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The Antiglycation Ability of Typical Medicinal Plants, Natural and Synthetic Compounds: A Review

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Abstract

Given the prevalence of diabetes and the increasing number of diabetics, it is essential to find medicines to decrease the chronic complications of diabetes. Several studies have demonstrated that chronic hyperglycemia and its complications are directly related to protein glycation. Thus, identifying natural inhibitors to stop glycation of proteins may play a crucial role in managing the chronic complications of diabetes. Currently, various natural and synthetic compounds with anti-glycation attributes have been reported. The use of natural compounds in herbs (medicinal and non-medicinal) may be of particular importance due to fewer side effects and a wide range of therapeutic properties. Accordingly, this mini-review provides a list of common natural medicines and synthetic compounds with anti-glycation activity. As well, it provides brief information on the formation of advanced glycosylated end products (AGEs), their side effects, and glycation prevention mechanisms.

Keywords: AGEs, Diabetes complication, Anti-glycation compounds

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Introduction

Almost all plasma proteins are sensitive to reactions with reducing monosaccharides, both enzymatic and non-enzymatic. The enzymatic reaction of different sugars with proteins is called glycosylation, while protein glycation is a non-enzymatic process in which 'reducing sugars' randomly interact with their free amino groups (1,2). This process was first discovered by the German scientist 'Louis Camille Maillard'. During food packaging and storage, the Maillard reaction can change the taste and color of foods. The formation of dicarbonyl compounds through the Maillard reaction is an essential step to the formation of methylglyoxal (MG), which is among the most deleterious dicarbonyl compounds playing significant role in aging and diabetes (3,4). The level of MG reaches ~0.4mM in the blood of diabetic patients, which is much higher than non-diabetics. Therefore, active dicarbonyl species such as MG cause metabolic disorders, and develop their consequences (5,6).

The glycation process does not occur under normal conditions, whilst the blood glucose levels persist chronically, glycation causes the production of advanced glycation end products (AGEs). However, extreme AGEs in the diet have been reported to induce many of diseases in humans (7,8). Accumulation of elevated level of AGEs in different tissues can play significant role in the chronic complications of diabetes. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), which ultimately increases the risk of DNA mutation, cells vulnerability, activation of destructive signaling pathways, as well as inflammatory cascades, are all originate from AGE adducts. Cellular and tissue damage by AGE may result from protein modification, structure conversion, and functional degradation. Accordingly, high level of pentosidine causes wall thickness and stiffness of the heart arteries (9,10).

Accordingly, high levels of pentosidine due to the formation of AGE increase the wall thickness and stiffness of the arteries of the heart. On the other hand, bovine serum albumin (BSA) has been shown to undergo profound structural changes due to glycation, gaining more beta plates than the native sample (6,11).

Recently, anti-glycation agents have been one of the most critical goals in slowing down the rate of aging and the spread of disease (12). *In vitro* and *in vivo* studies have established the antioxidant and anti-glycation capacity of different medicinal plants. The natural compounds of medicinal plants with high antioxidant ability, metal chelating capacity, trapping of dicarbonyl compounds, and suppression of the receptors of advanced glycation end products (RAGEs), prevent the formation or production mechanisms of AGEs (13,14). Therefore, this mini-review of medicinal herbs, natural and synthetic compounds with anti- glycation activity is introduced (Table 1), to help pharmacological researchers find the best way to treat the complications of diabetes.

AGEs formation

There are two different pathways for the formation of AGEs that show a link between oxidation and glycation. In the first stage, oxidation of glucose in the presence of metal ions leads to the formation of ketoaldehyde radicals. After the ketoaldehyde reacts with the NH2-protein groups, ketominin is formed, leading to the production of AGEs (24). The second route involves the autoxidation of by-products, which eventually produce AGE and radical superoxide (25). Thus, free radicals damage biomolecules and alter their function. In diabetes, the production of free radicals' damage biomolecules and weakens antioxidant systems. Accordingly, antioxidants can play a key role in preventing the chronic complications of diabetes (26). Most of the plants introduced in this study have antioxidant properties.

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AGEs effects on proteins

Glycation of proteins alters the catalytic activity of enzymes, enhances the crosslinking of proteins, produces free radicals, and reduces the binding affinity of ligands and regulatory molecules (18), which are discussed below.

Effects on protein cross-linking

Protein cross-linking occurs in the termination stage of the glycation process and leads to tissue damage. For example, protein cross-linking in the extracellular matrix hardens and reduces the flexibility of proteins, resulting in a thickened basement membrane and impaired organ function, as seen in diabetic neuropathy (27,28). *Achillea pachyephala*, *Azadirachta indica*, *Satureja hortensis*, *Thuja orientalis*, *Eucommia ulmoides* are among the medicinal herbs capable of reducing protein cross-linking (15,17).

Enzyme Inactivation

The most likely mechanism of enzyme inactivation requires the binding of glucose to the epsilon-Lysin amine group at the active site of the enzyme. If this epsilon-Lysin plays a major role in catalytic activity, the enzyme is inactivated (29). One of the most important examples is the glycation of the Lecithin cholesterol acyltransferase (LCAT), which leads to a loss of fat function (30).

Production of free radicals

AGEs accumulated in the body produce active sites for the catalysis of one-electron reduction reactions that catalyze free radicals' production. These active sites, which exhibit enzyme-like properties (Nanozymes), may be produced Schiff base products that can catalyze the metal- like oxidation reactions (8,31,32).

Effects of AGEs through binding to RAGEs

Once the AGEs connect to their receptors, RAGEs (receptors for AGEs), multiple messaging factors are activated, followed by activation of factors such as NF-*k*B, AP-1, STAT-3 NF-*k*B, AP-1 and STAT-3 are stimulated. These factors affect the expression of some genes, and can lead to a variety of

Table 1. List of several different types of plants with antiglycation and antioxidant properties with their function

S.NO.	Family	Herbs noun	Functional
1	Asteraceae	*Achyrocline satureioides*	Suppression the production of MG (15)
2	Lamiaceae	*Melissa officinalis*	Metal-chelating capacity, low affinity AGE to RAGE (11), and protection of hemoglobin (Hb) against fructose (16).
3	Asteraceae	*Achillea pachyephala*	MG-induced change, BSA-AGE Secondary restructuring, and Changing hydrophobic sites in the BSA-AGE (10) High levels of phenols, flavonoids, and power reducing ability (17)
4	Meliaceae	*Azadirachta indica*	Inhibit BSA-AGE, HbA1c production; reduce protein glycation and MG rate in diabetic rate.
5	Lamiaceae	*Satureja hortensis*	Prevention of α-helix change by hiding glycation sites and reducing solvent access (18)
6	Lamiaceae	*Rosmarinus officinalis*	Eliminate free radicals, prevent AGEs formation, and display reducing activity BSA –MG seystem (19).
7	Eucommiaceae	*Eucommia ulmoides*	Inhibition of glycation (20).
8	Fabaceae	*Trifolium pratense*	Blockage of ROS production and Hb glycation (21).
9	Cupressaceae	*Thuja orientalis*	Contains high flavonoid content that reduces the activity of the aldose rductase. Prevention the glycation by breaking the AGEs adducts (22).
10	Apiaceae	*Anethum graveolens*	Stops the schiff base level. Suppress the production of MG and •OH (23).
11	Lamiaceae	*Scutellaria baicalensis*	Inhibitory ability of α-glucosidase, α-amylase and AGE production
12	Solanaceae	*Withania somnifera*	Decrease of BSA-glycation.
13	Lamiaceae	*Salvia divinorum*	Antiglycative and antioxidant capacity, decrease of free radical level.
14	Ericaceae	*Vaccinium macrocarpon*	Inhibition of Hb-AGE and BSA-AGE by scavenging dicarbonyl compound.
15	Rosaceae	*Pyrus pyrifolia*	Protection of formation BSA-fructose in vitro.
16	Asteraceae	*Siegesbeckia orientalis*	Prevention the formation of amadori and carbonyl compounds.
17	Rutaceae	*Zanthoxylum ailanthoides*	Inhibition glycation and aldose reductase. Fe2+ chelating, reducing power and free radical scavenging activity.
18	Scrophulariaceae	*Limnophila aromatica*	Suppression carboxymethyl lysin (CML) and decrease LDL cholestrol.

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events (33). For instance, activation of NF-*k*B, regulates the immune response to infections, the process of apoptosis, and the ability of cells to survive. Accordingly, impaired NF-*k*B production leads to cancer, autoimmune diseases, inflammation, and viral infections (34-36). AP-1 is involved in cell differentiation and proliferation as well as apoptosis. Therefore, the ligand binding to RAGEs with the production of AP-1 can cause complications in these processes (37,38). STAT protein is involved in regulating many features of cell growth, viability, and differentiation. Disruption of the STAT pathway plays an essential role in tumor formation, increased angiogenesis, increased tumor viability, and inhibition of the immune system against tumors (39,40).

The mechanisms to prevent the AGEs formation

AGEs play a key role in altering physiological processes and enhancing pathophysiological pathways. Therefore, preventing the formation of AGEs can be a promising treatment strategy to overcome the complications of diabetes and similar 'conformational diseases' such as Alzheimer's and Parkinson's diseases. Mechanisms of AGE suppression include, strengthening the cascades of the body's natural defense system, or consuming natural compounds and/or chemical inhibitors (33,34). Some of body's defense mechanisms are briefly mentioned below.

The body's defense mechanism against the glycation

In general, our body has different mechanisms against non-enzymatic glycation of biomolecules that can be divided into five main groups consisting of, plasma amines, macrophages, glyoxalase system, relevant enzymes, and antioxidant system.

Natural and chemical inhibitors

Due to their therapeutic properties, there is a lot of attention to AGE inhibitors. Anti-glycation agents may act by suppressing carbonyl groups, trapping MGOs, and suppressing ROS to prevent the formation of AGEs (8,41). Because natural compounds from medicinal plants have the ability to prevent the formation of AGE, they may allow the complications of diabetes to be suppressed. Table 2 shows a number of natural and synthetic compounds with anti-AGE properties as well as their performance.

Conclusions

Identification of natural anti-glycation compounds provide useful platform for treatment of many conformational diseases. The present communication examined a list of typical plants, natural and synthetic compounds with established anti-glycation properties, which direct the pharmacological researchers to find a better way for treating the consequences of diabetes. The anti-glycation function includes suppressing the production of methylglyoxal (MG), preventing the α-helix deformation, blocking the production of reactive oxygen species (ROS), and reducing

Table 2. A number of natural and chemical antiglycation as well as their function

Compounds	Agent type (N/C*)	Antiglycation functional	Ref.
Quercetin	N	Trapping of MGO and GO (44)	(42)
Lignan	N	Suppression of NADPH & ROS(45)	(43)
Curcumin+Chlorogenic acid	N	Neutralize the effect of AGEs aggregation	(1)
Aminocoumarins	C	Prevention of detrimental AGEs formation	(44)
Aspirin	C	acetylation of free amino groups	(45)
Resveratrol	N	Suppression of MG	(46)
Losartan	C	Decreased serum AGEs	(4)
Hesperitin+Stilben	N	Block RAGEs	(47)
Thiazolidine Derivative	C	Prevent the accumulation of AGEs in the renal glomeruli	(4)
Pyridoxamine	C	Inhibitor of the change of Amadori product to AGEs	(48)

*:N; Natural, C; Chemical

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the advanced product formation of glycation. Therefore, such studies provide useful information toward understanding the anti-glycation mechanisms and efficacy of natural compounds.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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