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Review Article

Unraveling Advanced Glycation End Products: Mechanisms, Pathophysiology, and Emerging Natural Therapeutic Interventions

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ABSTRACT

Protein glycation is an emerging issue that needs attention because it presents a hazard to the health of individuals. Through a sequential succession of non-enzymatic biochemical reactions occurs during glycation of protein, Advanced Glycation End products (AGEs) are formed which makes proteins nonfunctional and through accumulation in the body leading to serious pathogenic conditions. Their accumulation is accelerated in hyperglycemic and oxidative environments, linking them closely to chronic diseases such as diabetes, cardiovascular disease, neurodegenerative disorders, and kidney dysfunction. AGEs exert their pathological effects through direct cross-linking of extracellular matrix proteins and interaction with cell-surface receptors, particularly the Receptor for AGEs (RAGE). However, there are several substances that can be used to diminish the development of AGEs and the problems brought through glycated proteins. These synthetic antiglycation drugs have ineffective pharmacological outcomes and limited efficacy. Utilizing bioactive substances from natural sources is a better strategy to treat glycation-related issues and to prevent AGEs-associated pathogenesis since they have fewer adverse effects and are more effective. In regard with this the current review has included the developmental phases for AGEs, complications related with buildup AGEs and inhibitors of protein glycation i.e., synthetic, and natural substances.

Keywords: Advanced glycation end products, Antiglycation, Protein glycation, Chronic diseases.

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INTRODUCTION

Protein glycation is the common term for the covalent association of free amino residues of proteins with carbonyl or aldehyde groups of sugar molecules, such as glucose, fructose, galactose, ribose, etc. The series of actions eventually leads to the development of irreversible products with a diverse class of substances known as Advanced Glycation End Products (AGEs). Protein glycation was initially documented in the field of food chemistry in 1912 by Louis-Camille Maillard and called "Maillard reaction". The non-enzymatic nature of this protein glycation makes the reactive process lengthy and necessitates several days or even several weeks to finish. The chief glycation sites for proteins are the ε-amino groups of lysine residues and/or at the N-terminal amino acid's α-amino group. An amino-carbonyl initiated reaction form an unstable Schiff base and rearrangement of Schiff base over a period of days then produces stable product, Amadori or ketoamine-based products. Cross-linked compounds result from the rearrangement of Amadori products via processes such cyclization, oxidation, and dehydration collectively termed as AGEs which are irreversible, autofluorescence and yellow-brown color products.[1] Diabetes is a long-term medical disorder marked by high blood sugar. One of the main factors associated with hyperglycemia is the subsequent non-enzymatic glycation of biological proteins, which encourages the irreversible synthesis of reactive AGEs.

The development of AGEs encompasses three main phases

Initial phase: When reducing sugars like glucose, fructose, or ribose interact with the terminal amino groups of proteins, unstable Schiff bases are created, which triggers the start of the Maillard process. After that, the unsteady Schiff base foundations are transformed into a highly steady product, keto-amines. Following rearrangement, the keto-amines are converted to Amadori products. All reactions in the initial phase are changeable and contingent upon the concentration of substrate along with the duration of the reaction. Furthermore, when Schiff bases are oxidised, they generate free radicals, which lead to the creation of active carbonyl intermediate products.[2]

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Intermediate phase

This phase involves metal ion or oxygen catalysis, which produces the oxidation function during the Amadori product rearrangement process. Several carbonyl compounds, such as Methylglyoxal (MGO) and 3-Deoxyglucosone (3-DG), also referred to as alpha-dicarbonyls or oxoaldehydes, will be produced by this oxidation. The polyol route produces fructose-3-phosphate, which is produced by the hydrolysis of Amadori adducts and monoxidative rearrangement, which together produce 3-DG. Anaerobic glycolysis also produces methylglyoxal through non-oxidative mechanisms. It has recently been proposed that Amadori products, such fructosamine, can create MGO, 3-DG, and glyoxal through Schiff's breakdown of glucose or during the intermediate phases of glycation.

Advance phase

The ultimate stage of the Maillard reaction involves the production of isomers of dicarbonyl molecules with protein residues, namely lysine and arginine. These isomers are irreversible compounds known as Advanced Glycation End products (AGEs). The AGEs, that accumulate on proteins with a lengthy lifespan and impair their physiological functions, are yellowish brown in color that are frequently luminous and insoluble.[3] Figure 1 depicts the series of biochemical reactions that result in the creation of Advanced Glycation End products (AGEs), which are harmful compounds formed by three successive non-enzymatic processes. Examples of AGEs include N-(Carboxylethyllysine) (CEL), S-(Carboxymethyl) Cysteine (CMC), pyrraline, 3 deoxyglucosone derived imidazolium crosslink, glucosepane, glyoxal lysine dimer, crosslinks, and fluorolink.[4,5]

Alternative routes for the development of AGEs

Reactive Carbonyl Species (RCS) including the auto-oxidation of glucose via the Wolff pathway, Schiff's base via the Namiki pathway, or Amadori products via the Hodge pathway can yield glyoxal, methylglyoxal, and 3-deoxyglucosone. These three approaches generate highly reactive intermediates that can react with free amino groups to generate a wide range of AGEs.[6] The Wolf pathway is another way for the generation of AGEs, focused on the reaction between the ketoamine intermediate 3-Deoxyglucosone (3-DG) and protein lysine residues. This mechanism states that 3-DG, which is created from the fragmentation of Amadori adducts created early in the glycation process, combines with lysine residues on proteins to create a Schiff base foundation. This Schiff base is subsequently rearranged and oxidized to generate N-(Carboxymethyl)Lysine (CML), an AGEs. A product of autooxidation, fructosamine eventually develops CML by removal of R-NH2.[7] The Wolf pathway posits that this specific reaction between 3-DG and lysine residues can be a key contributor to AGE production, particularly in the context of diabetes, where higher levels of 3-DG have been seen. It suggests that 3-DG can directly change proteins, resulting in the formation of CML.[8] Schiff bases can oxidize when exposed to oxidative stress or Reactive Oxygen Species (ROS). This is accomplished via the Namilki pathway, which allows for the fragmentation of Schiff bases.[9] This reaction involves the breaking of the carbon-nitrogen bond in the Schiff base, resulting in the release of glyoxal and methylglyoxal that are a few instances of reactive carbonyl substances. These reactive carbonyls can then participate in subsequent glycation processes or aid in the development of AGEs. The Hodge pathway describes a different mechanism for AGEs production through the autoxidation of Amadori products. During autoxidation, Amadori products can react with molecular ROS and RCS sch as glyoxal and methylglyoxal, are more efficient glycation agents than the initial reducing sugar and react with proteins to create AGEs.[10]

AGEs associated consequences

AGEs are also known as glycotoxins since they can be damaging to the body if present for a lengthy period.[5] During the normal physiological condition ageing process there is a steady rise in AGEs production which typically targets proteins with a long half-life. Under the consequences of oxidative stress and hyperglycemic condition, the rate of protein glycation accelerates, potentially causing structural alterations in short-lived proteins.[11] While being a contributing element in the development of diabetes, the accelerated rate of AGEs formation under diabetic conditions has also been connected to several pathologic conditions, including atherosclerosis, tumor, cardiovascular disorders, and neurological diseases. Oxidative stress and inflammatory pathways in AGE-RAGE mediated chronic disease progression is depicted in Figure 2. AGEs aid in the occurrence of various health problems via three key approaches: 1) AGEs could connect to their RAGE (receptor for Advanced glycation end products) receptors on the cell's surface and activate cell signaling, leading to the formation of ROS. 2) AGEs can impair the stability and role of some catalytic proteins by causing glycation of their active site. 3) Glycated matrix proteins, such as collagen, can react with other extracellular matrix protein molecules via protein crosslinking by several typical AGEs structures, resulting in an impairment of function.

In addition to diabetic consequences, the quick glycation of proteins and the creation of AGEs cause Heart-related disease, Alzheimer's disease, and age-related illnesses, tumor development, and organ failure resulting in major harm and malfunction, affecting the kidneys, nerves, heart, and eyes.[12] The interaction between AGEs (Advanced Glycation End-products) and their receptor, RAGE, triggers oxidative stress and initiates an inflammatory cascade. This cascade involves the activation of NF-κB, the production of cytokines like IL-2, IL-6, and TNF-α, as well as the formation of cross-linked adducts. These processes contribute to the development of microvascular and macrovascular complications, such as atherosclerosis, diabetic

nephropathy, retinopathy, neuropathy, and impaired wound healing.[13] Protein glycation lead the production and aggregation of the β-sheet structure, which culminates in fibrillar structures that cause neurological diseases. Glycation was observed to cause aggregation, conformational shift, and crosslinking of lens crystalline in a few investigations.[14] The inducible form of nitric oxide synthase is affected by Advanced Glycation End products (AGEs), which may decrease blood flow to nerves and lead to hypoxia in peripheral nerves.[15] Glycation also alters the function of antioxidant enzymes such as glutathione reductase, catalase, and glutathione peroxidase.[16]

Strategies to prevent the accumulation of AGEs

The biochemical processes of antiglycation reactions typically encompass any mechanism that might slow down or stop the glycation process, hence inhibiting the development of AGEs. Since the production of AGEs requires several phases various substances that can impede this process at various stages have been assessed. Inhibitors interfering with sugar attachment with proteins: To block glycation at an early stage, it is important to prevent the linkage of reducing sugar to the protein. Some inhibitors could obstruct the first bonding of reduced carbohydrates to the amino residues of proteins. As one of the synthetic substances that acetylates the amino groups in proteins, aspirin able to hinder the first connection between carbohydrates and amino residues.[17]

Inhibitors with radical scavenging properties: Some substances, which may have the ability to scavenge free radicals, can delay or decrease the development of AGEs. When glycation is occurring, antioxidants prevent the production of free radicals. Free radicals are created early phase in the glycation process. At the beginning of the glycation process, Schiff bases are formed, which are susceptible to oxidation and contribute to the production of reactive carbonyl groups and free radicals. Therefore, the use of antioxidant compounds that can scavenge reactive components presents a potential method for inhibiting glycation process at an early stage.

Inhibition of Amadori product formation: A potential approach for preventing glycation should be to restrict the production of the Amadori product, which is reversible. Furthermore, glycation can be avoided by preventing the development of late-stage Amadori products.

Cross linking breakers: Glycation can be prevented by removing the crosslinking structures present in the produced AGEs. In this situation, the inhibitor may attach to the AGEs and then release them from the protein molecule. They function as AGEs breakers, dissolving AGEs that have already accumulated or AGEs cross-links that have already formed, allowing the smaller peptides to be eliminated by urine.

Metal ion chelators: In the intermediate stage of the glycation reaction, Amadori products undergo an arrangement change that is facilitated by metal ions. Since the production of AGEs is associated with the presence of metal ions, metal ion chelation may stop AGE development.

Blockage of receptors of AGEs: In order to trigger cellular response, AGEs must interact with their receptor on the cell surface. In order to prevent glycation, blocking the AGE receptors

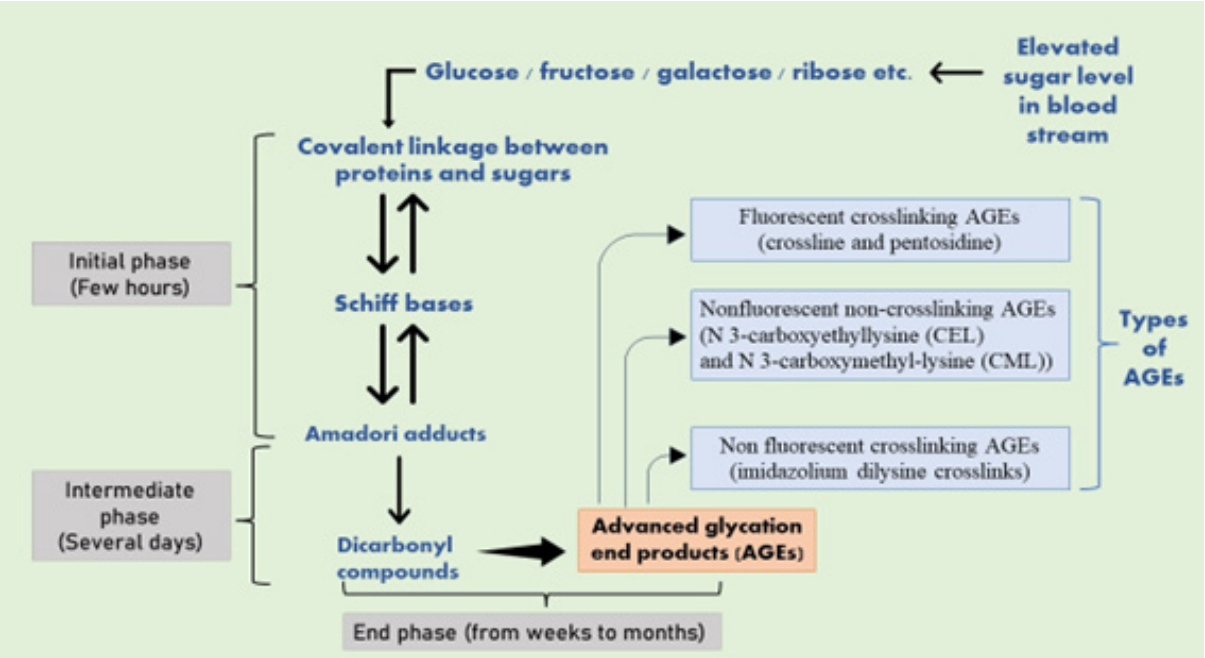

Figure 1: Biochemical reaction cascade for the occurrence of AGEs: Advanced Glycation End products (AGEs), that are hazardous adducts, are finally formed by the three consecutive non-enzymatic processes. The fluorescence properties and crosslinking behavior of the produced AGEs are used to categorize them.

may offer a means of repressing the occurrence of oxidative stress and inflammation.

Therapeutic approaches

Compounds having antiglycation function can aid in reducing glycation-associated disease considering the role that AGEs play in the development of many diseases and complications related to diabetes. Many artificial and natural compounds are being studied to evaluate their anti-glycation properties.

Synthetic glycation inhibitors

Challenges in Safety and Efficacy

Various synthetic therapeutic compounds have been explored, with aminoguanidine, benfotiamine, pyridoxamine, and others emerging as the most promising glycation inhibitors[18] but numerous artificial inhibitors of AGE production were taken out of medical studies due to concerns regarding safety, insufficient pharmacokinetics, and somewhat low effectiveness. Aminoguanidine was the initial AGEs inhibitor to be introduced[19] which, by inhibiting the development of AGEs, avoided diabetic renal, retinal, and neurological problems.[20] Due to safety concerns raised by its negative side effects, such as suppression of NO synthase,[21] and pro-oxidant activities[22] aminoguanidine was not therapeutically relevant. Furthermore, Aminoguanidine demonstrated poor efficacy even as a strong antiglycation agent, causing negative side effects like vasculitis, lupus, influenza-like syndrome, pernicious anemia, gastrointestinal symptoms, and induced toxicity at higher doses.[23] A popular anti-diabetic medicine metformin, reduced glucose concentrations in blood stream and promotes the enzymatic capability of glyoxalase I, which helps reduce the level of Methylglyoxal (MGO), a key precursor of AGEs.[24]

Synthetic antiglycation agents are toxic and cannot be taken long-term as they cause adverse effects on human health. Synthetic compounds are not appropriate for human consumption because of safety concerns. When it comes to safety, natural sources provide the most promising research directions with good therapeutic activities. Nature origin sources may act as multistage antiglycation agents by preventing the carbonyl and amino residue association and inhibiting the formation of Schiff bases and Amadori adducts (early stage), by inhibiting of oxidation of Amadori adducts and reducing the development of dicarbonyl moieties (middle stage), and by inhibition of fluorescent AGEs formation (late stage). Consequently, it is necessary to find bioactive substances from natural sources that are more effective and have fewer negative effects. Natural products are considerably

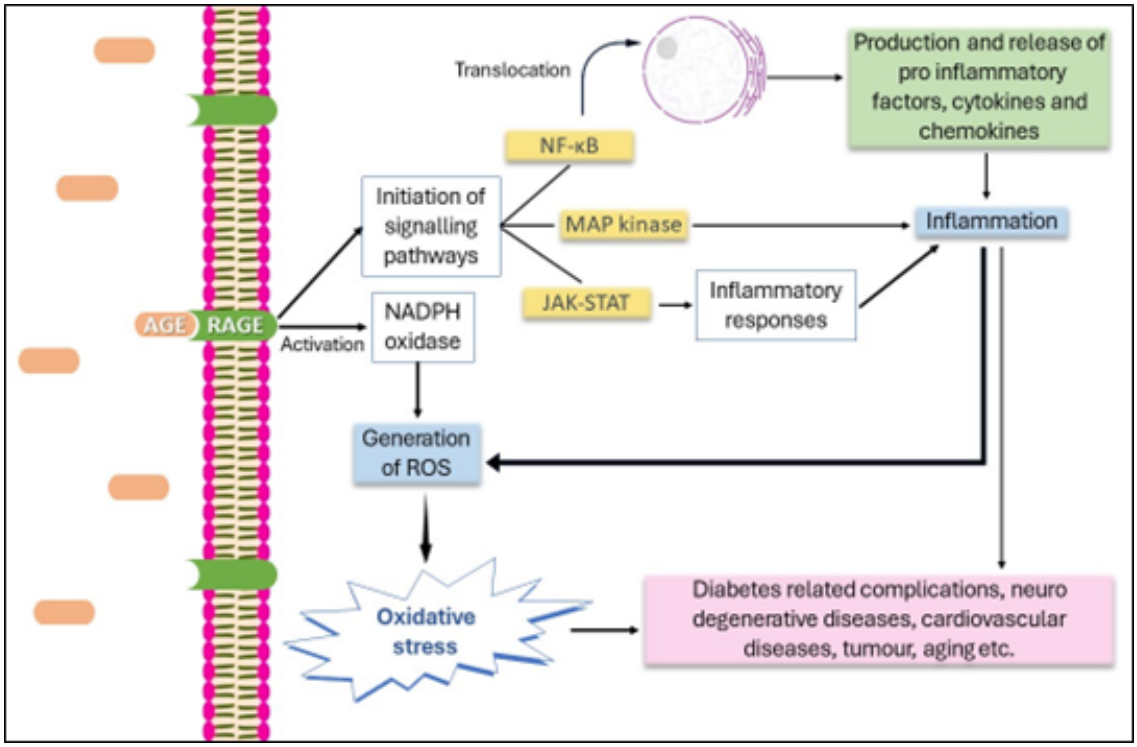

Figure 2: A typical association of AGEs with RAGE: Several physiological and pathological mechanisms, like oxidative stress, inflammation, and the onset of chronic conditions including diabetic complications, neuro degenerative diseases, cardiovascular problems, tumor, aging etc. are arise by the binding of AGEs (Advanced Glycation End Products) with RAGEs (Receptor for Advanced Glycation End Products). Free radicals are produced when NADPH oxidase is activated, which is started by the AGE-RAGE complex. Reactive oxygen species are produced, which worsen oxidative stress and further harm cells. Furthermore, the AGE-RAGE interaction triggers many signal transduction pathways, counting MAP kinase, JAK-STAT, and NF-kβ, which result in inflammation, a major cause of oxidative stress and associated clinical illnesses with it.

safer for human ingestion than manufactured medications. According to studies, substances that were extracted from several natural sources exhibit have distinctive pharmacological attributes and may have the ability to have antiglycation effects. Additionally, it is suggested that natural substances that have both antioxidant and antiglycation properties are more effective therapeutically. Phytochemicals shown many antiglycation mechanisms, including effects on glycation inhibitory processes, such as impacts on the utilization of glucose, a decrease in reactive oxygen species generation and accumulation, dicarbonyl molecule elimination, and control of gene expression.[25] This offers a much more efficient approach with minimum toxicity for protein glycation and its consequences.[26] Research has indicated that an extensive array of natural substances such as vitamins, plant secondary compounds and polysaccharides are among the promising possibilities for the invention of novel medications to suppress the production of AGEs. In this regard numerous plant-based extractions as well as purified compounds were reported anti-AGEs abilities via a variety of mechanisms, including the ability to trap dicarbonyl intermediates, to decrease hyperglycemia, to reduce RAGE expression, and to possess strong free radical scavenging abilities. The natural substances may prevent the formation of AGEs through eliminating free molecular species, binding to ionized metals, gathering bioactive carbonyl compounds, covering glycation domains in proteins, and lowering glucose levels in bloodstream.[27] Concerning the issue protein glycation and drawbacks of synthetic agents, the antiglycation properties of bioactive substances originating from natural sources including plants, algaes, mushrooms and beans or cereals have been reviewed in the present literature.

Natural antiglycation agents: Combating oxidative stress and glycation-linked aging and chronic disease

Antiglycation agents from natural therapeutic approaches play a critical role in managing oxidative stress and preventing glycation-related damage in the body, which is linked to aging and chronic diseases such as diabetes and cardiovascular issues. These agents often possess strong antioxidant properties, which help to neutralize free radicals and protect cellular integrity and also support overall metabolic health by improving glucose regulation and reducing inflammation.

Chrysanthemum morifolium R. contains chlorogenic acids which have been demonstrated to alter antioxidant enzymes' genetic regulation and scavenging free molecular species as well as metal ions. Additionally, they could obstruct the uptake of glucose. Besides AGEs, protein cross-linking is hindered by 3,5-di-O-caffeoyl-epi-quinic acid.[28] 3,5-di-O-caffeoyl-epi-quinic acid prevents AGEs and protein cross-linking obtained from a leaf and stem extractions of *Erigeron annuus*.[29] Ferulate conjugated acid, by serving as a protective agent for damage caused by oxidants, lowering the premature degradation of Maillard Reaction Intermediates and self-oxidation of glucose, can decrease the Luminous AGE production and CML formation more than ninety percent *in vitro*.[30] In addition to this *Chrysanthemum* species and *Erigeron annuus* also composed of Kaempferol that decreased induction of NF-B linked to ageing and inheritor inflammation via lowering AGEs-induced NADPH oxidase activity.[31] Rutin metabolites, notably 3,4-Dihydroxyphenylacetic Acid (DHPAA) and 3,4-Dihydroxytoluene (DHT), are potent inhibitory substances of ADP-ribose-induced CML and luminous byproducts in histone H1. It is anticipated that certain rutin intermediates will effectively neutralize methylglyoxal and plasma glyoxal. and methylglyoxal concentrations found from fruits and vegetables.[32] The leaves of *Stelechocarpus cauliflorus* composed of flavonoid compounds counting engeletin, taxifolin, and astilbin[33] were revealed to be beneficial in the management of diabetic problems and to provide protection against oxidative damage. induced by AGE formation.[34] Other flavonoids including catechin, epicatechin, procyanidin B2, and proanthocyanidins were suppressed the development of pentosidine and CML by more than 50% obtained from cinnamon bark extract.[35] Among initially reported natural substances, a catechin compound obtained from green tea, Epigallocatechin-3-Gallate (EGCG) has the most significant trapping capability for reactive dicarbonyl molecules like methylglyoxal and glyoxal.[36] A polyphenolic compound eriocitrin, is a main substance in *M. piperita* that exhibited a potent AGEs inhibition and methyl glyoxal trapping capability.[37]

Under hyperglycemic circumstances, EGCG has shown to decrease the AGE generation within cells and the production of cytokines that promote inflammation in monocytes.[38] Chinese herbal tea *Polygonum multiflorum* has 2,3,5,4'-Tetrahydroxystilbene 2-O--D-Glucoside (THSG) which was reported to scavenge more than 60% of MGO in 24 hr effectively.[39] Labdadiene is a terpenoid compound obtained from *Alpinia zerumbet* that inhibited oxidation of proteins caused by glycation and the generation of alfa dicarbonyls effectively than the positive controls rutin and quercetin.[40] A natural pentacyclic triterpenoid saponin, Arjunolic acid (2,3,23-trihydroxyolean-12-en-28-oic acid) present in *Terminalia arjuna*, has been determined to decrease the production of AGEs, HbA1c, reactive oxygen compounds, reactive nitrogen compounds and demises oxidative stress signaling pathways.[41] Flavonoid compounds comprising vitexin, isovitexin, orientin, and isoorientin were extracted from bamboo leaf considerably inhibit the production of compounds from protein oxidation as well as fluorescent AGEs.[42]

Phlorotannins were abundant in methanolic extracts from certain kinds of brown algae, such as *Padina pavonica, Sargassum polycystum*, and *Turbinaria ornata*. These extracts efficiently inhibited the glycation of proteins caused by glucose and the production of fluorescent AGEs attached to proteins.[43] Dieckol,

the most effective AGE inhibitor found in *Ecklonia cava*, a brown alga, is a great natural source of anti-glycation chemicals.[44] According to,[45] marine microalgae-derived fucoxanthin has a powerful repressing effect on the production of AGEs. According to,[46] the ability of Phlorotannins from *F. vesiculosus* capture reacting carbonyl moieties which may be a factor in their effectiveness in inhibiting the development of AGEs. According to a different study, the Japanese Lessoniaceae's crude phlorotannins have an inhibitory effect on the production of fluorescence-bound AGEs.[47] Phlorofucofuroeckol-A has substantially stronger inhibitory efficacy than aminoguanidine. Even *E. stolonifera* possessed phlorofucofuroeckol-A, which prevented glycation brought on by ribose and glucose.[48] The primary antiglycation drug that demonstrated potent inhibitory activity by reducing plasma glycated and N-(carboxymethyl) lysine levels is a bioactive fraction II composed of Pheophorbide A, the most prevalent chemical isolated from the algae *Kappaphycus alvarezii*.[49] In addition to, fraction II was administered to diabetic rats, which resulted in decreased RAGE expression and decreased CML levels.[49]

Boletus snicus (BS), an economically essential mushroom species contains two polysaccharides (BSP-1b and BSP-2b), which exhibit substantial inhibitory effects on glycation. More antiglycation action was displayed by BSP-2b than by BSP-1b. Research regards to BSP-2b demonstrated that it was capable of efficiently preventing the construction of Advanced glycation end products.[50] *Agaricus bisporus* and *Pleurotus ostreatus* were exposed to UV-B radiation, which demonstrated potential abilities to prevent the events of oxidation and glycation of proteins.[51] A milk mushroom called *L. rhinocerus* was used to make the medium-molecular-weight fraction, which was found to have strong anti-glycation properties. In a system including human serum albumin and glucose, the bio-fraction explicitly prevented the synthesis of N-(carboxymethyl) lysine, pentosidine, and other AGEs compounds.[52]

It has been observed that the Feruloyl Oligosaccharides (FOs) from wheat bran, which are ferulate esters of oligosaccharides, are naturally occurring antioxidants that exhibit a decrease in the intense fluorescence nature of AGEs.[53] The flavone C-glucoside components of mung beans, vitexin and isovitexin, were found to have the highest anti-glycation activity.[54] The high tannin content of sorghum may slow the rate at which AGE products are generated and contribute to the problems associated with persistently high glucose metabolic conditions. Even more, by reducing methylglyoxal-mediated glycated albumin, a high phenolic sorghum bran variety (sumac) reduced glycation.[55] Red-kerneled rice's proanthocyanidin-rich fractions and beard extract were tested for their ability to prevent AGEs production by inhibiting the glycation of HSA with glucose and fructose as well as their ability to break down AGE crosslinks.[56] The proanthocyanidins prevented the synthesis of fructosamine and severely reduced the production of AGEs and dicarbonyl compounds.

CONCLUSION

The development and buildup of AGEs is a primary cause of problems associated with diabetes mellitus. Several compounds including reactive oxygen species and dicarbonyl moieties are generated during the process of protein glycation which triggers other intracellular signaling pathways and promotes other harmful health problems. The current literature has significance for building the scientific groundwork for the assessment and isolation of biologically active compounds to develop natural antiglycation medicines for the management of AGEs-associated pathogenesis. It also has implications for future research design to treat diabetic complications. The potential therapeutic value of natural sources like medicinal plants, herbs, edible algae and mushrooms as well as cereals and beans should thus be investigated at the biochemical and molecular levels.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AGEs: Advanced glycation end products; **MGO:** Methylglyoxal; **3-DG:** 3-Deoxyglucosone; **CEL:** N-carboxylethyllysine; **CMC:** S-(Carboxymethyl) cysteine; **RAGEs:** Receptor for Advanced Glycation End Products; **DHPAA:** 3,4-dihydroxyphenylacetic acid; **DHT:** 3,4-dihydroxytoluene; **ROS:** Reactive oxygen species; **NO:** Nitric oxide; **EGCG:** Epigallocatechin-3-gallate; **FOs:** Feruloyl oligosaccharides.

AUTHOR CONTRIBUTIONS

Literature Search, Data Analysis, original draft preparation: Dipeksha Macwan, Conceptualization, Final Drafting and editing: Hiteshkumar V. Patel.

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