Review Article

Prevention of non-enzymatic glycosylation (glycation): Implication in the treatment of diabetic complication

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Abstract:

Non-enzymatic glycosylation (glycation) plays an important role in the development of physiological and pathophysiological processes such as aging, diabetes, atherosclerosis, neurodegenerative diseases and chronic renal failure. Preventing glycation can minimize diabetic complications. Glycation can be prevented by the natural defence system in the body, synthetic inhibitors and natural inhibitors. Synthetic inhibitors may prevent glycation through several possible mechanisms. They might inhibit the glycation by interfering with the attachment of sugars with proteins, by inhibiting the late stage of glycation or by preventing Amadori product formation. Furthermore, their ability to scavenge free radicals and to break cross-links might be other mechanisms responsible for their potential to inhibit glycation. Naturally occurring phytochemicals/products have been found to be relatively non-toxic as compared to synthetic compounds, and are inexpensive and available in an ingestible form. A large number of plants and natural biomolecules have been shown to have antidiabetic effects. Several hypoglycaemic compounds have anti-oxidant properties. The present review describes the various ways in which glycation can be prevented.

Key words: Glycation, diabetic complications, natural defence system, synthetic inhibitors, natural inhibitors

Abbreviations: AGEs, advanced glycation end products; ROS, reactive oxygen species; GSH, gluthathione; MG, methyglyoxal; RNS, reactive nitrogen species; AG, aminoguanidine; ARIs, Aldose reductase inhibitors.

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Introduction

Glycation or Maillard reaction is a spontaneous, naturally occurring, non-enzymatic and complex network of reactions which is initiated by reaction of carbonyl group of a reducing sugar (e.g., glucose, galactose, fructose, mannose or ribose) with a free amino group, typically the ε-amino group of lysine residues and the α-amino group at the N-terminus of a protein to form an adduct commonly referred to as the Schiff base [1] (Fig. 1). [2]

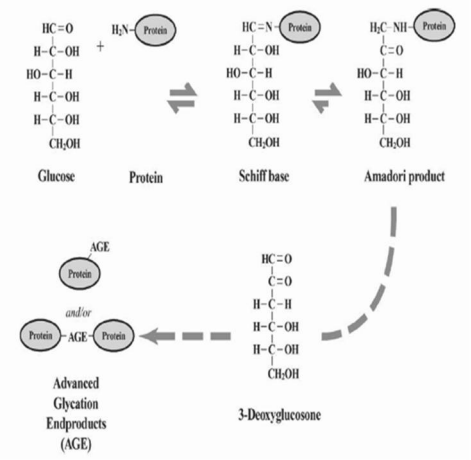

Figure-1: Glycation of proteins. The initial reaction between glucose and protein amino groups forms a reversible Schiff base that rearranges to a ketoamine or Amadori product. With time, these Amadori products form AGEs via dicarbonyl intermediates. [2]

The Schiff bases undergo Amadori rearrangement and through a series of further rearrangement, cyclizations etc. form a variety of diverse compounds collectively described as advanced glycation end products (AGEs). [3, 4] AGE formation is accompanied by the formation, among others of a number of reactive oxygen species (ROS), α-oxoaldehydes, that further react and damage the proteins and other important biological molecules

The formation of AGEs is increased under diabetic conditions. [5] AGE formation is highly increased in patients with diabetes mellitus type 2 as compared to type 1 diabetic patients. [6] Glycation is one of the major pathways for the formation of AGEs. The highly reactive carbonyl species, including glyoxal, methylglyoxal and 3-deoxyglucosone are formed in all the steps of the glycation process, and also during the process of lipid peroxidation, glucose autoxidation and the polyol pathway in diabetes mellitus (type 2). [7, 8] Glyoxal than further leads to production many AGEs that include Nε-(carboxymethyl) lysine (CML), [9] glyoxal-derived lysyl dimer (GOLD), [10] Nω-(carboxymethyl) arginine (CMA) [11] or S-carboxymethylcysteine. [12] And methylglyoxal leads to the formation of Nε-(carboxyethyl) lysine (CEL), [13] methylglyoxal-derived lysyl dimer (MOLD), [14] argpyrimidine, [15] methylglyoxal-derived hydroimidazolone MG-H1, [16] etc, whereas 3-deoxyglucosone leads to the formation of pyrraline, [17] pentosidine, [18] imidazolone or also CML. [19] Glucose-derived dicarbonyl precursors are the chief sources of formation and hence, intracellular accumulation of AGEs. [20, 21]

AGEs accumulation has been found to be implicated in several chronic diseases including typical diabetic complications, atherosclerosis, Alzhimer's disease, rheumatoid arthritis and chronic heart failure. [22, 23] Interaction of AGEs with their receptors (RAGEs) causes the oxidative stress and initiation of inflammation cascade. The inflammation cascade involves the activation of MAPK pathway, NF-Kb, IL-6, TNF-α, expression of ICAM-1 and VCM-2. All of these are collectively responsible for diabetic complications. [24] Increased glycation and build up of tissues AGEs can alter enzymatic activity, decrease ligand binding, modify protein half-life and alter immunogenicity, so they have been considered to be involved in pathogenesis of diabetic conditions. Glycation has been shown to play an important role in the development of physiological and pathophysiological processes such as aging, diabetes, atherosclerosis, neurodegenerative diseases and chronic renal failure. [25]

Diabetes is one of the most common serious metabolic diseases worldwide. All kinds of diabetes are characterized by hyperglycaemia, lipidaemia, oxidative stress and long-term complications affecting the eyes, nerves, blood vessels, skin, and kidneys. Hyperglycaemia is considered to be the driving factor of glycation and gradual build-up of AGEs in body tissues. Although, intracellular AGEs may be involved in the activation of intracellular signalling pathways and modification of the functions of intracellular proteins, there are several evidences that accumulation of AGEs is an

important causative factor for the pathogenesis of diabetes, cataracts, atherosclerosis, diabetic nephropathy, and neurodegenerative diseases. [2, 26-30] Furthermore, enhanced production of free radicals leads to oxidative stress during diabetic conditions.

Inhibition of glycation and prevention of diabetes

In experimental diabetic animal models, blocking of the Maillard reaction has shown to be beneficial against diabetes. Conversely, several antidiabetic agents have been found to reduce the formation of AGEs. Glycation and accumulation of tissue AGEs have a great role in diabetes and its pathology. Thus, inhibiting any step of glycation and preventing the formation of intermediate and end products, scavenging of free radicals, detoxification of liver enzymes, etc., can help in the prevention of diabetic complications. The antidiabetic potential of a possible drug can be considered to be related with inhibition of glycation.

Controlling the blood sugar level is a very effective and natural method to inhibit glycation in diabetes, and inhibition of protein glycation is a complex process that could occur at any step in the formation of AGEs. Hence, several mechanisms can be considered to deal with and prevent AGE formation in the body. And, this protection is supported by detoxifying liver enzymes, as well as plasma amines and antioxidants. Basically, glycation can be prevented by natural defence system present inside the body or by inhibitors that may be synthetic or natural (Fig. 2).

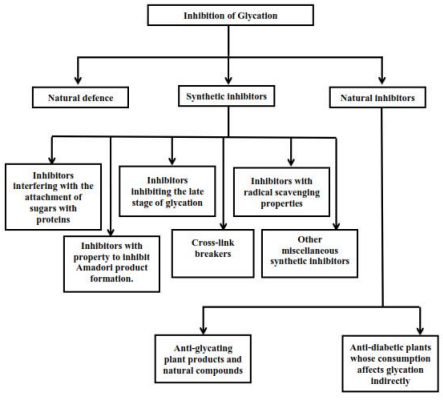

Figure-2: Inhibition of glycation: Possible strategies.

Natural defence

Several researchers have proposed the concept of an enzymatic defence against glycation that offers protection against cell damage mediated by glycation. This concept is based on the enzymatic activities that involves the prevention/suppression of glycation adducts formation and catalysis of glycated protein repairing. Glyoxalase system (both I and II), aldehyde reductase, aldose reductase and the liver enzyme, α-ketogluteraldehyde dehydrogenase are considered to be included in these natural enzymatic defence mechanisms against glycation and AGEs accumulation. [31, 32]

Amadoriosis, an exclusive enzyme found in *Aspergillus*, catalyzes the deglycation of Amadori products. [33] Human fructosamine-3-kinase is able to reverse the non-enzymatic glycation at an early stage. [34] Reactive dicarbonyl compounds are detoxified by oxoaldehyde dehydrogenase and aldehyde reductase that are NADPH dependent. [35, 36] During the reduction of peroxide or superoxide, gluthaothione (GSH) system work both as antioxidant and coenzyme. Furthermore, GSH has an important role to facilitate the detoxification of methyglyoxal (MG) in glyoxylase pathway. [32] Numerous plasma amines are present in body that may react with sugar and Amadori carbonyl groups to decrease AGEs.

Antiglycating compounds

Several types of antiglycating agents have been described. [37] These can interfere with different potential sites to inhibit glycation and AGE formation (Fig. 3). [38] Some may have the ability to compete for the amino groups on the protein. [38, 39] Others can directly bind to the protein or to the glycation intermediates to stop the progression up to the AGE formation stage. [38] Otherwise, they may have the property to eliminate the open chain form of glycating sugars. [38] Furthermore, several probable AGE inhibitors have been proposed. [40, 41] Various inhibitors have been developed and some of them are in advanced clinical studies/trials. [42, 43] The concept of inhibitory mechanism is primarily concentrated on blocking of the sugar attachment to proteins, attenuating glycooxidation and oxidative stress through trapping or scavenging some glycation intermediates including ROS, reactive nitrogen

species (RNS) and dicarbonyls, as well as breakage of AGEs crosslinks. [5] Another means of inhibition or protection from AGEs can include creating antibodies for Amadori products, chelation of transition metals, deglycation enzymes, dissolution of crosslinking or blocking 17 of RAGEs. Primarily, inhibitors can be divided into two groups: synthetic and natural inhibitors.

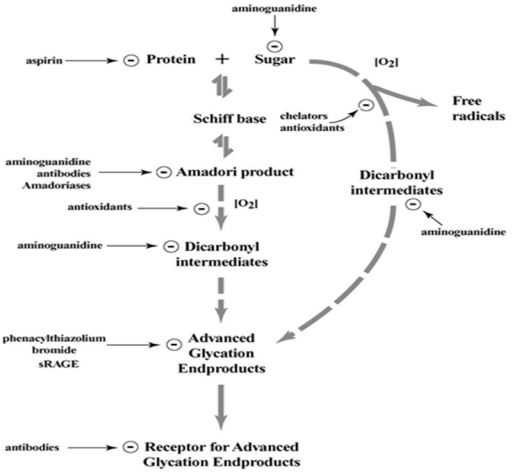

Figure-3: Potential sites where pharmacological compounds can act to inhibit protein glycation and AGE-mediated damage. [2]

Synthetic inhibitors

(1) Inhibitors interfering with sugar attachment with proteins. It has been found that only a few of the synthetic inhibitors have the property to interfere with the initial attachment of reducing sugars to the amino groups of proteins. For example, aspirin inhibits the glycation process by acetylating free amino groups of proteins, therefore it can block the attachment of reducing sugars with amino groups. [44, 45] An anti-inflammatory drug, diclofenac can make a covalent interaction with proteins and thus, can block the attachment of sugars with proteins. It has been shown to block at least one of the major glycation sites of human serum albumin. [46] Inositol is a synthetic and potent antiglycating agent because glucose can be scavenged out by it, and it was found that the glycation process in the human eye lens protein decreased by 57-67% in the presence of inositol. [47] Arginine and arginine-lysine can prevent the alterations of rat tail tendon that are induced by glycation because of competitive attachment of these amino acids to glucose. [48] Metformin is a well-known blood sugar lowering agent and has been reported to have moderate inhibitory effects on early stage of glycation. [40] Pioglitazone and pentoxifylline are other synthetic drugs that exert the same inhibitory effect on the early stage of glycation. [41]

(2) Inhibitors inhibiting the late stage of glycation. Some synthetic inhibitors have the ability to scavenge both reactive carbonyls and reactive free radicals formed during glycation or can block the formation of Amadori products. Aminoguanidine (AG) and pyridoxamine are potent carbonyl and free radical scavengers, and have been widely studied to investigate their AGE inhibiting property. AG was the first AGE inhibitor to be studied both *in vitro* and *in vivo*. [49] AG has a significant potential to react with dicarbonyl intermediates formed during glycation. [49, 50] Thus, AG helps in preventing diabetic complications. [51] AG is a potent AGE inhibitor and also prevents diabetic complications that include nephropathy, neuropathy and vasculopathy. [51] Pyridoxamine and thiamine pyrophosphate are potential dicarbonyl scavengers and have a strong inhibitory effect on AGE formation. Pyridoxamine offers more protection against AGE formation [52-54] as compared to AG [55] by trapping dicarbonyl compounds. [53, 56] Thiamine pyrophosphate has also comparable inhibitory effect on AGEs formation. [57] Buformin [58] and carnosine [59, 60] can prevent *in vitro* protein glycation and cross-linking.

(3) Inhibitors with radical scavenging properties. Some compounds have been reported to retard or suppress AGE formation because of their possible radical scavenging properties. Calcium antagonists [61], amlodipine [62], kinetin [63] and quinine [64] are good examples.

(4) Inhibitors with property to inhibit Amadori product formation. Some antiglycating compounds have the ability to inhibit the formation of Amadori products. Tenilsetam is able to attach with sugar-derived moieties of glycated proteins. [65] Thus, reactive sites are blocked and this stops the further polymerization reactions. Some researchers have also reported the inhibition of formation of Amadori products

and reduction in the level of AGEs by pencillamine. [66] Ethanol can be metabolized into acetaldehyde *in vivo* which forms a stable complex with Amadori products, thus ethanol may exert inhibitory effect on AGE formation. [67]

(5) Cross-link breakers. Cross-linking between AGEs and proteins is the reason behind the stiffening of arteries and cardiovascular damages. [68] Hence, breakage of AGE cross-links is a very good method to prevent diabetic complications caused by cross-linking. The concept of AGE breakers suggests that they can release albumin from preformed AGE-albumin-collagen complexes and can be able to dissociate the immunoglobulin adducts from red cells of diabetic rats. [69] Another view implicates the involvement of AGE breakers in the prevention of cross-linking and/or reversing of the cross-links once they are formed. [70] One more way by which AGE breakers can work is metal chelation. [71] N-phenacylthiazolium bromide was the first cross-link breaker reported. [72] Alagebrium (ALT-711) is a small synthetic compound and is able to decrease cardiovascular stiffening [73] and [74] in diabetic rats. Furthermore, TRC4186 is a pyridinium analog that is able to break AGE cross-links. [75]

(6) Other miscellaneous synthetic inhibitors. Some anti-inflammatory drugs including acetylsalicylic acid, ibuprofen, indomethacin and diclofenac act as antiglycating agents because they inhibit oxidative stress. [76] Specific iron chelators like desferoxamine was also helpful in treating diabetes. [77] Aldose reductase inhibitors (ARIs) can block excessive glucose metabolism. Eplarestat is an ARI and it brings about the lowering of the level of fructose-3-phosphate in diabetic patients [78] and also lowers down imidazolone and carboxymethyl lysine (AGEs) due to decreased peroxidation of lipids. [79] Angiotensin II Receptor Blocker and Angiotensin converting Enzyme Inhibitors (ACEI) also have inhibitory effects on AGEs. The possible mechanisms of action may include chelating of metal ions, scavenging of free radicals, trapping of carbonyl compounds and/or inhibition of carbonyl compound production. [80]

Natural inhibitors

Although synthetic compounds are strong antiglycating agents or strong inhibitors of AGE formation, they might exert severe adverse effects. For example, the clinical trials of AG were terminated because of safety concerns because AG was found to have many adverse effects like gastrointestinal disturbances, rare vasculitis, anaemia and flu-like symptoms. [81] Its interference with vitamin B6 metabolism is another major limitation. [80] Metformin, another synthetic antiglycating compound exerts several adverse effects including nausea and diarrhoea. [82] Therefore, recently much interest has been developed in the search of natural phytochemicals from plants that effectively inhibit glycation and have fewer side effects. [83] Naturally occurring phytochemicals/products have been found to be relatively safe for human consumption as compared to synthetic compounds and are relatively non-toxic, inexpensive and are available in an ingestible form. A large number of plants and natural biomolecules have been discussed in literature for their antidiabetic effects. [83-85] Some plant extracts have been tested for antiglycating activities. [86] However, the mechanism is often not completely understood.

It is well established that glycation and AGEs formation are accompanied and accelerated by oxidative stress, therefore antioxidant compounds may be promising agents for the prevention of glycation and AGE formation. Polyphenolic compounds especially flavonoids have received most attention with regard to their antidiabetic properties. [85] Anthocyanins are flavonoids with high antioxidant capacity.

Anti-diabetic plants and their role in the prevention of diabetes

Plants are considered to be an excellent source of drugs for the treatment of various diseases and pathological conditions and several currently available drugs are obtained directly or indirectly from them. Many plants have been used by the local Indian tribes for antidiabetic therapeutics since a long time, but only a few of them have been scientifically studied e.g. *Flemingia macrophylla, Potentilla fulgens* L., *Albizzia lebbek*, *Curcuma amada*, *Gymnoptela cochinchinesis* and *Ixeris gracilis* DC. [87]

Aqueous/ethanolic extracts of *Allium cepa* (skin), *Illicium religiosum* (bark and wood), *Fagopyrum esculentum* (hull) and *Origanum officinalis* (leaf) have been shown to have effective antiglycating and antioxidant properties. The results also showed that their antiglycating activities significantly correspond to their antioxidative capacities. [88] Ethyl ether extract of dried *Allium cepa* powder has been shown to have anti-hyperglycaemic effect in alloxanized diabetic rabbits. [89] Oral administration of ethyl-ether extract of garlic, *Allium sativum* causes significant reduction in blood sugar level in alloxan treated diabetic rabbits. [90] One major component of garlic extract, allicin is a sulfur-containing compound and has been shown to have significant hypoglycemic activity. [91] The age-related increase in collagen cross-linking and fluorescent products in C57BL/6 mice can be decreased by green tea extract. [92] *Aloe vera* also has antidiabetic and lipid-lowering properties, since oral administration of its extract significantly reduced fasting blood glucose level and improved lipid profile status in streptozotocin-induced diabetic rats. [93] The methanol extract of *Salacia chinensis* stems provides strong inhibition against the formation of Amadori compounds and AGEs in addition to its anti-hyperglycemic action. [94] The seeds of *Acacia arabica* induced hypoglycemic effect in mice by initiating the release of insulin from pancreatic beta cells. [94] The aqueous extract of *Aegle marmelos* leaves reduces blood sugar, urea and serum cholesterol levels in diabetic rats as compared to the control. [95]

Azadirachta indica is widely distributed throughout India. The leaf extracts of this plant have been shown to have anti-hyperglycemic effect in diabetic rats. [96] Beta vulgarosides isolated from roots of *Beta vulgaris*, have been proved to enhance glucose tolerance in OGTT conducted in rats. [97] *Ocimum santalum* is considered to be a sacred plant in Indian culture. Its aqueous extract significantly reduces the blood sugar level in diabetic rats. [98] The aqueous extract of *Mangifera indica* also proved to have hypoglycemic activity which may be due to the reduction of the intestinal absorption of glucose. [99] *Momordica charanta* is considered to be very popular antidiabetic and antihyperglycemic vegetable in India as well as in other Asian countries. The hypoglycemic effect of extracts of its fruit pulp, seed, leaves and whole plant have been proved in various animal models. [100] *Phyllanthus amarus* is a herb and is used by the local people of south India in treating diabetes. Potent antioxidant activity has been found in the methanolic extract of *P. amarus*. In diabetic rats, its extract reduced the blood sugar level. [101] In addition, several studies have reported the AGE formation and crosslinking inhibiting potential of curcumin in diabetic rats. [40]

Brassica juncea is one of the most commonly used spices in India. Oral feeding of its diet, has been reported to induce hypoglycaemia, stimulation of glycogen synthetase, suppression of glycogen phosphatase and other gluconeogenic enzymes, [102] and it has been found to have antioxidant and hypolipidemic activity. [103-105] Fruit powder of *Capparis decidua* was orally given to alloxanized diabetic rats and caused significant hypoglycaemia. [106] In addition, its antioxidant and hypolipidemic activities also have been reported. [106-108] *Citrullus colocynthis* is an annual herb and is widely cultivated throughout India. Aqueous extract of its fruit has been shown to increase insulin secretion in a dose dependent manner. [109] Dried leaf powder of *Gymnema sylvestris* induces anti-hyperglycaemic effects, decrease in the activity of gluconeogenic enzymes and reversal of pathological effects during hyperglycaemic phase in alloxan treated diabetic mice. [110] Oral administration of aqueous extract of its leaves has been found to induce the regeneration of β cells in streptozotocin treated diabetic rats. [111]

Plants and natural products with antiglycating potential

Numerous medicinal herbs and dietary plants have been reported to possess antiglycating potential of similar [112] or even of higher order [113, 114] than that of AG. Several evidences have demonstrated that their antiglycating potential is correlated significantly with the total phenolics present in their extracts. [115-119] Methanol extracts of whole plants of *Calendula officinalis* and fruits of *Juglans regia* have shown antiglycating activity with respect to bovine serum albumin (BSA) *in vitro*, and their antiglycating potential is comparable to that of AG on the weight concentration basis. [120] During *in vitro*

conditions, ethyl acetate extracts of *Erigeron annuus* inhibited glycation of BSA, prevented opacification of lenses and inhibited aldose reductase. [114] Extract of *Empetrum nigrum L.* inhibits the glycation *in vitro* and its anti-glycating activity is correlated with the radical scavenging activity. [121] Maltol showed a significant *in vitro* AGE inhibiting activity as compared with AG. [113]

Polyphenolic compounds are natural phytochemicals and are common constituents of plant based foods including fruits, vegetables, cereals, seeds, nuts, chocolate, and beverages, such as coffee, tea, and wine. Their consumption is associated with many health benefits, such as prevention of cancer, [122] neurodegenerative diseases [123], cardiovascular diseases [124] and diabetes. [125] Polyphenols are classified on source of origin, biological functions, and chemical structures.

Chlorogenic acids, present in *Chrysanthemum* species, are free radical and metal scavengers and may interfere with glucose absorption and alter gene expression of antioxidant enzymes. [126] Cinnamic acid derivatives such as ferulic acid (3-methoxy-4-hydroxycinnamic acid) also have shown AGEs inhibiting activity. [127-129] Ellagic acid prevents the glycation-mediated β-sheet formation in hemoglobin and lysozyme that shows its antiglycating ability. [130] Quercetin is a flavonoid and belongs to the subclass flavonols. It is widely distributed in many plants: flowers, leaves, and fruits. Quercetin possesses strong anti-diabetic activity. (131) It has the ability to trap MG and glyoxal and thus, can inhibit AGEs formation. [132] Quercetin offers protection against lipid peroxidation and also has antioxidant effect in diabetes. [133] It is a strong antioxidant. [134] Thymoquinone, an active principle component of the volatile oil of *Nigella sativa* seeds possess several pharmacological activities including anti-diabetic effects. [135] Research in my laboratory has recently shown that thymoquinone also has good antiglycating activity. [136, 137]

Possible mechanisms of inhibition of glycation by antidiabetic plants

The complexity of Maillard reaction is the major obstacle in identifying the mechanisms of inhibition of glycation by natural products and molecules. AGEs are considered to be major pathogenic culprits for diabetes and its complication. Several mechanisms have been proposed for the inhibition of glycation by plant products and natural compounds, which target essential stages of glycation as well as their free radical scavenging activity (Fig. 4).

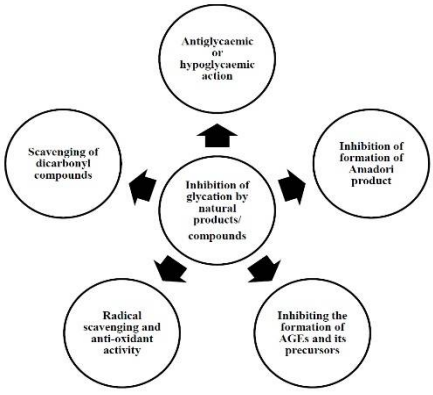

Figure-4: Possible mechanisms for the inhibition of glycation by natural products/compounds.

These mechanisms can correlate antiglycating activity with antidiabetic potential of plants and their products/compounds. The mechanisms include: antiglycaemic or hypoglycaemic actions of plant products and their compounds e.g. *Albizia odoratissima,* [138] *Allium cepa;* [89] inhibition of Amadori products formation e.g., *Salacia chinensis,* [94] etc.; inhibition of the formation of AGEs and its precursors e.g. *Ilex paraguariensis* [119], etc.; reduction of crosslinking e.g. green tea extract; [92] radical scavenging and anti-oxidant activity e.g. extracts of wild berries, [121] Aegle marmelos, [139] olive leaves, [140] etc.; scavenging of dicarbonyl compounds e.g. catechin and epicatechin procyanidin B2 isolated from cinnamon bark extract, [118] etc.

Current limitations of natural and synthetic inhibitors

Synthetic drugs are often associated with some limitations such as high cost, development of hypoglycaemia, gastrointestinal disturbances, liver toxicity, weakness, fatigue, shortness of breath, nausea, dizziness, lactic acidosis, and kidney toxicity etc. [141, 142] Some renal patients are not allowed to take some specific type of synthetic drugs. Sometimes, flatulence is also found to be associated with intake of synthetic drugs. Current limitations of natural inhibitors include lack of dose

dependent standardization of inhibitors for their efficacy and safety, [143] poor bioavailability and poor aqueous solubility etc.

Future perspectives

Based on in vitro studies and animal models, several plant products/compounds have been proposed to be effective supplements against glycation and hence, in management and prevention of its long term complications of diabetes mellitus. However, it is very necessary to investigate their clinical effects in human beings, appropriate physiological concentration of inhibitors as well as their mode of action to confirm their beneficial effects as supplementary treatments for diabetic patients. Bioavailability of polyphenols is influenced by several factors including bioaccessibilty, molecular structures, transporters, metabolizing enzymes, etc. Therefore, it is very necessary to develop new techniques such as nanotechnology and homogenization that can enhance bioavailability of natural inhibitors including polyphenols. Nanoparticles and nano-encapsulation based albumin and polyphenols been developed. [144, 145] In future it is very likely that there will be more investigations regarding the long term and acute hypoglycaemic, antiglycating and hypolipidemic effects of these homogenization, nanoparticles and nanoparticle encapsulation on type 2 diabetes.

Conclusion

Glycation is considered to be the main molecular basis of several diabetic complications. The antidiabetic potential of a possible drug can be considered to be related with inhibition of glycation. Current antidiabetic therapy is based on synthetic drugs that very often have side effects. Alternative medicines and natural therapies have stimulated new interest of research to find for more efficacious agents with lesser side effects. Plants are excellent sources of drugs and many of the modern drugs have been obtained directly or indirectly from them. Consumption of plant based foods including fruits, vegetables, etc., is associated with many health benefits, such as prevention of cancer, [122] neurodegenerative diseases, [123] cardiovascular diseases [124] and diabetes. [125] A wide range of plant extracts have been used worldwide to prevent diabetes. Some plant products/compounds can inhibit glycation and hence can prevent diabetic complications. Furthermore, naturally occurring phytochemicals with anti-diabetic and antiglycating activities are relatively nontoxic, inexpensive and available in an ingestable form**.** The details of the inhibitors of glycation have been discussed in this review. A summary of the antidiabetic effects of some of the synthetic and natural inhibitors is shown in Table 1 and Table 2, respectively.

Table 1: Synthetic inhibitors with antidiabetic effects.

S. N.	Synthetic Inhibitor	Effect	Mode of Action	Reference
1	Aspirin, Diclofenic	Antiglycating	Blockage of attachment of reducing sugar with protein	44, 45, 46
2	Inositol	Antiglycating	Glucose can be scavenged	47
3	Arginine, arginine-lysine	Antiglycating	Competitive attachment of these amino acids to glucose	48
4	Metformin	Inhibition of early stage of glycation	Blood sugar lowering	40
5	Pioglitazone, pentoxifylline	Antiglycating	Blood sugar lowering	41
6	Aminoguanidine, pyridoxamine	Blockage of Amadori product formation	Potent carbonyl and free radical scavengers	49
7	Pyridoxamine, thiamine pyrophosphate	Inhibition of AGEs formation	Dicarbonyl scavengers	52, 53, 54, 57
8	Buformin, carnosine	Prevents *in vitro* protein glycation and cross-linking	Trapping of carbonyl compounds, antioxidants	58, 59, 60

9	Calcium antagonists, amlodipine, kinetin, quinine	Retardation of AGEs formation	Radical scavenging properties	61, 62, 63, 64
10	Tenilsetam	Inhibition of Amadori product formation	Attach with sugar-derived moieties of glycated proteins	65
11	Pencillamine	Inhibition of Amadori product AGEs formation	Reacts with Amadori-derived fragmentation products	66
12	N-phenacylthiazolium bromide, Alagebrium	Cross-link breaker	Reacts with and cleaves covalent, AGE-derived protein cross-links	72, 73, 74
13	TRC4186	Cross-link breaker	Potent free radical scavenging activity, reduction in accumulation of AGEs	75, 146

Table 2: Natural inhibitors with antidiabetic effects.

S.N.	Natural inhibitor	Plant source	Effect	Mode of action	Reference
1	Bark and wood extract	*Illicium religiosum*	Antiglycating	Antioxidant	88
2	Ethyl extract of dried leaves	*Allium cepa*	Anti-hyperglycaemic and antiglycating	Antioxidant	88, 89
3	Hull extract	*Fagopyrum esculentum*	Antiglycating	Antioxidant	88
4	Leaf extract	*Origanum officinalis*	Antiglycating	Antioxidant	88
5	Ethyl ether extract	*Allium sativum*	Hypoglycaemic	Stimulation of insulin secretion	90
6	Allicin	*Allium sativum*	Antidiabetic	Hypoglycemic	91
7	Leaf gel extract	*Aloe vera*	Hypoglycaemic	Reduction in blood sugar, improvement in plasma insulin	93
8	Extract of seeds	*Acacia arabica*	Hypoglycaemic	Stimulation of insulin secretion from beta cells	94
9	Beta vulgarocides	*Beta vulgaris*	Antiglycating	Anti-hyperglycaemic, Enhanced glucose tolerance	97
10	Methanolic extract	*Phallanthus amarus*	Reduce blood sugar level	Antioxidant	101
11	Dried leaf powder	*Gymnema sylvestris*	Anti-hyperglycaemic	Decrease in the activity of gluconeogenic enzymes	110, 111
12	Caffeic acid	*Ilex paraguariensis*	Antiglycating	AGEs inhibition by acting on Methylglyoxal	119
13	Extract	*Empetrum nigrum L.*	Antiglycating	Radical scavenger	121

14	Chlorogenic acids	*Chrysanthemum sp.*	Interfere with glucose absorption and alter gene expression of antioxidant enzymes	Free radical and metal scavenging activity	126
15	Cinnamic acid derivatives such as ferulic acid	*Cimicifuga heracleifolia*	Antiglycating	AGEs inhibitor	127, 128, 129
16	Ellagic acid	Numerous fruits and vegetables	Antiglycating	Inhibition of CML through a dicarbonyl trap	130
17	Quercetin	Many plants	Antidiabetic and Antiglycating	Antioxidant, traps MG and Glyoxal	131, 132, 133
18	Thymoquinone	*Nigella sativa*	Antiglycating	Antioxidant	136, 137

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