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Review

A systematic review of antiglycation medicinal plants

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ABSTRACT

Background and objectives: The present review shows a list of anti-glycation plants with their anti-glycation activity mechanisms that can attract the attention of pharmacologist for further scientific research towards finding better remedy for diabetic complications.
Materials: Google scholar, Pubmed, Web of Science and Scopus were searched. The terms were advanced glycation end products (AGEs), medicinal plants, antiglycation products.
Results: plants that studied in this review inhibit glycation in several possible mechanisms. Some of these plants inhibit the production of shiff base and amadori products. The others inhibit the generation of amadori products in the advanced phase. Some others blocked the aggregation of AGEs and some plants have antioxidant activity and reduce AGEs formation by preventing oxidation of amadori product and metal-catalyzed glucoxidation.
Conclusion: This review can help pharmacologist to find antiglycation natural substance that can be useful in treatment of diabetic complications.

1. Introduction

Proteins in human body can take part in reaction with sugars in both enzymatic and non-enzymatic forms. The enzymatic reaction of proteins with sugars that results in the production of glycoproteins is called glycosylation [1]. The non-enzymatic reaction of sugar and protein, called glycation, is not carried out under normal conditions extensively in the body; but, when blood glucose is high for long periods of time as in untreated diabetes, glycation process is done leading to products called advanced glycation end products, termed AGEs [2]. Enhanced production of ROS induced by AGEs can potentiate DNA damage and elevate risk of mutagenesis [3]. Collagen connections that occur as a result of AGEs, play an important role in the development of vascular hypertrophy [4]. It has also been observed that increasing pentosidine (one types of AGEs) levels leads to an increase in wall thickness and cardiac artery hardness. Also, in type 2 diabetic patients with peripheral artery disease, the levels of pentosidine and malondialdehyde (formed as a result of lipid peroxidation) increase [5].With regard to the role of AGEs in the pathogenesis of diabetic complications and other diseases, compounds with anti-glycation property can help to reduce glycation-associated disease. A variety of natural and synthetic compounds have been evaluated to test their anti-glycation properties. The use of natural compounds seems to be a better treatment for inhibiting the glycation process and AGEs formation due to their fewer complications compared to synthetic compounds. Therefore, the anti-glycation property of many plants has been reportedso far.The present review shows a list of anti-glycation plants with their anti-glycation activity mechanism (Table 1). Because the process of forming AGEs is a multi-stage process, anti-glycations compounds may inhibit the formation of AGEs at each of these steps. For example, antiglycation compounds may inhibit the formation of AGEs by interfering with metals, by blocking AGEs, or reduce cellular changes induced by AGEs.

2. Materials and methods

2.1. Search strategy

Google scholar, Pubmed, Web of Science and Scopus databank were searched from 2000 to 2018 for antiglycation plants. The terms were AGEs, medicinal plants, antiglycation products.

2.2. Study selection

The studies that examined the antiglycation properties of a

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Table 1
The studies on different plants with antiglaycation effects.

Number	Plant name	Extract	Mechanism of action	Ref
1	Aloe Sinkatana Reynolds	Leaves (ethanol and methanol extract) 2,8dihydroxy 6 (hydroxymethyl) 1-methoxyanthracene 9,10dione	Decrease HbA1c levels and inhibit AGEs formation.	[6]
2	Anethum graveolens L. (dill)	Leaves (Aqueous extract)	reduce AGEs formation and fructosamine levels, protein carbonyl, thiol group oxidation, amyloide cross β and fragmentation in BSA-Glc system	[7]
3	Allium victorialis	Leaves	Reduce AR activity, AGEs formation, AGE-RAGE binding	[8]
4	Acca sellowiana	Fruit (Hexane extract)	Inhibit the formation of AGEs, reduce the levels of fructosamine and CML, preventing of oxidative damage of proteins as well as an effect on the oxidation of thiol groups and carbonyl content in BSA-Glc system.	[9]
5	Azadirachta indica	Leaves	Inhibit BSA glycation, HbA_{1c} formation, glycation and oxidation of LDL, decrease serum-glycosylated protein in diabetic rats, decrease the renal MG level in diabetic rats,	[10]
6	Achyrocline satureioides	Whole plant (Water extract)	Inhibit the formation of AGEs, preventing MGO-induced inhibition of plasminogen and antithrombin 3	[11]
7	black currant	Fruit	Inhibitory effects on the formation of dicarbonyl compounds and AGEs but weaker inhibition Amadori compound production	[12]
8	Buniumpersicum	Seeds	Inhibit albumin glycation in a dose dependent manner and also decrease the levels of thiol group oxidation and BSA aggregation	[13]
9	Boswellia sacra	Resin-methanol extract fractions	Inhibit the formation of AGEs and show antioxidant properties	[14]
10	Byrsonima crassifolia	Fruit and seeds (Hexan chloroform and methanol extract)	Inhibitory activity against AGEs formation and antihyperglycemic activity.	[15]
11	Benincasa hispida	Fruit (Polysaccharides)	Inhibit the formation of AGEs and scavengene DPPH radicals.	[16]
12	Camellia nitidissima	Leaves (ethanolic extract and ethyl acetat fraction)	Inhibit fluorescent AGEs formation	[17]
13	Clitoria ternatea	Flower (The aqueous extract)	Inhibit the formation of AGEs in a concentration dependent manner, reduce the levels of fructosamine and the oxidation of proteins, prevent free thiol depletion.	[18]
14	Costus speciosus	Leaves (Methanol extracts)	Inhibit α-glucosidase, fructosamine formation, glycation and glycation induced protein cross-linking.	[19]
15	Coccinia grandis (L.)	Fruit	Methanol extract scavenge DPPH radical, supeoxide anione radical, and hydrogen peroxide. It also inhibit the formation of AGEs, decrease the levels of fructosamine, suppresse an increase in protein carbonyl content of fructose-glycated BSA.	[20]
16	Ceylon cinnamon (cinnamomum zeylanicum blume)	Leaf and bark	Inhibit AGEs formation and show glycation reversing activity in BSA-Glc and BSA-MGO system.	[21]
17	*Carpobrotus edulis*	Leaves	Inhibit AGEs formation, antioxidant activity.	[22]
18	Chinese olive (canarium album L.)	Fruit (water/ethanol extracts)	Scavenging effects on free radicals and strong inhibitory effects on AGES formation.	[23]
19	Citrus grandis L. Osbeck	Pulp	Reduce the level of fructosamine, reduce oxidation of thiol groups, inhibit the formation of CML	[24]
20	Cuminumcyminum	Seeds (Methanolic extract)	antihyperglycemic activity and inhibition of AGEs formation in STZ-induced diabetic rats	[25]
21	Derris indica	Stem bark isolated flavonoids	Inhibit the formation of AGEs.	[26]
22	Eremurus persicus	Flowering aerial parts (methanol extract)- 5,6,7trimethoxy coumarin	Antiglycation activity	[27]
23	Eucommia ulmoides	Leaves - quercetin 3-O-β-l-arabinopyranosyl-(1 → 2)-β-d-glucopyranoside and kaempferol 3-O-β-d-glucopyranoside (astragalin) and quercetin 3-O–_-d-glucopyranoside (isoquercitrin)	Glycation inhibitory activity	[28]
24	Fagopyrum tataricum	Seeds	Inhibit the formation of AGEs, suppresses α dicarbonyl compounds and decrease the levels of fructosamine (an amadori products), scavenge DPPH and ABTS radical.	[29]
25	Hydnora johannis	Roots (ethanolic extract)- catechin and protocatechuic acid	Inhibition of AGEs formation.	[30]
26	Ilex paraguariensis	Whole plant (Water extract)- cholorogenic acid and caffeic acid and oleanolic acid	Inhibit the formation of AGEs and prevent MGO- induced inhibition of plasminogen and antithrombin III.	[31]
27	Ixora undulate	compounds isolated from the leaves (corchoionoside, robinobioside, robinobioside4-E-*p*-coumarate)	Inhibit the formation of AGEs.	[32]
28	Iris locizy	Rhizome	A flavanone (2′, 5-dihydroxy-6,7-methylenedioxy) exhibit antiglycation activity, the compound (arborinone and 5,7dihydroxy-2′,6dimethoxyisoflavone) exhibit promising activity against α-glucosidase enzyme.	[33]
29	*Misgurnus anguillicaudatus*	polysaccharides from Raw	Inhibit the schiff base formation, dicarbonyl compounds and the formation of AGEs, scavenged hydroxyl radical and superoxide radical anion.	[34]
30	Mulberry (morus alba Linn.)	Leaves (Ethanolic extract)	Inhibit the AGEs formation and show antioxidant properties	[35]

Table 1 (*continued*)

31	Momordica charantia	Flesh and pulp	Inhibit the formation of MGO derived crosslinked AGEs and CML in a dose dependent manner with pulp being the most potent.	[36]
32	*Nelumbo nucifera*	Leaves	Show antioxidant properties and inhibit AGEs formation.	[37]
33	Passiflora manicata (juss.)	Leaves	Protective against reactive oxygen species and antiglycation activity.	[38]
34	Plantago asiatica	Methanol extract-active compound (plantamajosida)	Glycation inhibitory activity and antioxidant activity.	[39]
35	Polygonum multiflorum thunb	Whole plant (isolated Polysaccharides)	A gradual decrease of the formation of AGEs and also scavenge superoxide anion, hydroxyl radical and hydrogen peroxide and inhibit lipid oxidation in rat liver, heart and kidney.	[40]
36	Piper betle Linn	Leaves	Inhibit glucose-induced glycation, thiol group modification and carbonyl formation.	[41]
37	Piper auritum	Leaves (Hexane extract)	Inhibite AGEs formation and show antioxidant activity	[42]
38	Pueraria lobata	Root	Inhibit AGEs formation	[43]
39	Punica granatum	Rind	Free radical scavenging activity, inhibit the formation of AGEs, inhibit the formation of fructosamine.	[44]
40	Red grape	Skin	Antioxidant activity, inhibit AGEs formation, decrease the levels of fructosamine and CML, prevent the depletion of protein thiol group.	[45]
41	Retama sphaerocarpa	Fruit	Antiglycation and antioxidant activity.	
42	Salvia (choloroleuca, mirzayanii, santolinifolia)	Aerial parts	Anti-glycation and antioxidant activity, inhibitory effect on hydroxyl radical generation, pentosidine formation, radical-mediated DNA damage.	[46]
43	Saraca ashoka	Flowers-Flavenoid fraction	Inhibit the AGEs formation and LDL oxidation, inhibitory potential against −glucosidase and −amylase enzymes.	[47]
44	Siegesbeckia orientalis	Aerial parts	Inhibit the formation of amadori products, decrease the formation of dicarbonyl compounds.	[48]
45	Stauntonia hexaphylla	Leaves (Ethanol extract)	Significant inhibitory activity on the AGEs formation, RLAR, ABTS and DPPH radical.	[49]
46	Terminalia bellerica	Fruit (Methanol extract)	Inhibit α-Amylase and α-glucosidase, show antiglycation and antioxidant activity, inhibition of the oxidation of LDL under in vitro condition	[50]
47	Vaccinium macrocarpon	Berries- phytochemical fraction	Inhibition of glycation human hemoglobin and serum albumin by scavenging reactive carbonyls	[51]
48	Withania somnifera (solanaceae)	Root (powder and withania extract)	Reduce the collagen glycation and cross-linking. The effect of withania extract was more effective as compared to withania root powder.	[52]
49	Stelechocarpuscauliflorus R.E.Fr.	Leaves (Ethyl acetate extract)-fractions of ethyl acetate extract and isolated compounds (engeletin and astilbin)	Inhibit AGEs formation and aldose reductase.	[53]
50	Zingiber officinalis	Rhizomes (aqueous extract)	Did not normalize bodyweight, decrease blood glucose level, unaffected insulin level, reduce glycated protein in soluble fraction of lens, counter hyperglycemia-induced osmotic stress in the lens, increase proportion of cross linked and aggregated proteins.	[54]

particular plant were selected and those that were about the antiglycation property of other natural source such as fungi were removed. All studies were carefully examined and duplicate studies were deleted and those with positive antiglycation effects were presented in this article.

3. Results and discussion

Information about 50 medicinal plants with antiglycation activity are summarized in Table 1.

3.1. Effects on formation of amadori products

Glycation is a spontaneous non-enzymatic reaction between the carbonyl groups of reducing sugars and the free amino group of biological molecules, such as lipids, proteins and nucleic acids that leads to an unstable shiff base and then shiff base rearranged into an amadori product such as fructosamine [55]. Some of the plants mentioned in this review (Acca sellowiana, Clitoria ternatea, Costus peciosus, Coccinia grandis (L.), Fagopyrum tataricum (buck wheat), Punica granatum, Red grape) inhibit the formation of fructosamine [9,18–20,24,29,44,45].

3.2. Effects on oxidation of thiol groups in proteins

Amadori products converted into active dicarbonyl compounds such as glycoxal, methylglyoxal and 3-deoxyglucosone, during a series of chemical reactions. Finally, dicarbonyl compounds converted to irreversible compounds called AGEs. This process is called millard reaction [56].The non-enzymatic reaction of sugar to the proteins causes the carboxylation of the cysteine residues of proteins and decrease the reduced thiol content. Decrease in reduced thiol content of proteins such as albumin which is the most antioxidant in the circulation decreases its antioxidant activity [57,58]. Anethum graveolens L. (dill), Acca sellowiana, Bunium persicum, Clitoria ternatea, Piper betle Linn, Red grape prevent the oxidation

of thiol groups [7,9,13,18,24,41,45].

3.3. Effects on protein cross-linking

Protein crosslink occurs at the later part of glycation process. Protein cross-linking leads to damage tissues. For example protein cross-linking in extracellular matrix cause hardening and reduce the flexibility of these proteins, resulting in a thickening of the base membrane, and damage organ function, as observed in diabetic nephropathy [59]. Anethum graveolens L. (dill), Costus speciosus, Momordica charantia, Withania somnifera (solanaceae), Zingiber officinalis reduce protein cross-linking [7,19,36,52,54].

3.4. Antioxidant activity

There are two important pathways for AGEs formation, which demonstrate the relationship between oxidation and glycation; firstly the oxidation of glucose in the presence of metal ions, which leads to the production of ketoaldehyde and radical superoxide. Ketoaldehyde reacts with amino groups of proteins and produces ketoimines, which leads to the formation of AGEs [60]. The second mechanism for auto-oxidation of amadori products is the presence of intermediate metals and molecular oxygen, which leads to the production of AGEs and also radical superoxide. Free radicals are highly reactive because of unconjugated electrons [61]. Therefore, the presence of these agents in the body results in extensive damage to macromolecules in the body. In diabetics, the excessive production of free radicals and defective antioxidant systems, damage DNA, proteins, carbohydrates and lipids, which can cause cell dysfunction and cell death. Studies have shown that reactive oxygen species (ROS) produced by glycation of albumin in the presence of transition metals such as iron can cause damage to hepatocyte cells in rats [62].Therefore, the use of antioxidants can be useful in preventing complications of diabetes. Most of the plants named in this review have shown antioxidant activity [14,16,22,23,29,34–39,42,44–46,50,51,63].

4. Conclusion

Considering the prevalence of diabetes in today's world and the wide range of complications of diabetes, it is necessary to find drugs to reduce complications of diabetes. Different studies have shown that high blood sugar that occurs during diabetes plays a major role in the complications of diabetes by glycation of proteins. Therefore, finding inhibitors to prevent glycation may be effective in reducing diabetes complications. Today, various natural and synthetic compounds with anti-glycation properties have been investigated. It seems that the use of herbal compounds should be more effective than synthetic compounds due to their various properties and medicinal and nutritional effects. As a result, in this article a list of medicinal herbs with anti-glycation properties is presented and discussed.

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