Chapter 12
Bionanoparticles in the Treatment of Glycation-Induced Secondary Complications of Diabetes

Pamela Jha and Ahmad Ali

Abbreviations

AGE	Advanced glycation end products
CML	Carboxymethyl-lysine
GA	Glycated albumin
HbA1c	Glycated hemoglobin
MG	Methylglyoxal
NP	Nanoparticle
RAGE	Receptors for advanced glycation end products

12.1 Introduction

The European Commission has defined nanomaterial (NM) as a natural, incidental, or manufactured material containing particles in an unbound state or in an aggregate or agglomerate in which ≥50% of the particles in the number size distribution have one or more external dimensions in the size range 1–100 nm (Mu et al. 2014).

The rationale of nanoparticles (NPs) being an attractive alternative of bulk material is based on their unique features, such as their surface to mass ratio, which is much larger than that of any other particles or materials. This allows catalytic promotion of reactions as well as their ability to adsorb and carry other compounds. The reactivity of the surface originates from quantum phenomena and can make them unpredictable, immediately after their generation. NPs may have their surface modified, depending upon the presence of reactants and adsorbing compounds, which may instantaneously change with the changing compounds and thermodynamic conditions. Therefore, on one hand, NP has a large (functional) surface which

P. Jha
Amity Institute of Biotechnology, Amity University, Navi Mumbai, Maharashtra, India

A. Ali (✉)
Department of Life Sciences, University of Mumbai, Mumbai, Maharashtra, India

A. Husen, M. Iqbal (eds.), *Nanomaterials and Plant Potential*,
https://doi.org/10.1007/978-3-030-05569-1_12

is able to bind, adsorb, and carry other compounds like drugs, probes, and proteins; on the other hand, this surface might be chemically more reactive, compared to their fine analogues (Paul et al. 2004). There are different types of NPs like liposomes, nanocrystals, solid lipid NPs, polymeric NPs, dendrimers, silicon-based structures, carbon structures, and metal structures. Each of these types has its specific advantages and dedicated applications (Husen and Siddiqi 2014a, b, c; Siddiqi and Husen 2016; Husen 2017; Siddiqi et al. 2018a, b).

Diabetes has affected millions of the people all over the world (Shaw et al. 2010). Due to prolonged accumulation of glucose in the body, there is an overproduction of a group of harmful compounds commonly known as advanced glycation end products (AGEs). These products are generated as a result of nonenzymatic and covalent interaction between the carbonyl group of sugars and amino groups of proteins, nucleic acids, and lipids (Suji and Sivakami 2004). AGEs have been implicated in various secondary complications of diabetes and neurodegenerative disorders (Singh et al. 2014). A range of artificial and natural antiglycating agents have been designed to prevent the accumulation of AGEs and adverse effects of these compounds (Abbas et al. 2016; Ali et al. 2014). Recent upsurge in application of NPs in the field of medicine has led to their utilization in the management of glycation as sensors and antiglycating agents. This chapter deals with the process of glycation and application of plant-based NPs in the detection and prevention of glycated products.

12.2 Applications of Plant-Mediated NPs in Medicine and Healthcare

Nanoparticles have found many applications in the field of Science and Technology. Generally three approaches are used to synthesize NPs: chemical, physical, and biological. In the last few years, there are several reports in the literature regarding the toxicity of non-bioNPs. Accordingly focus has shifted toward the synthesis of bionanoparticles using microbes, algae, and plants. Plant-mediated NPs have found various applications in areas of medicine and healthcare and are used for diagnostics, biological imaging, biosensors, and drug development (Husen and Siddiqi 2014b; Husen 2017; Siddiqi et al. 2018a, b). The antioxidant, antimicrobial, antimalarial, and antidiabetic properties of plant-mediated NPs have made them suitable for use in medicine. The antidiabetic activity of drugs and NPs is mostly concerned with decreasing the release of glucose, increasing the utilization of glucose and insulin release. However, with increasing evidence of glucotoxicity playing major roles in secondary complications of diabetes, focus has been shifted toward the use of these NPs in diagnosis and treatment of glycation. The main theme of this chapter is to highlight the mechanism of glycation, its prevention by natural agents and plant-mediated NPs.

12.3 Glycation

Diabetes mellitus, which affects around 1–2% of the world population, has come up as a significant medical problem. Diabetic patients are prone to long-term micro- and macrovascular complications such as cardiomyopathy, atherosclerosis, retinopathy, cataract, neuropathy, and nephropathy (Suji and Sivakami 2004). Hyperglycemia has an important role in the pathogenesis of long-term complications, and the diabetic patients with poor blood glucose control are particularly at risk. Many mechanisms have been worked out to show the correlation. Production of AGEs through protein glycation reaction is one such mechanism, which depicts the role of hyperglycemia in the pathogenesis of diabetic complications. The high blood glucose nonenzymatically interacts with intracellular proteins, leading to the generation of different heterogeneous AGEs. The AGEs formed in the plasma interact with receptors for AGEs (RAGE) and activate proinflammatory response. Several lines of evidence suggest that AGE/RAGE axis could profoundly be involved in diabetic complications, cardiovascular diseases, neurodegenerative diseases, cancer, and aging (Daroux et al. 2010). Additionally, diffusion of AGEs out of the cell gives them an opportunity to react and modify the extracellular matrix molecules present in the vicinity, thereby causing cellular dysfunction since this affects the signalling between the matrix and the cell (Smit and Lutgers 2004). Elevated production of the glycation precursors, namely, the dicarbonyls methylglyoxal (MG) and glyoxal, is witnessed in hyperglycemia, aging, cancer, and neurodegeneration. This leads to increase in AGEs and the subsequent pronounced molecular glycation damage (Pun and Murphy 2012).

12.3.1 Biochemistry of Glycation

Glycation is a nonenzymatic reaction in which carbonyl groups of sugar react with amino group of proteins and nucleic acids. Research on glycation began with the discovery by Louis Camille Maillard that heating amino acids and reducing sugars together result in a color change to yellowish brown (Thorpe and Baynes 1996). For this reason, the process of glycation is also known as “Maillard reaction” (Ashraf et al. 2016). Glycation involves posttranslational modification of proteins which is responsible for various diseases such as diabetes, cataract, Alzheimer’s, Parkinson’s, dialysis-related amyloidosis, atherosclerosis, physiological aging, etc. (Suji and Sivakami 2004).

Glycation is initiated by the reversible formation of a Schiff base between a reducing sugar and the amino group of a protein, DNA and lipoproteins. The Schiff base, which is relatively unstable, undergoes rearrangement to form a more stable Amadori product, which in turn undergoes a series of reactions like oxidation, reduction, hydration, etc. to form AGEs. The accumulation of these AGEs in the tissues is thought to be involved in diabetic complications and aging (Ashraf et al.

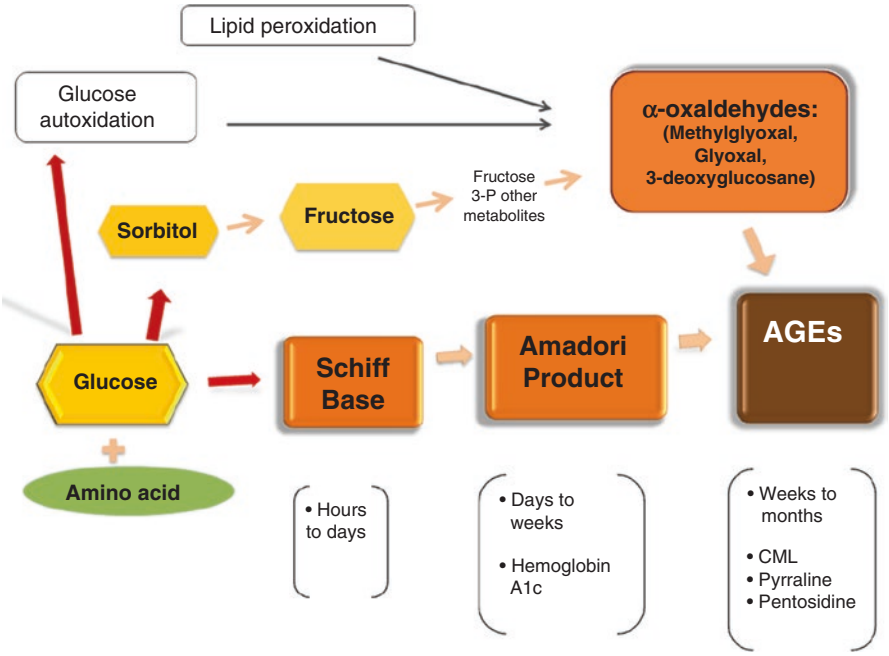

Fig. 12.1 Mechanism of the formation of advanced glycation end products. (Adapted from Luevano-Contreras and Chapman-Novakofski 2010)

2016). This process completes within few days, weeks, or months, and it is an irreversible process (Fig. 12.1). AGEs are very stable and therefore accumulate inside and outside the cells and interfere with the function of macromolecules.

The early and advanced glycation end products are continuously synthesized in the body, even at normal glucose levels. However, the deleterious effect of these products is observed due to their consequential accumulation after sometime and particularly when the blood glucose level increases above the normal range. Glycated products interfere with the homeostasis mechanism of the body, which results in various diseases (Ali and Sharma 2015). AGE formation progressively increases along with the normal process of aging even in the absence of any disease. However, they are formed at an extremely accelerated rate in diabetic condition (Ashraf et al. 2014). There are three stages of glycation: early, intermediate, and late (Fig. 12.2).

Early Stage The carbonyl group of a reducing sugar interacts in a nonenzymatic way with an amino acid to form an unstable compound known as Schiff base (Nass et al. 2007). Sugars are reactive toward lysine residues, while dicarbonyls are mainly reactive toward arginine residues.

Intermediate Stage During this phase, the Schiff base may undergo hydrolysis and produce the original sugar and amino acid, or it may undergo cyclization, and then

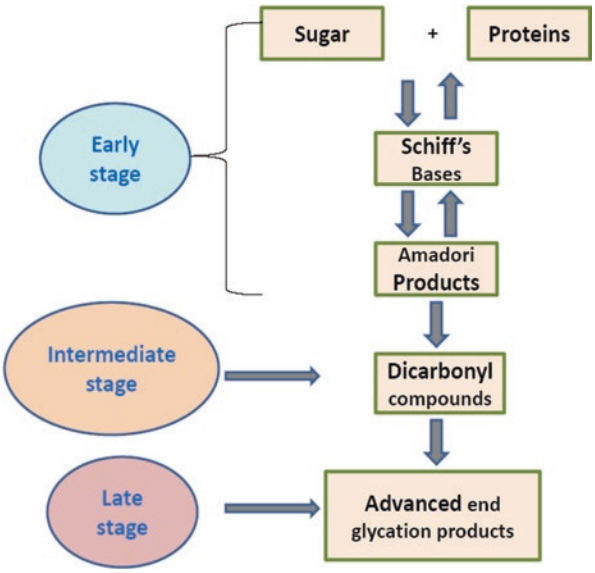

Fig. 12.2 The process of glycation comprising of three successive stages

Amadori rearranges to form Amadori products, which are relatively more stable compounds (Singh et al. 2014). However, under physiological and non-oxidative conditions, 90 percent of Amadori products may sustain a reversible reaction to the initial sugar and amino acid.

Late Stage In this phase, Amadori products can generate AGEs by oxidative or non-oxidative cleavage (Thorpe and Baynes 2003). The principal AGE produced in oxidative cleavage is carboxymethyl-lysine (CML), whereas dicarbonyl derivative 3-deoxyglucosone is produced in non-oxidative cleavage. This derivative can react with an amino acid and form CML or other AGE cross-links like pyrraline, pentosidine, imidazolone, etc.

12.3.2 Prevention of Glycation

The Amadori products and AGEs accumulate in the body even during the normoglycemic level as the process of glycation takes place continuously between the sugars and proteins. The amount of AGEs increases with an increase in the level of glucose in the blood, and, accordingly, the body is more severely affected by the deleterious effects of these products. AGEs bring about structural alteration of proteins and other biomolecules and in turn cause the functional loss. The other mechanism by which AGEs interfere with the normal functioning of cells is through the generation of reactive oxygen species. In the last few decades, efforts have been

made to develop anti-AGE therapeutics. There are several stages at which AGE formation can be prevented. The simplest mechanism is to inhibit the formation of Schiff base by blocking one of the two reacting groups, carbonyl or amino. The other stages which can be interfered with are the formation of Amadori products and modification of these products to AGEs. Some common strategies for the prevention of glycation are:

(i) Use of inhibitors such as ascorbic acid, aspirin, metformin, etc., to prevent the formation of AGEs
(ii) Use of drugs, e.g., hydrazine, for deglycation and transglycation approach for Schiff bases/Amadori products
(iii) Reversal of AGE-induced modifications such as cross-links and aggregations, e.g., phenacylthiazolium bromide (PTB)
(iv) Prevention from the deleterious effects of accumulated AGEs in the body, e.g., resveratrol and curcumin

12.3.2.1 Pharmacological Intervention of Deleterious Reactions

The deleterious effects of glycation products on the human health have been discussed above. These can be prevented by inhibiting their accumulation and associated damage to the biomolecules. The AGE inhibitors share a common feature in possessing a nucleophilic group such as amine or hydrazine that can react with intermediate carbonyl compounds formed during the process of glycation and AGE formation (Suji and Sivakami 2004).

Some of the approaches commonly accepted for prevention of the damaging effects of AGEs include the use of synthetic and natural compounds to inhibit the progression of glycation and repair the damage induced by AGEs (Ali et al. 2017). There are many classes of drugs which can help in the prevention of AGE formation; some of these act by preventing the glycation-induced oxidative damage of proteins and DNA (Ali and Sharma 2015). The radical-trapping antioxidants and metal ion chelators belong to these classes of inhibitors. However, it is very difficult to reduce significantly the accumulation of AGEs by one class of inhibitors. At the same time, it can be assumed that a single inhibitor may exert its effect by more than one mechanism. The reason behind all these ambiguities is that the exact mechanism by AGEs-caused damage to the biomolecules has not been elucidated and the mechanism by which the inhibitors prevent the formation of AGEs is also not very clear. Several attempts have been made in the recent past to develop drugs, which can be used as multifunctional AGE inhibitor (Suji and Sivakami 2003).

12.3.2.2 Classes of AGE Inhibitors

Several classes of inhibitors have been identified on the basis of their mechanism of action (Abbas et al. 2016). Some of these are summarized in Table 12.1.

Table 12.1 Major class of AGE inhibitors, their mode of action, and examples

S. No.	Type of inhibitor	Mechanism of inhibition	Examples
1.	Inhibition of sugar attachment with proteins	Modification of sugar or protein molecules or ability to compete for the amino groups on the protein	Aspirin, diclofenac, pyridoxal-5-phosphate, metformin, pioglitazone, pentoxifylline, etc.
2.	Inhibition by using antioxidants (radical scavengers)	Suppression of AGE formation by attenuating glycol oxidation and preventing oxidative stress	Calcium antagonists, amlodipine, quinine, acetylsalicylic acid, ibuprofen, etc.
3.	Inhibition by metal chelators	Reduction of the metal ion catalyzed free-radical generation	Deferoxamine, DETAPAC, phytate, etc.
4.	Inhibition of dicarbonyl intermediates	Ability to scavenge both reactive carbonyls and reactive free radicals formed during glycation	Aminoguanidine, pyridoxamine, thiamine pyrophosphate, etc.
5.	Inhibition of Amadori product formation	Reaction with the sugar-derived moieties of glycated proteins and Amadori products, blocking of AGE receptors, i.e., RAGE	Tenilsetam and ethanol, antibodies against Amadori products, etc.
6.	Inhibition of AGE and protein cross-links	Breaking the cross-linking in the formed AGEs	N-Phenacylthiazolium bromide, alagebrium (ALT-711), TRC4186, etc.

12.4 Natural Inhibitors

The naturally occurring phytochemicals/products have been found to be relatively safe for human consumption, as compared to synthetic compounds. Natural compounds are relatively nontoxic and inexpensive and can be made available in an ingestible form. A large number of plants and natural biomolecules have shown antidiabetic effects. Plant extracts have been tested for antiglycating activities, but the mechanism is yet to be fully understood. It is well established that glycation and AGEs formation are accelerated and followed by oxidative stress. The antioxidant compounds may likely be promising agents for the prevention of glycation and AGE formation. The polyphenolic compounds, especially the flavonoids, have received the maximum attention with special focus on antidiabetic properties (Soumyanath 2006).

12.4.1 Natural Antiglycating Agents

There are numerous medicinal herbs and dietary plants that have been reported to possess antiglycating potential of similar or even higher order than that of aminoguanidine, an artificial AGE inhibitor (Kang et al. 2008). Plant-derived natural

products possess significant antiglycating potentials (Ali et al. 2014). Studies depict that antiglycating potential is correlated with total phenolics present in plant extracts (Hsieh et al. 2007). The methanolic extracts of whole plants of *Calendula officinalis* and fruits of *Juglans regia* have shown antiglycating activity with respect to bovine serum albumin. Similarly, ethyl acetate extracts of *Erigeron annuus* inhibited glycation of BSA, prevented opacification of lenses and inhibited aldose reductase in the in vitro experiments (Jang et al. 2010). The extract of *Empetrum nigrum* L. inhibits glycation in vitro, and its antiglycating activity can be correlated with radical scavenging activity (Harris et al. 2014). In the in vitro conditions, maltol showed a significant inhibiting activity, as compared with aminoguanidine (Kang et al. 2008). Thus, antiglycating activity is exhibited by several plant species.

The polyphenolic compounds are the natural phytochemicals and are common constituents of plant-based foods which include fruits, vegetables, cereals, nuts, seeds, and chocolate and beverages like tea, coffee, and wine. The consumption of polyphenolic compounds is associated with several health benefits such as the prevention of cancer (Landis-Piwowar et al. 2007), neurodegenerative diseases (Mandel and Youdim 2004), cardiovascular diseases (Vinson et al. 2006), and diabetes (Kowluru and Kanwar 2007). Polyphenols are classified on the basis of source of origin, biological functions, and chemical structures, whereas chlorogenic acids present in *Chrysanthemum* species act as free-radical and metal scavengers and can interfere with the absorption of glucose and alter gene expression of antioxidant enzymes (Fiuza et al. 2004). The derivatives of cinnamic acid such as ferulic acid (3-methoxy-4-hydroxycinnamic acid) also display AGEs' inhibiting activity (Banan and Ali 2016; Meeprom et al. 2013). Ellagic acid also prevents glycation-mediated beta sheet formation in hemoglobin and the lysozyme that shows its ability of antiglycation (Torres-Piedra et al. 2010). It has the ability to encage MG and glyoxal and can thus inhibit AGEs formation.

12.4.2 Mechanisms for Inhibition of Glycation

Complexity of Maillard reaction is the major hurdle in identifying the mechanism behind inhibition of glycation by molecules and products of natural origin. It can be stated that AGEs are the major pathogenic culprits for diabetes and its complication. Several mechanisms have been proposed for inhibition of glycation by means of plant products and natural compounds that target essential stages of glycation.

These are certain mechanisms which can correlate antiglycating activity with antidiabetic potential of plants and their compounds (Tupe et al. 2016). The mechanisms include antiglycemic or hypoglycemic actions of plant products and their compounds (e.g., *Albizia odoratissima*, *Allium cepa*); inhibition of Amadori product formation (e.g., *Salacia chinensis*, etc.); inhibition of the formation of AGEs and its precursors (*Ilex paraguariensis*); reduction of cross-linking (green tea extract), radical scavenging and antioxidant activity (extracts of wild berries), and scavenging of dicarbonyl compounds (catechin and epicatechin, procyanidin, B2 isolated from cinnamon bark extract); etc.

12.5 Plant-Mediated NPs in Detection of Diabetes

We have discussed the significance of bioNPs in medicine and the strategies for inhibition of glycation-mediated secondary complications of diabetes. However, the natural as well as synthetic inhibitors have their own limitations. Synthetic drugs are associated with certain limitations like high cost, gastrointestinal disturbances, liver toxicity, development of hypoglycemia, fatigue, weakness, shortness of breath, nausea, dizziness, kidney toxicity, lactic acidosis, etc. (Modak et al. 2007). Renal patients are not allowed to take certain specific type of synthetic drugs. Limitations of natural inhibitors, on the other hand, include lack of dose-dependent standardization of inhibitors for their efficacy and safety (Ernst 2005). Different types of NPs, such as glucose sensors, glycated protein (Hb and albumin) sensors, protein oxidation sensors, and AGE's sensors, are used for assessment of glycation-induced complications of diabetes.

In the field of diabetes management, nanotechnology is applicable to glucose monitoring, insulin delivery, drug delivery, and wound healing. Fluorescent glucose nanosensors provide continuous glucose monitoring in contrast to the conventional finger prick tests. Whereas the conventional sensors are based on enzymes like glucose oxidase, the nanosensors incorporate the same enzyme, an oxygen-sensitive fluorescent indicator and a fluorescent dye insensitive to oxygen as a reference (Xu et al. 2002). The other enzyme, hexokinase, known to bind glucose and induce a conformational change in the protein, was used in nanosensors which caused a 25% reduction in its intrinsic fluorescence (Hussain et al. 2005). Another major issue with diabetes control is insulin delivery. The low oral bioavailability and short half-life of insulin can be overcome by encapsulating it in NPs. Insulin-loaded NPs delivered orally demonstrate a sustained effect of decreasing the blood glucose level over a longer period of time, as compared to subcutaneous injections (Lin et al. 2007). Many drugs of diabetes management have a short half-life and poor absorption characteristics. Nanodrug delivery systems, such as gliclazide-loaded Eudragit (L100 and RS), can release the drug in a controlled manner for extended periods of time (Devarajan and Sonavane 2007). One major impact of diabetes is the slow wound healing. Nanofibers have exhibited higher wound-healing rates in comparison to controls; the poly-n-acetyl glucosamine (sNAG) biodegradable nanofibers were found highly effective. Epidermal growth factor (rhEGF)-conjugated nanofibers have also been used for in vivo wound healing of diabetic ulcers in mice (Choi et al. 2008).

12.5.1 Glucose Sensors

Monitoring of glucose in an individual is the key factor in the management of diabetes. Therefore, the last four decades have observed evolution of glucose meters, noninvasive glucose monitoring (NGM) devices and continuous glucose monitoring

systems (CGMS) (Rahisuddin 2018). With reference to the use of nanotechnology, the following two primary approaches have been incorporated into glucose sensors (Cash and Clark 2010).

In the first approach, the sensors can be designed inclusive of macro- or microscale components (such as electrodes and supporting hardware) but include either a nanostructured surface or a nanomaterial. The advantages of these designs are high surface area (leading to increase in current and prompt responses) and enhanced catalytic activities. These approaches with modified designs would be implemented for continuous monitoring of glucose. However, these sensors need to be studied thoroughly for their fouling and shelf life before implementation.

In the second approach, nanofabrication techniques can be used to make glucose sensors that are nanoscale in all dimensions. The advantages of these designs are that they can be used as injectables with an ease in implantation and administration. In this approach, the shelf life is potentially longer than the earlier one. However, these sensors have a limited clinical data and hence need to be researched more before implementation on a commercial scale.

12.5.2 Glycated Protein Sensors

In a recent study, Ghosh et al. (2017) have investigated an optical sensor comprising of DNA aptamer, semiconductor quantum dot, and AuNPs for the detection of glycated albumin (GA). The system "turn on," due to increase in photoluminescence intensity, was caused due to addition of GA to the sensor. This might be possible due the structure of DNA aptamer, which undergoes folding to form a hairpin loop, before the addition of analyte. In order to bind to GA, this loop is supposed to open up after the addition of the target to the sensor.

This pushes the quantum dot and the AuNPs away leading to increase in photoluminescence. A linear increase in photoluminescence intensity and quenching efficiency of the sensor is observed as the GA concentration is changed. The present work demands further studies with higher number of clinical samples to be effectively and largely employed in efficient diagnosis and monitoring of diabetes mellitus.

12.5.3 Protein Oxidation Sensors

For the electrochemical analysis of proteins, a number of sensors have been developed based on techniques including the direct as well as indirect electrochemistry following a selective reaction. Carbon nanotubes have been introduced to utilize their faster electron transfer kinetics and to provide a wire to the redox site of a protein. Applications cover a very broad range of proteins (Jacobs et al. 2010).

12.5.4 AGE's Sensors

The vanadium oxide nanoplates synthesized through microwave assistance were used as an interface material in the fabrication of modified Au working electrode for electrochemical MG (predominant precursor of AGEs) biosensor. These nanosensors showed a very high sensitivity with a linear range of 3–30 μM and a response time less than 8 s toward MG. The lifetime and percentage recovery of the sensor were found to be 25 days and 102.5–108.7%, respectively (Bhat et al. 2008). Previously, Ghosh et al. (2007) demonstrated the application of gold NPs synthesized on a protein template in the sensing of AGEs. This sensing property of gold NPs of glycated protein was confirmed using the techniques like transmission electron microscopy, surface plasmon resonance, CD, and FTIR.

12.6 Plant-Mediated NPs in Prevention of Glycation and Treatment of Diabetes

The most commonly used NPs for the treatment of glycation-induced diabetic complications are Ag, Au, and Se. The general strategy for checking the effect of NPs on glycation is to incubate NPs with the glycation system (protein + sugar) and then compare the amount of glycation products in the presence and absence of NPs. The glycation products are measured by several established methods including the measurement of browning, fructosamines, carbonyl content, total AGEs by spectrofluorimetry, HPLC, protein structural characterization by CD, and gel electrophoresis (Ali et al. 2017). The NP is classified as an antiglycating agent if there is a significant decrease in the AGEs in the glycation system.

In one report, Pickup et al. (2008) emphasized that NPs are potent therapeutic agent to control diabetes with very few side effects. They asserted that the AgNPs were efficient in control of the sugar level of 140 mg dl^{-1} in mice successfully. Manikanth et al. (2010) found that α-amylase inhibitory components are abundantly present in the ethanolic extract of *Sphaeranthus amaranthoides*. In a similar study, AgNPs synthesized by using the same plant, Swarnalatha et al. (2012) reported that these NPs inhibited a-amylase and acarbose sugar in diabetes-induced animal model. In the same year, Daisy and Saipriya (2012) found AuNPs to have high therapeutic effects against diabetic models. The AuNPs used were significantly able to reduce the level of liver enzymes such as alanine transaminase, alkaline phosphatase, serum creatinine, and uric acid in treated diabetes mice. Also, these diabetic models treated with AuNPs showed a decrease in HbA1c (glycated hemoglobin).

Collagen has been a protein of interest to study glycation because of its stability, great abundance in the body, and its application in cosmetic surgical treatments. Kim et al. (2012) reported the antiglycating effect of gold NPs on collagen. Gold NPs (nearly 20 nm) significantly decreased the level of glycation products in the glycated collagen sample. The results presented by Kim and colleagues (2012) also

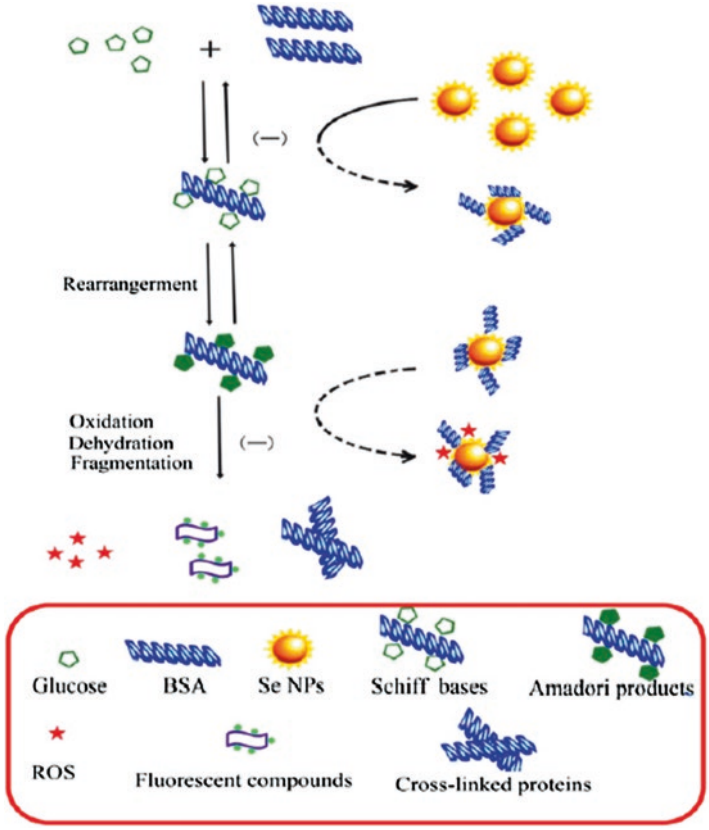

Fig. 12.3 Inhibitory effect of selenium NPs on glycated BSA. (Adapted from Yu et al. (2015)

suggest that gold NPs can be used for the prevention of glycation-induced skin aging.

In an initial effort on the use of selenium NPs in the prevention of glycation, Yu et al. (2015) studied the effect of SeNPs on BSA-glucose glycation system (Fig. 12.3) and found that SeNPs can prevent the progress of protein glycation in a concentration-dependent but time-independent manner under the specified reaction conditions (55 °C, 40 h). The mechanism inferred for the inhibitory efficacy of SeNPs might be related to NPs' (i) strong competitive activity against the available amino groups in proteins, (ii) very high scavenging activity on ROS, and (iii) inhibitory effect on the formation of α-dicarbonyl compounds. It was also proven that SeNPs protect proteins from structural modifications in the system and do not show any significant cytotoxicity toward BV-2 and BRL-3A cells up to 50 μg mL^{-1}. Thus, SeNPs may be extended to in vivo studies as the potent antiglycation agents.

Ashraf et al. (2014) observed inhibitory effect of gum arabic capped-AgNPs on AGEs formation, which proves the potential of these bioNPs to be an effective antiglycating agent. The mixtures of BSA and MG, incubated with different concentra-

tions of NPs, caused significant reduction in AGEs, as confirmed by UV-Vis, fluorescence spectrometry, and HPLC techniques.

Leaf extract of *Solanum nigrum* was used to synthesize AgNPs, which were evaluated for antidiabetic activity in alloxan-induced diabetic rats. The AgNPs-treated diabetic rats could significantly improve the dyslipidemic condition, similar to diabetic control. Reduction in the blood glucose level was observed over the period of treatment. The body weight was also improved, showing the *S. nigrum* extract-mediated AgNPs as a potential antidiabetic agent against the alloxan-induced diabetes in rats (Sengottaiyan et al. 2016).

In another report (Ashraf et al. 2016), inhibitory strength of AgNPs, synthesized with *Aloe vera* leaf, in HSA (human serum albumin) glycation was shown. These NPs were characterized using UV-Vis spectroscopy, energy-dispersive X-ray spectroscopy, high-resolution transmission electron microscopy, X-ray diffraction, and dynamic light-scattering techniques. The inhibitory effects of AgNPs on AGEs formation were assessed by checking the degree of reactivity of free amino groups (lysine and arginine residues), protein-bound carbonyl and CML content, and the impact on protein structure. It was found that AgNPs significantly inhibited AGEs formation in a concentration-dependent manner and also had a positive effect on protein structure. It was recommended that AgNPs may play a therapeutic role in diabetes-related complications (Ashraf et al. 2016).

In a recent report, ZnONPs synthesized from aqueous extract of *Aloe vera* leaf were found to be a potent antiglycating agent, as they could inhibit the formation of AGEs and protect the protein structure from modification. This proves the therapeutic efficacy of ZnONPs in controlling the AGE-related complications (Ashraf et al. 2018).

Curcumin, an active ingredient of turmeric, has been shown to assist in wound healing in diabetic mice (Merrell et al. 2009). Curcumin treatment enhanced the biosynthesis of extracellular matrix proteins and also increased the formation of granulation tissue. However, the low in vivo stability and low bioavailability of curcumin make it difficult for oral administration. Nanofiber matrices are able to mimic the diameter of collagen fibrils in the extracellular matrix. Curcumin-loaded poly (ε-caprolactone) nanofibers were shown to reduce inflammation and enhance wound closure in vivo in a diabetic mouse model (Merrell et al. 2009). Poly-N-acetyl glucosamine (sNAG) nanofibers were shown to be effective in wound healing and are biodegradable (Scherer et al. 2009). Plant-mediated metal NPs that are used for management of secondary complications of diabetes are mentioned in Table 12.2.

In a recent report, leaf of *Stevia rebaudiana* along with chitosan was used to establish their antidiabetic potential in experimental rat model of streptozotocin (STZ)-induced diabetes mellitus. These NPs showed a significant reduction in rat's mean fasting blood glucose level, compared with the diabetic control group. Also, the serum levels of various enzymes, viz., serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatases (ALP), lipid peroxidation, and antioxidant such as catalase (CAT), reduced glutathione (GSH), and superoxide dismutase(SOD), in these NPs-treated group were closer to normal levels than those in the diabetic control group (Perumal et al. 2016).

Table 12.2 Role of the plant-mediated NPs in glycation-induced diabetic complications

Name of the plant	Plant part	Metal used	Significance	Reference
Tephrosia tinctoria	Stem	Ag	NPs scavenged free radicals, decreased levels of enzymes that catalyze hydrolysis of complex carbohydrates (α-glucosidase and α-amylase), and increased the consumption rate of glucose	Rajaram et al. (2015)
Cassia fistula	Stem	Au	NPs-treated diabetic model showed a decrease of HbA1c level which is maintaining the normal range	Daisy and Saipriya (2012)
Sphaeranthus amaranthoides	Whole plant	Ag	Inhibitory activity on α-amylase and an IC50 was significantly lower than the standard drug, acarbose	Swarnalatha et al. (2012)
Sphaeranthus amaranthoides	Whole plant	Au	α-amylase inhibitory components are present in ethanolic extract of *S. amaranthoides*	Manikanth et al. (2010)
Acacia Senegal	Leaf	Ag	The mixtures of BSA and MG incubated with increasing concentrations of AgNPs showed significant reduction in AGEs	Ashraf et al. (2014)
Solanum nigrum	Leaf	Ag	AgNPs-treated diabetic rats showed significantly improved dyslipidemic condition as seen in the diabetic control. Blood glucose level was also reduced	Sengottaiyan et al. (2016)
Aloe vera	Leaf	Zn	Displayed strong capability of antioxidant and antiglycating agent as well as protected protein from damage by MG	Ashraf et al. (2018)

12.7 Conclusion and Future Prospective

Advanced glycation end products have been implicated in many pathophysiological conditions including diabetes, cataract, Alzheimer's, and Parkinson's diseases. Some artificial compounds have been tested during the last decade for their antiglycating potential, but a single drug, which can prevent the accumulation of AGEs, could not be developed so far. This has led to search for natural compounds and their derivatives with antidiabetic and antiglycating potential. Some compounds like phenolics, curcumin, and eugenol have shown promising results. Of late, NPs (both bio and non-bio) have been synthesized and characterized for their antidiabetic and antiglycating properties. Although the plant-mediated NPs with antiglycating potential are still very few, their advantage over the synthetic drugs makes them a suitable tool for diagnosis and prevention of glycation and glycation-mediated secondary complications of diabetes.

On the basis of in vitro and animal model studies, several plant products have been found to be effective supplements against glycation. It is therefore desirable to undertake their clinical trials on human beings in order to set their appropriate physiological concentration and understand their mode of action. Bioavailability of polyphenols is influenced by several factors such as bioaccessibility, transporters,

molecular structures, metabolizing enzymes, etc. It is necessary to generate new techniques such as nanotechnology and homogenization, which can enhance bioavailability of natural inhibitors such as polyphenols. The NPs and nanoencapsulation-based albumins and polyphenols have been generated. In future more intense investigations are likely to be undertaken with regard to the long-term and acute hypoglycemic, antiglycating, and hypolipidemic effects of this homogenization, NPs, and NP encapsulation on type 2 diabetes.

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