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NATURAL COMPOUNDS THAT INHIBIT PROTEIN GLYCATION: A REVIEW FOR RECENT FINDINGS

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Abstract:

Diabetes Mellitus is a chronic, lifelong disease currently impacting people throughout the world. A fundamental cause of Diabetes Mellitus: Non-enzymatic protein glycosylation (glycation) contributes to a group of metabolic diseases, including diabetes-associated late complications, atherosclerosis, chronic renal failure, Alzheimer's disease and inflammatory arthritis. It has been hypothesized that inhibition of glycation may prevent the diseases associated with diabetes. Inhibitors of glycation have been explored for several decades, chiefly using in vitro models, which resulted in discovery of different natural compounds capable of forestalling glycation, such as antioxidants, polysaccharide, metal chelators and peptides. Many peptides released from different proteins have proven to possess physiological functions besides their nutrient roles. Even the results of in vitro studies are not directly applicable on the in vivo situation due to differences in the conditions, mechanism of glycation and bioavailability issues. In this review article, we briefly discuss the mechanism of advanced glycation end products (AGEs) in promoting pathogenesis and then present the recent findings concerning the role of plant-based inhibitors and amino acid peptides in decreasing the formations of AGEs. These findings suggest that enrichment of diet with natural, anti-glycating agents may reduce glycation and as a consequence, diabetic complications.

Keywords: *Glycation, Diabetes, Hyperglycemia, AGEs-inhibitors, Retinopathy.*

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INTRODUCTION:

For the past few years, there is a steep rise in the incidences of diabetes around the world. Globally, an estimated 422 million adults had diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has climbed up from 4.7% to 8.5% since 1980 among the adults [1]. Saudi Arabia is one of the 19 countries and territories of the International Diabetes Federation (IDF), Middle East and North Africa (MENA) region, which has the seventh highest rate of prevalence of diabetes. There were approximately 3.4 million cases of diabetes in Saudi Arabia in 2015, and according to a recent estimate, almost 24.4% of the adult population is suffering from diabetes mellitus [2].

The term "diabetes mellitus" describes a group of metabolic disorders with varied etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from the defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [3], [4]. Long-term complications of diabetes include: retinopathy with potential loss of vision [5]; nephropathy leading to renal failure [6]; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints [7]; autonomic neuropathy causing gastrointestinal [8], genitourinary [9] and cardiovascular symptoms [10] and sexual dysfunction [11, 12]. Diabetic patients have an increased incidence of atherosclerotic cardiovascular [13], peripheral arterial [14], and cerebrovascular disease [15]. The long-term effects of diabetes are mostly due to protein glycation, also called the Maillard reaction that impairs the function of biomolecules [16]. The Maillard reaction was identified by a French scientist Louis Camille Maillard, in 1912. He discovered yellow-brown colors while sugar was heated with amino acids [17]. This reaction was introduced in the food industry for improving aroma, texture, and color of the food stuff and scientists discovered that this reaction also takes place in *in vivo* and is currently involved in the pathogenesis of various diseases [18–20].

GLYCATION AND ADVANCED GLYCATION END PRODUCTS (AGES)

Maillard reaction, also referred to as Glycation is a complex cascade of reactions. The reaction is typically slow at physiological conditions since it does not involve an enzyme catalyst, it requires several days or weeks to get completed [16]. The reaction starts when the aldehyde on reducing sugars, such as glucose, fructose, and ribose, is attacked by the terminal amino groups of proteins, nucleic acids [21] and phospholipids [22], forming an unstable Schiff base [23]. The Schiff base then undergoes a slow structural rearrangement (Amadori rearrangement/ Heyns rearrangement), and the reaction proceeds to a relatively more stable, irreversible Amadori products or keto-amines, for instance, HbA1c [24].

Oxidative decomposition of the Amadori products leads to the accumulation of a wide range of highly reactive intermediates like carbonyl and dicarbonyl compounds also known as oxoaldehydes. The products of these carbonyl compounds include 3-deoxyglucosone (3-dG), glyoxal (GO) and methylglyoxal (MGO) glycolaldehyde, 1-deoxyglucosone, 4, 5- dioxo pentose, and 5, 6-dioxohexose [25]. The MGO formation also occurs by a non-oxidative process in anaerobic glycolysis [26] and by oxidative degradation of polyunsaturated fatty acids [22]. The highly electrophilic nature of these dicarbonyl compounds makes them react relatively faster with guanidine, arginine and lysine residues, amino and sulfhydryl functional moieties of proteins to produce different irreversible adducts [23]. Furthermore, modifications of these glycation products, such as rearrangement, oxidation, polymerization and cleavage, produces irreversible conjugates known as AGEs [27]. AGEs include N^{ε}-(carboxymethyl) lysine (CML), N^{ε}-(carboxylethyllysine) (CEL), S-(carboxymethyl) cysteine (CMC), pyrraline, 3-deoxyglucosone-derived imidazolium crosslink, pentosidine, glucosepane, glyoxal lysine dimer, crosslinks and fluorolink [19]. As a result, Intra- and inter-molecular heterocyclic cross-linking and fragmentation of proteins occur. AGEs, senescent macroprotein heterogeneous moieties are the final products of the glycation process. The final products of the glycation process, the AGEs, have greater thermostability. Since AGEs are the final product of non-enzymatic glycosylation process, therefore it can be produced both in *in vivo* and *in vitro*. Formation of AGEs in a living organism is concentration-dependent and hence enhanced in hyperglycemic conditions while dietary intake of exogenous AGEs also contributes to the accumulation of AGEs and pathogenesis of AGEs related diseases. AGEs are found in some foods which are formed in normal conditions and can form in food during cooking, especially more in modern diets because they are largely heat-processed through frying, baking, roasting and comparatively less in foods prepared by boiling, steaming and stewing [28]. Smoking is another strong source of AGEs; It was reported that glycotoxins, which promote AGEs formation were isolated from aqueous extracts of

tobacco and cigarette smoke [29]. Some proteins in the blood serum of smokers were modified by nor-nicotine which is a metabolite of tobacco nicotine [24]. Skin of smokers had higher AGEs compared to non-smokers [30]. An overview of the various routes of AGEs formation and its toxic effects in different organs is depicted in **Fig. 1**.

MECHANISM OF AGES RELATED PATHOGENESIS

AGEs are implicated in diabetes mellitus, and it`s complications as reported by Rahbar et al. The elevated HbA1c, one of the Amadori product of hemoglobin in diabetic patients is a potent source of development of diabetes mellitus [31]. In diabetes, glucose modified-HSA resulted in AGEs formation and resulted in deleterious impairment in biochemical, electrochemical, spectroscopic, optical and fluidity properties of HSA at high concentrations of glucose [32]. It was proved that glycation of insulin and proinsulin occurs in the pancreas during the point of insulin synthesis and storage leading to insulin resistance and reduced glucose uptake [33]. Low-density lipoprotein is also glycated in diabetic atherosclerosis and is not recognized by the LDL receptor contributing to the hyperlipidemias, accelerated foam cell formation and glycation of high-density lipoproteins, hence, reducing its function during cholesterol transport [34]. Glycation of myelin has been identified in Diabetic neuropathy, and this modification of myelin stimulates macrophages to secrete proteases leading to nerve demyelination [12]. Immunohistochemical analysis revealed that AGEs were detected in diabetic renal tissue, wherein, thickening of the basement membrane, expansion of the mesangium developed resulting in renal failure. AGEs stimulate the release of transforming growth factor-b (TGF-b), which increases the synthesis of collagen matrix components and may account for the thickening of the basement membrane in diabetic nephropathy [35]. AGEs were also noticed in retinal blood vessel walls and were hypothesized to be involved in up-regulating RAGE mRNA levels. This cause pericytes to undergo apoptosis through triggering oxidative stress and finally severe visual impairment leading to diabetic retinopathy [36]. Lens crystalline was studied in diabetic cataract, and it was found that glycation of lens crystallin causes conformational changes, aggregation, crosslinking and opacification at the end stage [37]. A Recent study has shown that AGEs accumulation leads RAGE to stimulate both IL-33 release and ILC2 accumulation in the lungs to promote chronic and acute allergic airway disease [8]. AGEs in the human ovary may account for some age-related features of ovarian dysfunction, including impaired vascularization and consequent hypoxia due to reduced intake of nutrients by follicle cells [38]. Eventually, AGEs affect nearly all types of cell **(Fig. 1)** and molecules in the body and play a vital role as proinflammatory mediators.

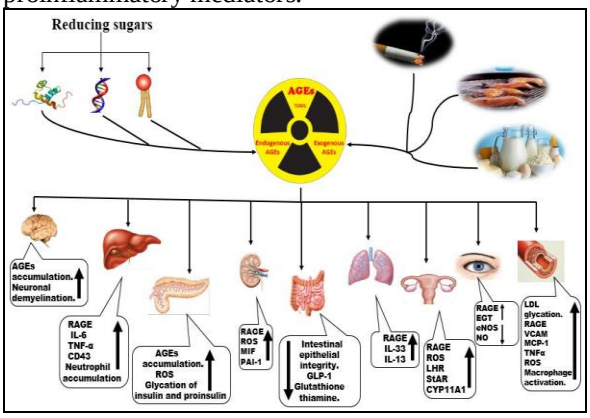

Fig. 1: Formation of AGEs and its toxic effects in different organ systems.

INHIBITORS OF AGES FORMATION

Phytochemical AGEs inhibitors

Phytochemicals are produced by plants through primary or secondary metabolism. They generally have biological activity in the plant host and play a major role in plants to help them thrive or defense against competitors, predators or pathogens [39, 40]. Phytochemicals have been used for centuries as traditional medicines and studied widely for their numerous biological activities such as anticancer, antimicrobial, antioxidant, and antiglycation. In order to provide an efficient therapeutic strategy for diabetes and its associated complications, natural antiglycation compounds which have limited side effects have been isolated from plants and widely studied. We have discussed listed the recent findings on phytochemical AGEs inhibitors in **Table. 1**.

Table 1: Overview of the recent findings on phytochemical AGEs inhibitors.

PLANT-BASED PHYTOCHEMICAL AGES INHIBITORS						
Source	**Solvent**	**Active component**	**Objective**	**Methodology for analysis**	**Results**	**Reference(s)**
Grape skin	---	phenolic content	Muffins	Determination of carboxymethyl lysine.	Reduced CML	[41]
Punica granatum Linn.	Methanol	steroids, triterpenoids, Glycosides, flavonoids, saponins and tannins. Phenolic content	Rat	Serum AGEs	Reduced AGE	[42]
Cissus quadrangularis Linn	Methanol	ethyl acetate fraction	Rat	HbA1c assay	Inhibited Glycation	[43]
Coptidis rhizoma	---	Berberine	Rat	Immunohistochemistry for RAGE.	Reduced RAGE	[35]
Green tea	---	epigallocatechin 3-gallate	Mice	Serum AGEs and tissue AGEs Western blot for RAGE.	Inhibited Glycation Reduced RAGE	[44]
garlic	Water	Organosulphur constituents	Rat	Immunohistochemistry for RAGE.	Reduced RAGE	[45]
Terminalia chebula Retz.	Ethyl acetate	chebulic acid	LX-2 cells	LX-2 cells were treated glyceraldehyde-derived advanced glycation end-products and chebulic acid.	Inhibited Glycation	[46]
Artocarpus communis	---	flavonoid content	(HCT116 cells THP-1 monocytes	BSA glycation test with glyceraldehyde. Western blot for RAGE	Inhibited glycation reduced RAGE	[47]
chilli peppers origin	---	Capsaicin	*In vitro*	BSA glycation test with glucose.	Inhibited Glycation	[48]
Osteomeles schwerinae C. K. Schneid.	Ethanol	phenolic content	*In vitro*	BSA glycation test with glucose and fructose. AGE-RAGE binding using ELISA. Detection of live cell-based AGE-BSA/RAGE binding.	Inhibited Glycation	[49]
Gynura procumbens leaves	Ethanol	phenolic content flavonoid content	*In vitro*	BSA glycation test with glucose.	Inhibited Glycation	[50]
heartwood of Pterocarpus marsupium	Ethanol	phenolic content flavonoid content	*In vitro*	BSA glycation test with fructose.	Inhibited Glycation	[51]

garlic ginger thyme parsley curry leaves peppermint turmeric onion green onion scallion coriander	Ethanol Water	Tannins Saponins Phlobatannins Anthraquinones Terpenoids Diterpenes Steroids Flavonoid phenolics	*In vitro*	BSA glycation test with glucose. BSA glycation test with fructose.	Inhibited Glycation	[52]
Canarium album L.	Water, ethanol, methanol, acetone, Ethyl acetate	Triterpenoid content phenolic content flavonoid content	*In vitro*	BSA glycation test with glucose. Determination of protein thiol group.	Inhibited Glycation	[53]
Camellia nitidissima Chi	Ethanol	dichloromethane fraction ethyl acetate fraction n-butanol fraction water fraction	*In vitro*	BSA glycation test with glucose and MGO Methylglyoxal scavenging assay.	Inhibited Glycation	[54]
Annona crassiflora Mart.	Ethanol	hexane, dichloromethane, ethyl acetate, n-butanol and water fractions	*In vitro*	BSA glycation test with fructose.	Inhibited Glycation	[55]
Carpobrotus edulis Foeniculum vulgare	Water Ethanol	phenolic content flavonoid content	*In vitro*	BSA glycation test with glucose. Determination of fructosamine by NBT assay, Determination of protein carbonyl content.	Inhibited Glycation	[56] [57]
Aphloia theiformis (Vahl.) Benn	Methanol Water	hexane, dichloromethane, ethyl acetate, and n-butanol fractions	*In vitro*	BSA glycation test with fructose	Inhibited Glycation	[58]

Coccinia grandis	Methanol	phenolic content flavonoid content saponins and dietary fiber content	*In vitro*	BSA glycation test with fructose Determination of fructosamine Protein bound carbonyl groups determined using DNPH. TNBSA assay to determine lysine modification Quantification. Circular dichroism measurements for the changes in the secondary structure of BSA	Inhibited Glycation	[59]
Ocimum americanum	Methanol, Water	phenolic content	*In vitro*	BSA glycation test with glucose	Inhibited Glycation	[60]
Red ginseng	Water	phenolic content		apolipoprotein A-I glycation test with fructose.	Inhibited Glycation	[61]
Algae	Water	phenolic content	*In vitro*	Lysine-Glucose Maillard reaction assay. BSA glycation test with glucose MGO.	Inhibited Glycation	[62]
sugarcane molasses	Water	phenolic content	*In vitro*	Lysine-Glucose Maillard reaction assay	Reduced CML and CEL	[63]
cruciferous vegetables		Sinigrin(glucosinolale)	*In vitro*	BSA glycation test with glucose, MGO. Determination of fructosamine Protein-bound carbonyl groups determined using DNPH. TNBSA assay to determine lysine modification Quantification. Circular dichroism measurements for the changes in the secondary structure of BSA	Inhibited Glycation	[64]
Jujube fruit Ripe fruit	Water	phenolic content flavonoid content	*In vitro*	BSA glycation test with fructose	Inhibited Glycation	[65]
phyllanthus emblica Cassia Auriculata	Water	phenolic content	*In vitro*	BSA glycation test with glucose	Inhibited Glycation	[66]
Ilex paraguariensis	Water	chlorogenic acid	*In vitro*	BSA glycation test with fructose and glucose	Inhibited Glycation	[67]

Syzygium jambolanum and Cephalandra indica	Water	Glycosides phenolic content flavonoid content	*In vitro*	BSA glycation test with fructose Determination of fructosamine by NBT assay, Determination of protein carbonyl content, Determination of protein thiol group Determination of free amino groups	Inhibited Glycation	[68] [66]
vanilla bean		Vanillin Resveratrol	*In vitro*	BSA glycation test with glucose, MGO Determination of protein carbonyl content, Determination of fructosamine by NBT assay Circular dichroism measurements for the changes in the secondary structure of BSA SDS page electrophoresis for glycation	Inhibited Glycation	[69] [70]
Houttuynia cordata		Quercetin	*In vitro*	HSA in vitro glycation test with glucose and glyoxal Circular dichroism measurements for the changes in the secondary structure of HSA Hemoglobin-δ-gluconolactone assay Methylglyoxal-HSA reactivity assay	Inhibited Glycation	[71] [72] [73] [74]

Phytochemicals extracted from medicinally used plants have shown promising antiglycation activity in *in vitro* and *in vivo*. Methanolic extract from *Coccinia grandis* was tested in an antiglycation assay in a BSA-fructose model. A concentration of 0.5 mg/ml showed significant AGEs inhibition after 28days. Levels of fructosamine and protein carbonyl content in the BSA-fructose system decreased to the same degree as in aminoguanidine group [59]. In an another study, ApoA-I glycation with fructose was inhibited by 100 µg/ml of Red ginseng water extract within 48 hours [61]. However, in a study performed by Kuda and colleagues, Algae aqueous extract interfered Lysine-Glucose Maillard reaction and inhibited BSA glycation with glucose and MGO [62]. In a separate study reported, Quercetin was extracted from *Houttuynia cordata* and evaluated for antiglycation activity in HSA- Glucose, glyoxal glycation model and it was demonstrated that AGEs formation was lowered and the changes in the secondary structure of HSA decreased [71, 72]. In a recent study, Flavonoid content prepared from *Artocarpus communis* was used to treat HCT116 colon cancer cells, it was observed that the malignancy enhanced by AGEs was decreased after the treatment along with the decline in the levels of and RAGE [47]. Additionally, Ethyl acetate fraction-chebulic acid- from *Terminalia chebula retz* inhibited AGEs induced hepatic fibrosis in LX-2 cells modulating Nrf2 translocation via ERK pathway [46]. Also, AGEs inhibitory activity of Epigallocatechin 3-gallate purified from green tea was studied in *in vivo*, the plasma AGEs level in HFD induced obesity mice were decreased accompanied by the inhibition of RAGE expression in liver [44].

Plant-based polysaccharides AGEs inhibitors:

Polysaccharides are natural polymeric carbohydrate molecules formed by glycosidic linkages between monosaccharide units. If all the monosaccharides in a

polysaccharide are of the same type, then the polysaccharide is called a homopolysaccharide, but if more than one type of monosaccharide is present, it is referred to as a heteropolysaccharide. Polysaccharides are stable, safe, non-toxic, non-carcinogenic components of plants and microorganisms with diverse bioactivities, such as anticancer, anticoagulant, antiviral, anti-inflammatory, anti-thrombotic, hypoglycemic and antioxidant activities [75]. Recent findings on plant-based polysaccharide inhibitors have been listed in **Table. 2**. Recently, many types of research have been conducted globally on polysaccharides, due to its high antioxidant and antiglycation activity. In a unique study, XU et al., extracted polysaccharides from black currant, consisting of galacturonic acid, xylose, mannose, glucose, and galactose. A concentration of 0.2 mg/ml showed significant antiglycation activity, and interestingly, the inhibitory action on protein glycation was more efficient in the later phases of AGEs and dicarbonyl compounds formation [76]. In a different study, polysaccharides extracted from *Boletus snicus* comprised of a large amount of glucose, uronic acid and a small amount of mannose, galactose, arabinose, glucosamine hydrochloride and glucuronic acid, exhibited significant antiglycation activity at lower concentrations [77]. In an another study, the mechanism of polysaccharides on antiglycation was attributed to its structure, M.Chaouch et al., extracted polysaccharides from *Opuntia ficus indica* and degraded them by sonication from 6,800,000 to 14,000 g/mol; they discovered that the polysaccharides degraded for 2 and 3 h showed even better antioxidant and antiglycation activities [78]. However, the antiglycation activity of polysaccharides is still unclear. This might be due to its structure, such as the type of glycosyl linkage, type of monosaccharides or other composition and also the molecular weight. Hence, the further in-depth study is needed to unravel the complex antiglycation mechanisms involved. In short, polysaccharides may be a promising drug candidate in the near future for inhibiting glycation.

Table 2: Polysaccharide inhibitors as antiglycation agents: Recent findings.

PLANT-BASED POLYSACCHARIDES AGES INHIBITORS						
Source	**Solvent**	**Active component**	**Objecti ve**	**Methodology for analysis**	**Results**	**Reference(s)**
Benincasa hispida (Thunb.) Cogn.	Water	Polysaccharides	*In vitro*	BSA glycation test with glucose.	Inhibited Glycation	[79]
Opuntia ficus indica	Water	Polysaccharides	*In vitro*	BSA glycation test with galactose.	Inhibited Glycation	[78]
black currant	Enzyme solution	Polysaccharides	*In vitro*	BSA glycation test with glucose. TNBSA assay to determine lysine modification. Quantification. Determination of protein carbonyl content.	Inhibited Glycation	[76]
Boletus snicus	Water	Polysaccharides	*In vitro*	BSA glycation test with glucose. TNBSA assay to determine lysine modification Quantification. Determination of protein carbonyl content.	Inhibited Glycation	[77]

Raspberry (R. idaeus L.) fruits	Water	Polysaccharides	*In vitro*	BSA glycation test with glucose. TNBSA assay to determine lysine modification Quantification. Determination of protein carbonyl content.	Inhibited Glycation	[80]
Pueraria lobata roots	Water	Polysaccharides	*In vitro*	BSA glycation test with glucose.	Inhibited Glycation	[81]
Dendrobium huoshanense	Water	Polysaccharides	*In vitro*	BSA glycation test with glucose. TNBSA assay to determine lysine modification Quantification. Determination of protein carbonyl content.	Inhibited Glycation	[82]
Polygonum multiflorum Thunb	Ethanol Water	Polysaccharides	*In vitro*	BSA glycation test with MGO.	Inhibited Glycation	[83]

Amino Acid and Peptide inhibitors:

Different peptides and amino acids also have the potential to reduce the formation of AGEs, if they are more reactive with reducing sugars than proteins and phospholipids. While studying the reactions of various peptides and amino acids with aldehydes, Zhou and Decker found that 5mM histidine reduced headspace trans-2-hexanal by only 8% when mixed with 0.5 mM of trans-2-hexanal and 5mM of β-alanine could not reduce headspace trans-2-hexanal at all. Glutathione was able to quench trans-2-hexenal and trans,trans-2,4-hexadienal by 47 and 21% respectively at glutathione concentrations of only 1 mM [84]. While in a different study, Hobart et al. found that histidine alone was more effective than carnosine in preventing glycation induced crosslinking of cytosolic aspartate aminotransferase, ceasing the formation at a 1:1 antiglycation agent to causative agent ratio; while Carnosine needed a 50:1 ratio to prevent protein modification by methylglyoxal [85]. In a study of yam hydrolysates, Han et al. compared the dipeptides asparagine-tryptophan and glutamine-tryptophan to carnosine, homocarnosine, and glutathione in their ability to prevent glycation of bovine serum albumin with galactose. Carnosine inhibited glycation approximately the same as asparagine-tryptophan, homocarnosine, and glutathione, interestingly, all of these were more effective than glutamine-tryptophan. At a concentration of 50 μM, carnosine was more effective than asparagine-tryptophan followed by homocarnosine, but glutathione and glutamine-tryptophan showed no such effect. When glucose was the reducing sugar, and 100 μM of the peptide was used, glutathione exhibited more activity than homocarnosine, which in turn was more effective than both asparagine-tryptophan and glutamine-tryptophan, which were almost equivalent. However, the antiglycation activity of carnosine was less than glutathione, homocarnosine, asparagine-tryptophan, and glutamine-tryptophan. At a concentration of 50 μM, asparagine-tryptophan and glutamine-tryptophan had negligible effects, while glutathione showed better results than carnosine. Pre-treatment of cells with asparagine-tryptophan and glutamine-tryptophan resulted in an increase of cell survival from 50% to 90% when stress was applied with methylglyoxal (one of the common reactive carbonyl species in the body). The various actions of the synthesized peptides from different studies and their active components are presented in **Table. 3**.

Table 3: Recent update on amino acid and peptide inhibitors as antiglycation agents.

AMINO ACID AND PEPTIDE INHIBITORS					
Source	**Active component**	**Methodology**	**Analysis**	**Results**	**Reference(s)**
Synthesized amino acid	Histidine	Addition of histidine to glyceraldehyde in 20:1 ratio and cytosolic aspartate aminotransferase before incubation.	Protein electrophoresis	20 mM caused 60% inhibition of crosslinking	[85]
Synthesized amino acid	B alanine	Addition of B alanine to glyceraldehyde in 10:1 ratio and cytosolic aspartate aminotransferase before incubation.	Protein electrophoresis	5 mM caused 36% inhibition of crosslinking	[85]
Synthesized Peptide	Anserine	20 mM of compound was added to previously glycated Glucose-ethylamine.	Nuclear magnetic resonance	20mM of anserine was able to reverse early glycation	[86]
Synthesized Peptide	asparagine-tryptophan	50 or 100 µM of peptide was added to bovine serum albumin and galactose or bovine serum albumin and glucose and heated.	sodium dodecyl sulphate–polyacrylamide gel electrophoresis and an anticarbocymethyllysine antibody	100µm reduced carbocymethyllysine to 30.7% of the control in galactose system and to 63.2% in glucose system	[87]
Synthesized Peptide	glutamine-tryptophan	50 or 100 µM of peptide was added to bovine serum albumin and galactose or bovine serum albumin and glucose and heated.	sodium dodecyl sulphate–polyacrylamide gel electrophoresis and an anticarbocymethyllysine antibody	100µm reduced carbocymethyllysine to 14.8% of the control in galactose system and to 58.8% in glucose system	[87]
Synthesized Peptide	Carnosine	20 mM of compound was added to previously glycated Glucose-ethylamine	Nuclear magnetic resonance	20mM of Carnosine was able to reverse early glycation	[86]
Synthesized Peptide	Carnosine	A crystallin was incubated with 10 mM ribose or deoxyribose with or without the addition of Carnosine	sodium dodecyl sulphate–polyacrylamide gel electrophoresis	50mM Carnosine prevented glycation entirely	[88]
Synthesized Peptide	Carnosine	Addition of Carnosine to glyceraldehyde in 10:1 ratio and cytosolic aspartate aminotransferase before incubation.	Protein electrophoresis	5 mM caused 68% inhibition of crosslinking	[85]
Synthesized Peptide	Carnosine	50 or 100 µM of peptide was added to bovine serum albumin and galactose or bovine serum albumin and glucose and heated and carboxymethyllysine was detected with an antibody.	sodium dodecyl sulphate–polyacrylamide gel electrophoresis	100µm reduced carbocymethyllysine to 13% of the control in galactose system and to 68.5% in glucose system	[87]

Synthesized Peptide	Carnosine	Streptozotocin -induced diabetic rats given oral dose of 1g Carnosine /kg body weight/day	quantitative retinal morphometry, analysis of retinal proteins, Histological examination of retinal paraffin sections	Oral dose of Carnosine Prevented retinal vascular damage primarily by altered gene expression	[89]
Synthesized Peptide	Carnosine	A diet composed of 0.001%, 0.01%, or 0.1% of Carnosine by mass was given to 2-deoxy-D-glucose induced diabetic rats	Blood sampling	0.01% or 0.001% Carnosine suppressed hyperglycemia,	[90]
Synthesized Peptide	Homocarnosine	50 or 100 µM of peptide was added to bovine serum albumin and galactose or bovine serum albumin and glucose and heated	sodium dodecyl sulphate–polyacrylamide gel electrophoresis and an anticarbocymethyllysine antibody	100µm reduced carbocymethyllysine to 17.8% of the control in galactose system and to 49% in glucose system	[87]
Synthesized Peptide	Glutathione	50 or 100 µM of peptide was added to bovine serum albumin and galactose or bovine serum albumin and glucose and heated	sodium dodecyl sulphate–polyacrylamide gel electrophoresis and an anticarbocymethyllysine antibody	100µm reduced carbocymethyllysine to 17.8% of the control in galactose system and to 49% in glucose system	[87]
Synthesized Peptide	Glucagon-like peptide-1	Murine podocytes	Western blotting	RAGE was down regulated	[91]
Garlic	c-glutamylcysteine derivatives	Maillard reaction systems with glucose L-lysine mixture	CML determination	Decreased CML	[92]

Alhamdani et al. studied the protection of human peritoneal mesothelial cells from the toxic effects of peritoneal dialysis fluid, which contained both glucose and glucose degradation products; both of which can produce AGEs, using many potential amino acids and dipeptides. It was reported that as far as protective effects are concerned, carnosine was more effective than homocarnosine followed by β-alanine, anserine and histidine [93]. Histidine and anserine both showed toxicity to the cells, with histidine displaying cell toxicity without a protective effect in the presence of the peritoneal dialysis fluid. Hipkiss et al. incubated 50 mM of various peptides with 500 mM of different sugars [88]. After HPLC analysis at specific times, the researchers found that homocarnosine showed lower reactivity with reducing sugars when compared to carnosine and thus may be less effective in decreasing early glycation.

The Inhibition of AGEs by amino acids and small peptides vary in each study. Differences between the models chosen, such as the type and amount of sugar used, the amount of protective agent added, the protein target and consideration of toxicity play a crucial role in concluding the results. There is an emerging trend that homocarnosine is less reactive than carnosine, which is less responsive than histidine with glucose and reactive carbonyls such as methylglyoxal. Carnosine and Homocarnosine have an additional advantage in that they display less toxicity than glycated amino acids in cell models. There are numerous sources of proteins and peptides that could have potential to decrease AGE formation. However, varied results between current studies indicate that more research is needed to identify which peptide structures that have the ability to reduce AGEs formation.

CONCLUSION:

These findings suggest that there is an urgent need to address the issue of bioavailability and fill up the void between the results obtained in *in vitro* and *in vivo* platforms for better clarification in further studies. In addition, many studies have found that the use of more than one plant-based antiglycation agent synergistically can give better results than a single agent. Further, the pace of research should be way ahead than the increasing incidences of glycation-

related diseases to develop functional foods from the natural sources.

CONFLICT OF INTEREST

The authors declare that they have no financial conflict of interest.

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