofibroblast model, caffeic acid reduced cyclooxygenase-2 expression and the biosynthesis of prostaglandins and certain pro-inflammatory cytokines in intestinal cells, indicating potential inflammation-mitigating activity. Additionally, caffeic acid has strong chelating and antioxidant properties, which may further limit AGE formation and alleviate oxidative stress and potential tissue damage. These results suggest that dietary polyphenols can also support intestinal homeostasis through modulation of inflammatory pathways and antioxidant protection. (Zielińska et al., 2021)

4. Discussion

Advanced glycation end products play a significant role in the pathogenesis of numerous chronic diseases, including metabolic, cardiovascular, and neurodegenerative disorders. Their accumulation in tissues leads to structural modifications of proteins and impaired cellular function, as well as activation of multiple signaling pathways associated with oxidative stress and inflammatory processes. A particularly important mechanism involves the interaction of AGEs with the RAGE receptor, which results in increased production of reactive oxygen species and enhanced expression of pro-inflammatory mediators. (Shen et al., 2020; Twarda-Clapa et al., 2022) The results of the analyzed studies indicate that natural bioactive compounds present in foods can effectively limit both the formation of AGEs and their detrimental effects. Of particular interest are plant polyphenols such as resveratrol, curcumin, quercetin, and green tea catechins. (Y. Zhang et al., 2025) These compounds possess the ability to neutralize reactive oxygen species, scavenge reactive carbonyl species, and modulate key signaling pathways involved in inflammatory processes, including NF-κB and the AGE-RAGE pathway. (Jin et al., 2023) Experimental and clinical studies have shown that these compounds can reduce oxidative stress markers, increase antioxidant enzyme activity, and limit the production of pro-inflammatory cytokines. Other compounds, such as anthocyanins and phenolic acids, may also play a significant role in inhibiting glycation. Studies have demonstrated that these compounds can limit AGE formation by scavenging reactive carbonyl species and inhibiting intermediate stages of glycation reactions. Additionally, their anti-inflammatory activity has been observed, associated with modulation of signaling pathways responsible for the production of inflammatory mediators. (Chao et al., 2010; Mo et al., 2024; Zielińska et al., 2021) It is also important to highlight the potential for synergistic effects of various bioactive compounds. Some studies suggest that combining multiple polyphenols may exert stronger antioxidant and

antiglycation effects than using single compounds alone. Such interactions may enhance the overall antioxidant capacity of the body and more effectively mitigate the adverse effects of oxidative stress. (Amini et al., 2021; Chrysikopoulou et al., 2025; Mehta et al., 2021) Despite the promising results of many studies, certain limitations of the available data should be considered. A significant proportion of research on natural AGE inhibitors has been conducted *in vitro* or in animal models. Therefore, further clinical studies are needed to more accurately determine the efficacy, bioavailability, and optimal dosages of these compounds in humans. A better understanding of the mechanisms of action of natural AGE inhibitors may contribute to the development of effective dietary and preventive strategies to support the reduction of oxidative stress and chronic inflammation.

5. Conclusions

Natural bioactive compounds, including polyphenols, anthocyanins, and phenolic acids, demonstrate significant potential in reducing the formation of advanced glycation end products (AGEs), oxidative stress, and chronic inflammation. Experimental and clinical studies indicate that these compounds can protect cells and tissues from oxidative damage, supporting metabolic, cardiovascular, and neurodegenerative health. Despite these promising results, further clinical research is needed to determine the optimal dosages, bioavailability, and mechanisms of action of these substances in humans. A better understanding of natural AGE inhibitors may contribute to the development of effective preventive and dietary strategies that mitigate the effects of glycation and oxidative stress.

Disclosure

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The authors deny any conflict of interest.

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In preparing this work, the author(s) used ChatGPT for language improvement and grammatical correction. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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