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Review Article

An Overview on Plants Inhibiting Protein Glycation in Diabetes

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ABSTRACT

In diabetes mellitus is a metabolic disorder characterized by hyperglycemia. The major cause of diabetic complications is the non-enzymatic reaction between amino groups of protein and carbonyl groups of reducing sugar which lead to formation of Schiff base and finally give irreversible amadori products known as advanced glycation end products (AGEs). The glycation process is accompanied by generation of free radicals, the oxidative stress is responsible in progression of AGEs. The present review article provides list of anti-glycation plants with probable mechanism of action which can be useful in identifying better components for diabetic complications.

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INTRODUCTION

Glycosylation or glycation is the process involving the nonenzymatic modification of tissue proteins and lipids. The process of translational modification of proteins is called “glycation or glycosylation” (Stanaway S.E., *et al*., 2000). Most commonly involved sugar is glucose and the process of glycation occur both intra and extra-cellularly. In diabetic patients more glycation occur due to increase plasma glucose levels. The products of protein glycosylation are called “advanced glycation end products (AGEs),” and it get accumulated in tissues over time and play significant role in the pathogenesis of diabetic complications (Stanaway S.E., *et al*., 2000; Nawale R. B., *et al*., 2006; Severin F.F., *et al*., 2013). Various proteins undergo such modificatns but well known example of protein glycation is of haemoglobinA (HbA) β chains. The plasma levels of glycated HbA is a biochemical indicator to monitor glycemic control. In diabetic patients, it is recommended to measure glycosylatedhaemoglobin (HbA_1C) in every 3 to 6 months (Stanaway S.E., *et al*., 2000).

Glycation Mechanism

In vitro, glucose combines nonenzymatically with α and ϵ amino group. *In vivo*, the discovery of HbA_1C, minor human haemoglobin component, is a product of slow condensation of aldehyde group of glucose and $–NH_2$ group of β chains of haemoglobin. The reaction occurs in two stages first, glucose forming a Schiff base with α amino group of at the N-terminus of β globin chains (Shapiro R., *et al*., 1980). This is a reversible reaction. It is followed by internal Amadori rearrangement. This yields a stable ketoamine derivative, known as “advanced glycation end-products”(AGEs) (Vistoli G., *et al*., 2013). Several studies suggest that these AGEs play important role in the pathogenesis of oxidative stress induced diseases such as diabetes, chronic heart failure, chronic renal failure and neurological disorders (Nawale R. B., *et al*., 2006). It is also mentioned that intraceullarly present glucose and other sugars can form AGEs by adduction to amino group of nucleotides. This may result in increased DNA mutation rate and ineffective repair of histone protein (Severin F.F., *et al*., 2013; Vistoli G., *et al*., 2013).

This review shows list of anti-glycation natural products that can be useful in diabetic complications.

MATERIALS AND METHODS

Scopus, PubMed, Google scholar, Researchgate, Web of Science and Taylor & Francis online databankwere searched from 1998 to 2021 for antiglycation plants. The key words used were AGEs, anti-diabetic plants, human haemoglobin glycosylation inhibition, medicinal plants, antiglycation products.

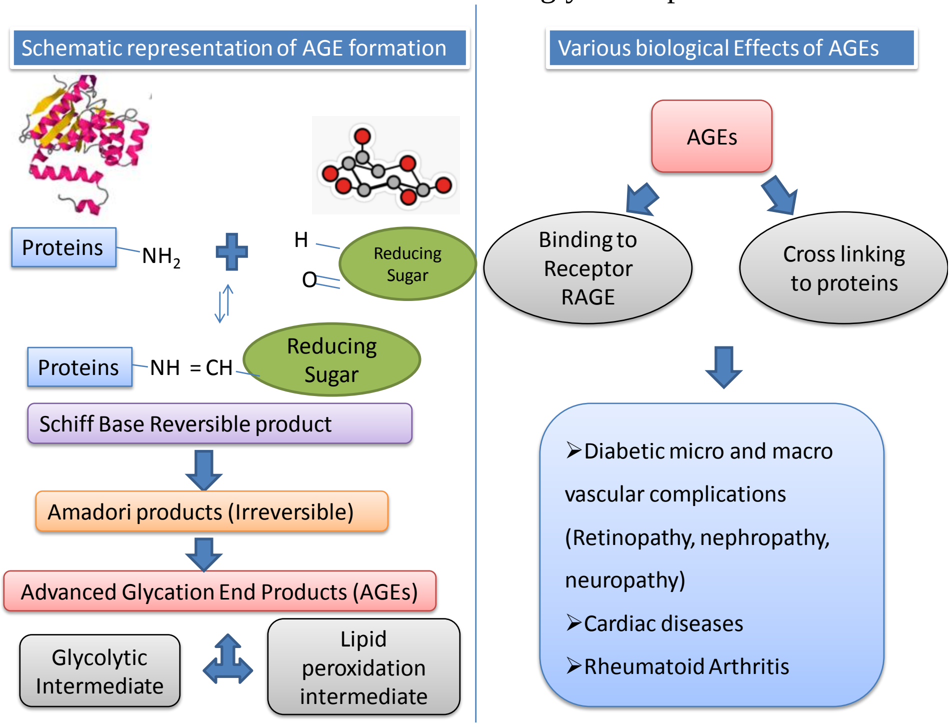

Fig. 1: Schematic presentation of Advanced glycation end products (AGEs) formation and its biological effects (Severin F.F., *et al*., 2013).

Anti Glycation mechanism

AGEs formation include many steps and hence glycation inhibition can occur at any of step. The possible mechanisms (Severin F.F., *et al*., 2013; Vistoli G., *et al*., 2013; Nawale R. B., *et al*., 2006) include-

1. Reduction in free radical generation: During early Millard reaction step, scavenging free radicals reduces oxidative stress and decreases production of reactive carbony as well as dicarbonyl groups.

2. Reduction in formation of Amadori products: Reduction in formation of reversible Schiff base ultimately reduces production of Amadori products and AGE formation by blocking carbonyl and dicarbonyl groups.
3. Inhibition of cross linking of AGEs
4. Inhibition of reactive dicarbonyl compounds.
5. Chelation of metal ions: Presence of transional metal ions is essential for AGE production, hence chelation of such metal ions may hinders AGE production.
6. Blocking the receptors for AGEs.

Poly phenols and flavonoids With anti-glycation Property

Phenols are aromatic organic compounds characterised by –OH group. These are secondary metabolites and most common polyphenol substances are phenolic acids, lignans, and flavonoids. Polyphenolic compounds are scavengers of free radicals and neutralises reactive species[6]. These compounds also inhibit methylglyoxal formation and able to detoxify the same. Studies have shown that Stilbenes, Phenolic acids and flavonoids found to inhibit formation of AGEs and also block RAEG (Receptor of advanced glycation end products) (Severin F.F., *et al*., 2013). Some studies indicated that phenolics quenches free radicals and inhibit AGE formation also phenolic acids act as metal chelators. Studies have indicated that flavonoids are polyphenolic compounds with highest potential for inhibition of glycosylation, glycoxidation and in addition these compounds able to inhibit glycation at early stages as well as at advanced stages of glycation for example, flavanols (catechin, epicatechin , epicatechin gallate) flavones (luteolin), flavonols (kaempferol, quercetin, rutin), and flavonols (naringenin) (Severin F.F., *et al*., 2013; Yeh W.J., *et al*., 2017).

Table 1: Plants with Anti-glycation activity

Plant name	**Part used**	**Chemical constituent**	**Mechanism of action**
Aegle marmelos Rutaceae	Methanolic extract of Fruits and seeds	Phenolics and flavonoids like	Decreases HbA_1C production prevent RAGE and AGEs accumulation. (Hafizur, *et al*., 2017; Safari M.R., *et al*., 2018).
Aloe arborescens Xanthorrhoeaceae	Leaf extract	Barbaloin, isobarbaloin and aloe emodin	Inhibit oxidative stress and related AGE production (Froldi G., *et al*., 2019).
Andrographis paniculata Acanthaceae	Aerial parts	Andrographolide, Deoxy 11,12-didehydro andrographolide	Antiglycation activity by inhibiting glucose-BSA (Bovine Serum Albumin) formation (Safari M.R., *et al*., 2018; Karunananda H., *et al*., 2020).
Artocarpus lakoocha,Moraceae	bark extract	Oxyresveratrol 2,4,3′,5′-tetrahydroxystilbene)	Inhibition of AGE- glycated BSA production (Pande A., *et al*., 2021).
Artocarpus heterophyllus, Moraceae	Methanolic extract of Leaves	prenylated and isoprenylated flavonoids	Inhibition of glycosylation of haemoglobin (Tanjung E., *et al*.,

			2015).
Azadirachta indica, Meliaceae	Chloroform extract of aerial parts	Phenolics and flvanoids like azadirachtin	Inhibit formation of glycated BSA and HbA_1C (Gutierrez, M.R., *et al*., 2015; Begum FM., *et al*., 2017).
Cinnamomum zeylanicum	Ethanolic extract of bark	proanthocyanidins	Inhibition of glycosylation of haemoglobin. Reverse BSA-Glc and BSA-MGO formation (Sirimal, P.G., *et al*., 2017).
Curcuma longa, Zingiberaceae	Rhizome	Curcumin	Inhibit HbA_1C and accumulation of AGE-collagen in diabetics (Kulkarni A.S., *et al*., 2017).
Emblica officinalis, Euphorbiaceae	Fruit	polyphenol with low and high molecular weight gallotannins.	Inhibit albumin AGEs aggregation (Begum FM., *et al*., 2017).
Eugenia jambolana Myrtaceae	Seeds	Polyphenols- iso-oenothein, rubuphenol, valoneic acid dilactone etc.	Inhibit fructose induced AGE formation with potent free radical scavenging property (Liu F., *et al*., 2018).
Fumaria officinalis, Fumariaceae	Methanolic extract of aerial parts	phenolic flavonoids and phenolic acids.	Neutralise free radicals and prevent albumin glycation (Safari M.R., *et al*., 2018).
Ficus deltoidea, Moraceae	methanolic crude extracts of fruits and leaves	vitexin and isovitexin	Inhibit AGEs in the BSA-fructose system also inhibit post-Amadori glycation in human serum albumin-glucose and human serum albumin-methylglyoxal assay (Dom N., *et al*., 2020).
Grape pomace	Residue of wine making	Anthocynin and proanthocyanidin, other phenolics	Inhibit protein carbonylation. (Sri Harsha P., *et al*., 2019).
Gymnema sylvestre, Asclepiadaceae	Hydroalcoholic leaf extract	Polyphenols	Inhibit GSH depletion and reactive oxygen and nitric oxide species thus decreases accumulation of AGEs (Kishor L., *et al*., 2015).
Hibiscus cannabinus, Malvaceae	Methanolic extract of leaves	p-coumaric, and trans-ferulic acids, kaempferol-3-Oglucoside	Antiglycation through anti-oxidant mechanism (James, A., *et al*., 2011).

Momordica charantia Cucurbitaceae	Aqueous flesh and pulp extract	Phenolic- catechin and flavonoid- Rutin content	Inhibition of glycated haemoglobin (HbA1c) and serum fluorescent AGEs through chelating property (Aljohi A., *et al*., 2016).
Piper betle, Piperaceae	Methanolic extract of Leaf	Triterpenoids, Phenolics and flavonoids	Inhibition of glycosylation of haemoglobin (Bhattacherjee A., *et al*., 2013).
Pterocarpus marsupium, Leguminoceae	heart wood extract	Pterostilbene (Trans-3,5-dimethoxy-4′-hydroxystilbene)	Inhibition of AGE- glycated BSA(Bovine Serum Albumin) production (Pande A., *et al*., 2021).
Rosa Damascene, Rosaceae	Methanolic Flower extract And its silver nano particles	Phenolic compounds	Antiglycation due to anti-oxidant property (Safari M.R., *et al*., 2018; Peron S., *et al*., 2021).
Stachys lavandulifolia, Lamiaceae	Methanolic extract of aerial parts	Flavonoid	Neutralise free radicals and prevent albumin glycation (Safari M.R., *et al*., 2018).
Salvia hydrangea, Lamiaceae	Methanolic extract of aerial parts	Phenolics and flavonoids	Neutralise free radicals and prevent albumin glycation (Safari M.R., *et al*., 2018).
Seriphium plumosum Asteraceae	Whole plant	Phenolics and flavonoids	Antioxidant mechanism (Beseni B.K., *et al*., 2017).
Silybum marianum, Asteraceae	Flower extract	Flavonoids& Phenolics like gallic acid, ferulic acid	Non-enzymatic anti-oxidative mechanism (Shin S., *et al*., 2015)
Scutellaria alpine, Scutellaria altissima, Lamiaceae	Ethanolic extract of shoots and roots	phenylethanoid glycoside , Baicalin and luteolin	quenchers of dicarbonyl intermediates, and metal ion chelators (Karolak, I.G., *et al*., 2015).
Withania somnifera Solanaceae	Ethanolic extract of roots	Withanaloids.	Reduces collagen glycation as well as cross linking (Anandh, B., *et al*., 2014).

CONCLUSION

Diabetes is a metabolic disorder and its prevalence is continuously increasing, about 2.8 % of global population is affected by this metabolic disorder. Several studies indicated that hyperglycemia causes increased non-enzymatic protein glycation which leads to increased AGEs formation and their accumulation in the body. This play vital role in pathogenesis of various micro-vascular and macro-vascular complications in diabetic subjects (Stanaway S.E., *et al.*, 2000; Severin F.F., *et al.*, 2013). Therefore compounds that inhibit glycation may be effective in counteracting the diabetic complications. Today, number of natural (Dil FA., *et al.*, 2019) as well as synthetic compounds (Abbas G., *et al.*, 2000) has been investigated for anti-glycation property. So, in this article a list of plants with anti-glycation activity is presented and discussed. Many studies indicated correlation of polyphenolic compounds, their antioxidant properties and abilities to scavenge free radicals and thus act as anti-glycation agents. Further investigation is thus required to establish the polyphenolic compounds as functional food to inhibit glycation and delay diabetic complications.

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