Impact of Non-Enzymatic Glycation in Neurodegenerative Diseases: Role of Natural Products in Prevention

Saheem Ahmad and Mohammed Farhan

Abstract Non-enzymatic protein glycosylation is the addition of free carbonyls to the free amino groups of proteins, amino acids, lipoproteins and nucleic acids resulting in the formation of early glycation products. The early glycation products are also known as Maillard reaction which undergoes dehydration, cyclization and rearrangement to form advanced glycation end-products (AGEs). By and large the researchers in the past have also established that glycation and the AGEs are responsible for most type of metabolic disorders, including diabetes mellitus, cancer, neurological disorders and aging. The amassing of AGEs in the tissues of neurodegenerative diseases shows its involvement in diseases. Therefore, it is likely that inhibition of glycation reaction may extend the lifespan of an individual. The hunt for inhibitors of glycation, mainly using in vitro models, has identified natural compounds able to prevent glycation, especially polyphenols and other natural antioxidants. Extrapolation of results of in vitro studies on the in vivo situation is not straightforward due to differences in the conditions and mechanism of glycation, and bioavailability problems. Nevertheless, existing data allow postulating that enrichment of diet in natural anti-glycating agents may attenuate glycation and, in consequence may halt the aging and neurological problems.

Keywords Glycation • Advanced glycation end-products (AGEs) • Diabetes mellitus • Neurological disorders • Polyphenols

Introduction

Glycosylation is the reaction between carbohydrates and the other functional groups of another molecule biological molecule (Ashraf et al. 2014). In biological terms, glycosylation is the process in which glycans are attached to the protein, lipid or

S. Ahmad (✉) • M. Farhan
Laboratory of Glycation Biology and Metabolic Disorder, Integral Research Centre-I, Department of Bio-sciences, Integral University, Lucknow, UP, India
e-mail: saheem@iul.ac.in; ahmadsaheem@gmail.com

M.M. Essa et al. (eds.), *The Benefits of Natural Products for Neurodegenerative Diseases*, Advances in Neurobiology 12, DOI 10.1007/978-3-319-28383-8_8

other organic molecule in the presence of enzymes. It is one of the forms of post-transnational modification. According to their binding nature, glycans are divided into five classes.

1. *N*-linked glycans specific to nitrogen of the asparagine and arginine side chains.
2. *O*-linked glycans specific to the hydroxyl oxygen of the serine, tyrosine, threonine, and hydroxyproline or hydroxylysine side chains.
3. Phosphoglycans attach through the phosphate of phosphor serine.
4. *C*-glycans. In this very rare type of glycosylation, sugar is added to a carbon on a tryptophan side chain.
5. Glypiation, the addition of a glycosylphosphatidylinositol (GPI) anchor that attaches protein to lipids with the help of glycans linkage.

This glycosylation process is essential and serves many functions such as some of the protein being misfolded without going under the glycosylation process (Drickamer and Taylor 2006).

Glycation (Non-Enzymatic Glycosylation)

The glycosylation process occurs in the absence of an enzyme reaction, and then this phenomenon is known as glycation or non-enzymatic glycosylation. The glycation process occurs both inside (endogenous) and outside the body (exogenous). It is completed through a series of complex reactions starting from the Amadori reaction, Schiff base reactions, and the Maillard reaction, which ultimately produces advanced glycation end products (AGEs; Fig. 1 (Munch et al. 1997; Ahmad et al. 2011).

Food with added sugar cooked at a high temperature (approximately 120 °C) accelerates the exogenous glycation reaction. However, slow cooking for a long time also promotes AGEs formation. Some studies have shown that glycation also contributes to the formation of acrylamide carcinogen during cooking (Stadler et al. 2002). For the last 50 years, food manufacturers have added AGEs to food as flavor enhancers to improve food quality and colorants to improve to make them appealing (Melpomeni et al. 2003).

Glycation Complications in Diseases

Researchers discovered that AGEs are formed after a non-enzymatic reaction to sugar and the amino group freely present on the protein or deoxyribonucleic acid (DNA) (Akhter et al. 2013; Raheem et al. 2014) and this process is involved in ageing. DNA glycation in the nucleus and the cytoplasm alters the protein product, ultimately changing the function of protein (Akhter et al. 2014; Mustafa et al. 2011). Sometimes it generates free radicals, causing structural alteration of the biomolecule. In diabetic patients DNA glycation causes the formation of neo-antigenic epitopes

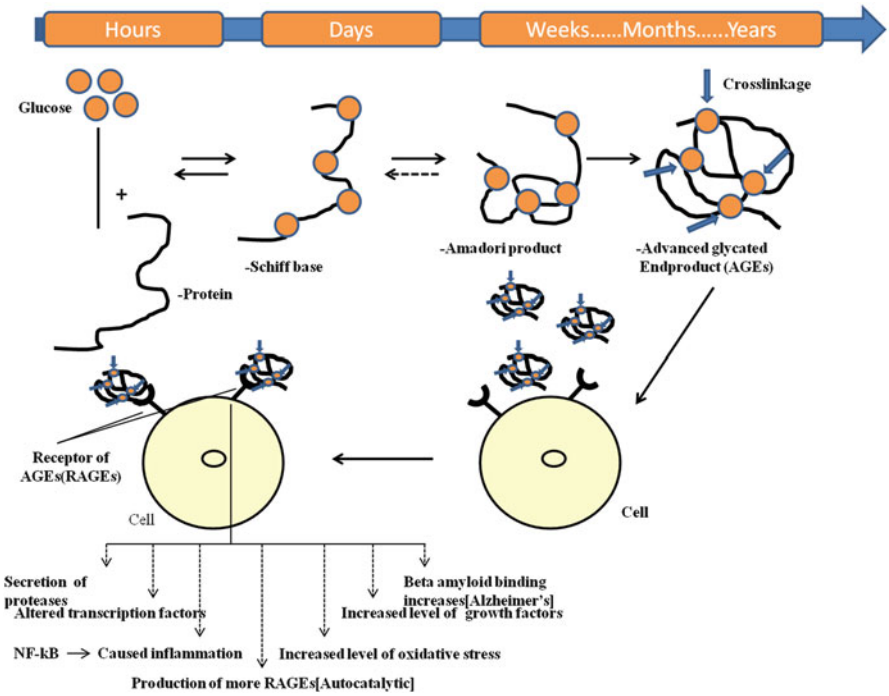

Fig. 1 Pictorial representation of steps involved in the glycation process and its implication in AGE-RAGE signaling

and increases problems in diabetes mellitus (Mustafa et al. 2011; Ahmad et al. 2014; Shahab et al. 2014). Fructose is a prompt glycating agent and a necessary component of the daily diet. In the body, it can modify DNA and generate antibody that can be the cause of the destruction of β-cells of the islets of Langerhans and other problems of diabetes (Takeuchi et al. 2010). Much research shows that hyperglycemia is the first step that causes tissue damage in diabetes because of repeated changes in the metabolism of glucose, or because of the accumulation of AGEs and glycated molecules. Glycation also affects proteins such as serum albumin, lipoprotein, hemoglobin, and insulin, and alters their function (Ahmad et al. 2013a, b, 2014). AGEs cross-link with extracellular matrix protein and activates their respective receptors (RAGEs), resulting in oxidative stress and proinflammatory signaling, which causes microvascular complication, arterial stiffening, and endothelial dysfunction (Negre-Salvayre et al. 2009).

Human serum albumin glycation is also detected in many diseases. It is ten times more reactive with glucose than with HbA1C protein. Human serum protein is present in plasma and it is the most abundant protein of plasma. Binding with the reducing sugars of plasma, it undergoes structural and functional changes and this property makes it sensitive for glycation. Because of its in vivo glycation process with plasma glucose it can be used as a new disease marker in place of HbA1C for diabetes

(Arasteh et al. 2014). The rapidness of glycation also depends on the nature of the carbohydrate, which binds in the process. For example, when we compare glucose and ribose together, ribose induces faster glycation than the glucose and gives rise to a product similar to amyloid products (Wei et al. 2009). In vivo research shows that in a healthy person glycated albumin is present in between 1 and 10 % (Peters 1996). But in the case of a diabetic patient, it increases two- to three-fold compared with a control (Bourdon et al. 1999). Glycated albumin is also implicated in other diseases, such as retinopathy, neuropathy, nephropathy, and coronary artery diseases (Brownlee 1995).

Glycation and Diabetic Problems

Glycation Complications in Diabetic Retinopathy

Retinopathy is the most common complication of diabetes among individuals between the ages of 30 and 70 years (Frank 2004; Chen et al. 2013). The last stage of retinopathy causes blindness. In brief, the processes involved in retinopathy increase blood vessel density, angiogenesis, the permeability of retinal capillaries and the thickness of the capillary basement membrane (Frank 2004). AGEs play a vital role in the succession of diabetic retinopathy and causes dysfunction and the death of retinal cells. The components of the AGE–RAGE complex may be hopeful targets for the treatment of diabetic retinopathy (Zong et al. 2011). Studies suggest that rats have an accumulation of AGEs, and lose the function of Muller glial cells during diabetic retinopathy (Curtis et al. 2011). Recent findings had revealed that the AGE *N*-epsilon-(carboxymethyl)lysine (N-(ε)-CML) is a modulator in the developmental stages of nonproliferative retinopathy in type 2 diabetic individuals (Choudhuri et al. 2013). Some reports show that AGEs are the major contributors to increasing the permeability of retinal endothelial cells. AGEs cross-linked with protein cause vascular stiffness and ECM protein modification, leading to decreased pericyte adherence (Vasan et al. 2003). AGEs also induce pericyte death and the signaling pathway involved is through the generation of oxidative stress, leading to the inhibition of protein kinase B/Akt phosphorylation (Stitt et al. 2004).

Glycation in Diabetic Cataract

Loss of transparency of the eye lens is the primary step of cataract development and AGEs play a key role in this process (Hashim and Zarina 2011). Reports revealed that in the diabetic individual the progression of cataracts is swift (Harding et al. 1993). In a diabetic individual's cataract the protein of the lens becomes glycated, which ultimately leads to blindness (Luthra and Balasubramanian 1993). Some research reports suggested that AGEs cause vision impairment by accumulating in the eye lens and inducing severe changes in structural protein. Finally, they lead to protein aggregation in the lens and these high molecular weight aggregates scatter light and hamper vision

(Nagaraj et al. 2012). A few reports revealed that AGEs, by changing the surface charge of the protein, affect protein–water and protein–protein interactions and finally decrease the transparent properties of the eye lens (Beswick and Harding 1987; Kumar et al. 2004). In diabetes, a patient's glucose level in aqueous humor increased and induced protein glycation. This process results in the generation of superoxide radicals and production of AGEs. In another piece of research, the binding of AGEs with the RAGE present on the epithelium of the lens elevated O^{2-} and H_2O_2 levels (Gul et al. 2008). All these reports demonstrated that protein glycation altered the protein structure, leading to changes in the amino acid involved in cataract development.

Glycation in Diabetic Neuropathy

Diabetic neuropathy affects both peripheral and autonomic nerves. It also causes diarrhea, constipation, and urinary incontinence. Studies have suggested that AGE–RAGE might play a key role in the pathogenesis of diabetic neuropathy (El-Mesallamy et al. 2011). It has already been shown in previous research that glycolaldehyde (one type of precursor of AGEs) at a physiological concentration slows down the viability of rat Schwann cells. This plays a significant role in diabetic neuropathy. The presence of AGEs has also been examined in the peripheral nerves of diabetic patients. CML is present in the basement cell and in Schwann cells (Sugimoto et al. 1997). Fiber loss, which occurs in human diabetic peripheral nerves, is due to the accumulation of AGEs. AGEs may also interfere with axonal transport and this leads to the development of atrophy and nerve fiber degradation. P0 protein, which is present in nerves modified by AGEs causes demyelination of the nerve fibers (Vlassara et al. 1981). Previous research revealed that the interaction between AGEs and RAGE triggered the transcription factors NF-αB and activator protein-1 (AP-1) and interleukin-6 (Schmidt et al. 1995).

Advanced Glycation in Atherosclerosis

Owing to the invasion and accumulation of white blood cells, the artery wall becomes thicker and atherosclerosis occurs. The accumulation also contains active white blood cells, which are producing inflammation and dead cells, including cholesterol and triglycerides. Atherosclerosis is further promoted by low-density lipoproteins without proper removal of cholesterol and fats from macrophages with the help of functional high-density lipoprotein (HDL). Much research revealed that advanced glycated product plays an important role in the modification of LDL that ultimately promotes atherosclerosis. Basically, AGEs start oxidative reactions that induce the formation of oxidized LDL. A recent study by Naila Rabbani et al. (Rabbani et al. 2011) shows that the glycation of LDL by methylglyoxal (MG) increases arterial atherogenicity. MG attached to the arginine residue of LDL results in the final product hydroimidazolone, also known as the MG-H1 complex. The study revealed that after the modification of

LDL, it becomes smaller and also has an effect on functional changes such as increasing aggregation, binding with proteoglycan, and increasing the accumulation of MG-H1 in the arteries. This peptide mapping and informatics study discloses that MG modified apoB-100 of LDL at the R18 target site. Another study by Basta et al. (Basta et al. 2009) suggests that AGE accumulation might amend vessel wall homeostasis in a pro-atherogenic fashion via multiple mechanisms: extracellular matrix permeability alteration, inflammatory cytokines and growth factor secretion, antithrombotic properties, endothelial alterations, and by the elevated level of adhesion molecules and chemokines on the surface of the vascular cells.

In their 2009 study, Basta et al. examined the plasma level of sRAGE, AGE, and carboxymethyl (lysine) (CML) adduct using an enzyme-linked immunosorbent assay and tissue levels of AGEs and RAGEs were detected by immunohistochemistry. The study was based on 29 patients with carotid atherosclerosis. In those patients, 10 patients had no symptoms of disease and 19 had symptoms. This study revealed that plasma levels of sRAGE were higher in symptomatic patients compared with asymptomatic patients. The researchers concluded that sRAGE in the plasma of symptomatic carotid atherosclerosis is higher than in asymptomatic carotid patients (Basta et al. 2009).

Previous studies showed that AGEs cross-link protein, which is helpful in altering the flexibility and digestibility of the collagen matrix in the vascular cell wall and in the skin. Since the receptor characterization of AGEs, it has been clear that AGEs initiate their biological effects via receptor-coupled signaling pathway. AGEs may also interact with the RAGEs of endothelial cells to activate cellular events such as the regulation of transcription factor NF-kB (Bierhaus et al. 1997), and the activation of p38 MAP kinase, NAD (P) H-oxidase (Wautier et al. 2001), and ERK1/2 MAP kinase cascades. In recent studies, S100/calgranulins have been reported to accumulate at the site of chronic inflammation. HMGB1 (amphoterin) was also identified as an activator of the RAGE–NF-kB axis. In the nucleus, NF-kB increases the transcription of RAGE and other genes relevant to atherogenesis such as VCAM-1, endothelin-1, intracellular adhesion molecule-1, and the pro-inflammatory cytokines interleukin-6, interleukin-1b, and tumor necrosis factor (Fig. 2). In the report by Basta et al. (2005) it is stated that exposure to CML–albumin increased the expression of VCAM-1 in endothelial cells and also RAGES-dependent reactive oxygen species (ROS) formation. These effects were inhibited by NAD (P) H-oxidase inhibition and by precise anti-RAGE antibody. The activation of RAGE genes and the RAGE gene-mediated signaling cascade triggered a vicious cycle. The production of AGE, cytokines, and ROS involved in atherogenesis may be interlinked and may connect, as shown in the schematic Fig. 2.

Role of Glycation in Ageing

Many studies suggested that glycation might play an important role in the process of ageing. The final products of glycation were seen and their accumulations were reported in several previous studies (Peppa et al. 2008; Nowotny et al. 2014). In

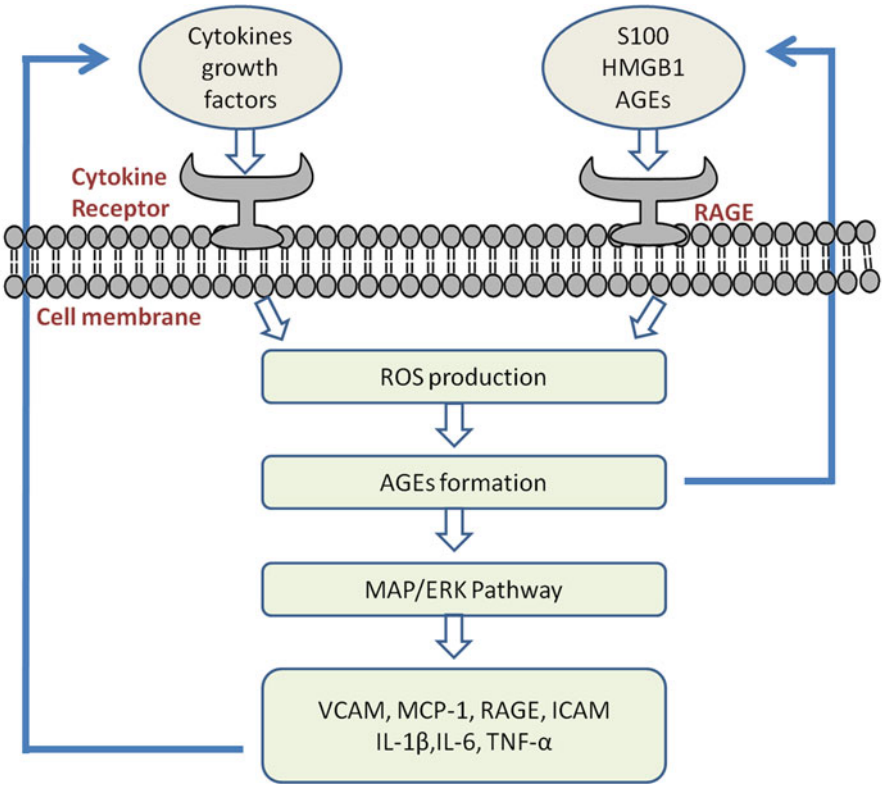

Fig. 2 Effect of ROS and AGEs formation in vascular cells and its involvement in MAP/ERK pathway which leads to the different cytokines secretion

1980, when AGEs were found to accumulate in the tissue of a living organism as it aged, this process engendered the theory of non-enzymatic glycosylation (Monnier et al. 1981). Many problematic age-related changes are actually caused by protein degradation, such as the accumulation of molecular waste, post-translational modification, functional disorders of the tricarboxylic acid cycle, deterioration of functional proteins, and activation of inflammatory pathways controlled by intracellular signaling. These changes are symptomatic of "glycation stress" (Ichihashi et al. 2011). Sometimes, proteases and other oxidizing degradation enzymes are metabolized within the proteasome and the waste product excreted. There are so many other enzymes that can modify AGEs and intermediate compounds. For example, glyoxalase 1 converts the highly reactive α-oxo-aldehydes into the α-hydroxy acids using L-glutathione as a cofactor. However, the activity of proteolytic enzymes decreases with age (Nowotny et al. 2014; Lee and Chang 2014). A decrease in oxidative stress with the application of α-lipoic acid also decreases the accumulation of AGEs, and this was also associated with a reduction in cell cycle reentry and a more euploid neuronal genome (Kuhla et al. 2015). Galactose is more

effective than glucose as a glycating agent. The amount of aldehyde present in the galactose is many times higher than the amount of the glucose (Dworkin and Miller 2000). A high amount of galactose in the diet has been shown to cause premature ageing and in this process cytochrome *c*, which is released from mitochondria, plays an important role by causing apoptosis (Lu et al. 2010). This effect was attenuated by salidroside, known as the inhibitor of RAGE (Mao et al. 2010). Metformin is an inhibitor that is used for the inhibition of AGEs formed by the monosaccharides, also known as geroprotectors (Severin et al. 2013). For the cellular level, aminoguanidine inhibitor was used and reported studies show an increase in the replicative lifespan of the human lung fibroblast from 54 up to 75 population doublings (at 4 mM aminoguanidine) and a decrease in the rate of telomere shortening by about 50%. Several mechanisms are known that can also contribute to the inhibition of glycation (Wang et al. 2007). Thus, it has been postulated that the aggregation of AGEs is the basis of the "biological clock" leading to ageing (Severin et al. 2013). Ageing is related to the chronic low-grade inflammatory status that also causes chronic disease such as kidney disease, age-related muscle wasting, and diabetes mellitus. AGEs are proinflammatory in nature. Studies on people with a low-AGEs diet show decreased inflammation, whereas in subjects with a high-AGE diet had increased inflammation (Van Puyvelde et al. 2014). Half of all the observational studies show the relationship between the inflammatory process and AGEs in food. The level of circulating AGEs and inflammation status are directly related to the dietary intake of AGEs. Restricting AGE intake may lower the level of inflammation and also decrease chronic disease-related inflammation. A previous study on mice (Van Puyvelde et al. 2014) shows that lowering the AGE content and the normal diet significantly curtails AGE accumulation. Short-term human trials revealed that a low AGE diet decreases inflammatory markers and the oxidant burden (Peppa et al. 2008). AGE accumulation plays an important role in skin ageing. The aggregation of AGEs has been noticed in various tissues during diabetes and ageing, including glomerular basement membranes, skeletal and smooth vascular muscles, and articular collagen (Verzijl et al. 2000a; Haus et al. 2007; Sell et al. 1993). Accordingly, the deposition of AGEs in these tissues has been involved in various age-associated pathological conditions such as diabetic angiopathy, nuclear degradation in diabetes, and osteoarthritis (Vlassara et al. 2002; Glenn et al. 2007; Stitt 2001; DeGroot et al. 2001).

The skin is the largest organ of the body. Its easy accessibility is an excellent prospect for the minimally invasive or non-invasive analysis of glycation, taking advantage of the typical autofluorescent properties of AGEs. Therefore, AGEs in skin have been studied thoroughly and detected in diabetes and also during chronological ageing (Jeanmaire et al. 2001; Sell et al. 1996; Schleicher et al. 1997). It is a general view today that AGE aggregation is dependent on the protein turnover value; thus, long-lived proteins are mainly modified by glycation (Verzijl et al. 2000b). Types I and IV collagen, showing a slow turnover value of about 10 years and one dermal protein fibronectin, mainly suffer from glycation at the time of intrinsic chronological ageing (Jeanmaire et al. 2001; Dyer et al. 1993). The first appearance of glycated collagen is observed at the age of 20. The yearly rate of

accumulation is about 3.7% and has increased 30–50% by 80 years of age (Jeanmaire et al. 2001). CML was histochemically detected in the human epidermis from healthy donors (Stitt 2001). The authors identified cytokeratin 10 (CK10) proteins, which are a target protein for CML modification. The total amount of CML in younger donors is less than in older ones. This study shows AGE involvement in the epidermal physiology and the probable involvement of short-lived proteins in glycation chemistry. Additionally, in an in vitro organ skin model, the epidermis and dermis functions were modified by glycation.

The effect of UV irradiation has been mainly recognized by proinflammatory changes, oxidative damage, apoptosis, mutagenesis, and matrix metalloproteinase induction (Nowotny et al. 2014). However, it has been revealed that sun-exposed skin has a higher accumulation of AGEs compared with sun-protected skin (Jeanmaire et al. 2001; Dunn et al. 1991). Accumulation of AGEs was higher in the sun-exposed skin, showing UV irradiation, which may also play a key role in the formation of AGEs in vivo (Mizutari et al. 1997). All those results show that, like smoking, another factor that ages the skin, AGEs accumulation is also involved in the various structural and functional modifications at the time of photoaging. Diet is also an environmental factor for ageing. Dietary AGEs are directly compared with inflammatory markers and serum levels of AGEs in healthy human subjects (Uribarri et al. 2007). It has been commonly accepted that AGEs, once formed, can be removed only when the degradation of the modified proteins occurs. However, it has now become noticeable that in the organism different enzymatic systems seem to be implicated in the degradation or elimination of AGEs. As shown above, GLOI is an enzyme that is also responsible for the elimination of reactive α-dicarbonyl compounds (Ramasamy et al. 2005). AGE existence in biological molecules modifies their functional and biomechanical properties. Lipids, nucleic acids, and proteins can be the main targets of advanced glycation, modifying protein–DNA interactions, enzyme–substrate interactions, protein–protein interactions, epigenetic modulation, and DNA regulation, thus interfering with several physiological functions of the organism. Although, AGEs are themselves reactive molecules, they interact with their receptors and activate various molecular pathways in vivo, thus becoming involved in inflammation, cell proliferation, immune response, and gene expression.

Glycation in Neurodegenerative Diseases

Parkinson's Disease

The blood–brain barrier (BBB) plays an important role in supplying nutrients to brain tissue and also in filtering harmful compounds from the brain back to the circulating blood. Disturbance of the BBB is linked to some neurodegenerative disorders, including Parkinson's disease (PD). Iron deposition, oxidative stress, and mitochondrial impaired function are risk factors for the degradation of the central nervous system (Schipper 2004). Additionally, it has been assumed that

inflammation in the BBB is related to the risk of the increased formation of cytokines, over-activation of the microglia, and the release of ROS (Whitton 2007).

Parkinson's disease is currently the most common neurodegenerative disorder; the current demographic drift indicates a life-time danger approaching 4 % (Schapira 2013). The average age at onset is 70 years, but most of the patients develop early-onset PD, before the age of 50 (Schrag and Schott 2006). The symptoms of this disease are tremors, slowness of movements, rigidity, and postural imbalance. The main pathological abnormalities are the pigment loss in the pigmented cells of the pars compacta in the substantia nigra, and the dopaminergic neurons, which decrease the dopamine level (Lu'o'ng and Nguyen 2012). The pathogenesis of neurodegeneration in PD is that patients have high levels of oxidized lipid and low levels of glutathione (Zeevalk et al. 2008; Obeso et al. 2010; Schapira 2012). The concentration of polyunsaturated free acids and phospholipids, which are highly susceptible to oxidants, is decreased in these patients, although malondialdehyde, a lipid oxidation marker, is increased (Dexter et al. 1989; Zhou et al. 2008).

In the age-related neurodegenerative disorders, such as Alzheimer's, Parkinson's, and Huntington's diseases, tissues have an abnormal accumulation or aggregation of proteins. These proteins come under glycation and form AGEs within the tissue, and AGE accumulation aggravates these diseases. Research by Shaikh et al. published in 2008 revealed that AGE accumulation promotes in vitro cross-linking in alpha-synuclein and accelerates the formation of alpha-synuclein-positive inclusion bodies (Shaikh and Nicholson 2008). As it is already known that alpha-synuclein is a protein that contains 140 amino acids, and is encoded by a single gene of seven exons situated in chromosome 4 (Chen et al. 1995). This protein is present in the nucleus and presynaptic nerve terminals and was also known as a synuclein. Recently, research by Guerrero et al. showed that α-synuclein present in neurons is glycated and glycosylated within the neurons and in vitro, which ultimately affects DNA binding properties. Glycated α-synuclein causes increased genome damage by its direct interaction with DNA and via the increased generation of ROS as a glycation byproduct (Guerrero et al. 2013).

α-Synuclein Aggregation and Cell Death

The aggregation and neurotoxicity of α-synuclein can be grouped into three major classes—mechanical, cellular disruption, toxic loss of function, and toxic gain of function. Common examples are the permeation of cellular membranes by amyloid aggregation. α-Synuclein oligomers bind to the lipid of membranes and break membrane bilayers (Auluck et al. 2010; Van Rooijen et al. 2010). Some α-synuclein has the properties to penetrate the membranes and form pore-like structure (Giehm et al. 2011; Volles and Lansbury 2003). It has also been proposed that amyloid oligomers cause membrane permeation without forming pores (Kayed et al. 2003). It is assumed that this is one of the key mechanisms of protein aggregate toxicity.

Additionally, α-synuclein degradation via proteasome inhibition by the copper-dependent generation of ROS has been proposed for the neurotoxicity of α-synuclein neurotoxicity (Brown 2010; Bennett 2005).

First, glycation reported in the locus ceruleus and substantia nigra shows an increase in immunoreactivity at the periphery of the Lew bodies (LBs) of PD patients (Castellani et al. 1996). Additionally, the colocalization of AGEs with α-synuclein is observed at a very early stage; in this case, α-synuclein is also present at the periphery of LBs (Munch et al. 2000). All the results taken together suggest that glycation might play an important role in the proteolytic resistance of the protein deposits and in the chemical cross-linking. Although glycation was also detected in the amygdala, cerebral cortex, and substantia nigra of older control patients, the level and the number of glycated proteins were substantially higher in PD patients (Dalfo et al. 2005). RAGEs were also highly expressed in PD individuals compared with controls, signifying the role of AGEs in PD.

In PD patients the cellular level of reduced glutathione (GSH) decreases in the early stages of the disease, which ultimately results in a decrease in the activity of the glyoxalase system. Glyoxalase is the main catabolic pathway of important glycation agents such as MG (Thornalley 1998). Carbonyl stress increases the concentration of AGEs, which elevates the oxidative stress that finally induces AGE formation. This harmful cycle may contribute to cell damage previously reported in dopaminergic neurons. Moreover, dopamine degradation and its autoxidation also contribute to increases in the level of oxidative stress (Lee et al. 2009).

Alzheimer's Disease

In a recent survey published in 2014, data showed that between 21 and 35 million individuals worldwide suffer from Alzheimer's disease (Querfurth and LaFerla 2010), most of the cases being found in people over 65 years of age. In 2010, about 486,000 people were dying of dementia (Lozano et al. 2012). This disease was first described by German pathologist and psychiatrist Alois Alzheimer in 1906 (Berchtold and Cotman 1998). The treatment for Alzheimer's is becoming increasingly expensive and is a major problem for developing countries. It belongs to a type of chronic neurodegenerative disease that progresses slowly and becomes worse over time (Burns and Iliffe 2009). The common symptoms of this disease are short-term memory loss. When the disease is advanced, symptoms include disorientation, loss of motivation, and problems with language. The cause of AD is not well understood; various hypotheses have been proposed to explain AD development. Sixty to seventy percent of dementia leads to AD. The term dementia describes symptoms including memory loss and problem-solving, language, and thinking difficulties.

Neurons are injured and dead in the hippocampal region of the AD patient, which is involved with memory and learning, but this degeneration affects the whole brain (Shaffer et al. 2013; Swardfager et al. 2010). Amyloid beta (Aβ) is a type of peptide

that is an abnormal proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP). The function of this protein is unclear, but it may be involved in neuronal development. Aβ is a monomer in nature and contains short regions of beta sheets at high concentrations. After dramatic conformational changes it is a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. Fibrils make a dense formation outside the neurons. This layer is called neuritic plaque. In Alzheimer's disease, one new protein aggregation was observed in neurons. It is a tau microtubule protein that is highly expressed in neurons. Tau protein works as a microtubule stabilizer in the cell cytoskeleton. Like other microtubule-associated proteins, tau is also regulated by the phosphorylation process. Hyperphosphorylated tau (P-tau) accumulates and forms paired helical filaments, which finally aggregate into masses inside the nerve cells in AD patients. These phenomena are called neurofibrillary tangles (NFTs) and dystrophic neurites linked to amyloid plaques (Goedert et al. 2006).

Recent evidence suggests changes in the cerebrospinal fluid (CSF) levels of P-tau, tau, and Aβ, and that the level of CSF might not be static over the course of the disease. The mechanism behind the senile plaque and NFTs is still unknown at present. Senile plaques and NFTs prompt the injury and death of neurons, and as a consequence memory loss and symptomatic behavioral changes. Inflammation within the brain and increased reactivity of the microglia toward amyloid deposition have been involved in the pathogenesis (Revett et al. 2013).

AGEs in Alzheimer's Disease

Amyloid beta peptide deposition starts early in the course of AD and increases markedly during progression of the disease. The advanced step of Alzheimer's leads to the generation of NFTs, which cause neuronal death (Selkoe 1994). Some studies revealed that the presence of AGEs in the senile plaque and NFTs were identified by the immunohistochemical analysis of samples obtained from the AD patient (Smith et al. 1994; Sasaki et al. 1998). Aβ glycation markedly increases its aggregation in vitro (Vitek et al. 1994). Glycation of tau protein and its hyperphosphorylation enhance the formation of paired helical filaments (Ledesma et al. 1994; Yan et al. 1994). Taking all data together, there is the implication that AGEs may be an important factor involved in the progression of neurodegenerative disorders. The deposition, aggregation and modification of the protein are the well-known part of many pathological processes and play a direct role in tissue damage. From recent studies, it has become clear that AGEs also play a role in neurodegenerative diseases such as AD (Sasaki et al. 2001), amyotrophic lateral sclerosis (ALS) (Kikuchi et al. 2002; Chou et al. 1998), PD (Castellani et al. 1996), and Creutzfeldt–Jakob disease (Sasaki et al. 2002).

Very little is known about the relationship between AD and glucose tolerance, and the higher occurrence of AD among diabetic patients is still controversial. Recently revealed links between AD and type 2 diabetes consist of the detection of

AGEs and increased AGE receptor in the brain tissue of patients with AD (Munch et al. 1998; Yan et al. 1996). Research suggests that patients with diabetes mellitus are at almost double the risk of AD and dementia. AGEs are implicated in diabetic complications, but the degradation of AGEs and AGE-modified protein is not clear at the time of renal dialysis in diabetic patients (Takeuchi et al. 1999; Makita et al. 1994). AGEs of low molecular weight have been shown to be chemically active and also contribute to the damage and further modification of tissue protein (Makita et al. 1994). It is an interesting point to determine that AGE formation is implicated in abnormal tau protein processing and Aβ deposition, which has been detected in the brain of patients at the time of renal dialysis (Harrington et al. 1994). Riviere et al. (1998) measured plasma protein glycation basically derived from glucose in AD patients (Riviere et al. 1998). In plasma, protein glycation evaluated by plasma furosine, was approximately two times greater in AD subjects than in controls. Recently, Shuvaev et al. (2001) quantified the level of an Amadori product, an early glycation product in CSF in late-onset AD and in aging. The amount of an Amadori product in CSF correlated with the glucose concentration of CSF, but did not change as age increased. In brief, the level of CSF Amadori product was found to be 1.7 times higher than in an age-matched control group (Shuvaev et al. 2001).

Role of Natural Products in the Prevention of Neurodegenerative Diseases

It is well established that 80 % of drug molecules are natural products or inspired by natural compounds. Discoveries of new drugs from natural products have been made since the Vedic period. Historically, plants and other natural product-derived drugs were used in the treatment of many major afflictions such as cancer, cardiovascular diseases and neurological conditions and also have their future utilization. The traditional Indian System of Medicine has a very long history of usage in a number of diseases and disorders, but there is a lack of recorded safety and efficacy data. Ayurvedic Indian and Chinese systems are great traditional systems that have relatively organized databases, and more exhaustive descriptions of botanical materials that are available and that can be tested using modern scientific methods. Both systems of medicine thus have an important role to play in the bioprospecting of new medicines. The investigation of natural products as a source of new human therapeutics reached its peak in the western pharmaceutical industry during the period 1970–1980, which resulted in a pharmaceutical landscape extremely influenced by nonsynthetic molecules. Recently, it has been suggested that drug discovery should not always be limited to discovery of a single molecule, and the current belief is that rationally designed polyherbal formulation could also be investigated as an alternative in multitarget therapeutics and prophylaxis. Development of standardized, safe, and effective herbal formulation with proven scientific evidence can also provide an economical alternative in several disease areas.

Many inhibitors have been discovered, both natural and synthetic, against the formation of AGEs. Synthetic inhibitors are divided into three classes:(1) Carbonyl-capturing agents, which attenuate carbonyl stress (2) Cross-link breakers(3) Metal ion chelators (Reddy and Beyaz 2006)However, all types of synthetic agents were withdrawn from the clinical trials because of their low efficacy, unsatisfactory safety, and poor pharmacokinetics (Kawanishi et al. 2003; Manzanaro et al. 2006). Aminoguanidine is also a nucleophilic hydrazine synthetic compound that blocks the formation of AGEs withdrawn from the third phase of clinical trials owing to the lack of efficacy and to safety concerns (Thornalley 2003). Alternatively, natural products have been proven to be safe for human consumption and many plant extracts have been tested for their antiglycation activity (Lee et al. 2006). Additionally, numbers of plant-derived agents have been shown to possess hypolipidemic, hypoglycemic, and antioxidant properties (Akhter et al. 2013; Vasu et al. 2005; Iqbal et al. 2014; Hashim et al. 2014). Phenolics (Choudhary et al. 2010), carotenoids (Sun et al. 2011), unsaturated fatty acid (Sun et al. 2010), polysaccharides (Meng et al. 2011), and many others have been shown to have antiglycating properties. Consequently, the consumption of dietary components on a daily basis from the plant source is potentially beneficial for the prevention of diabetes and its complications (Yazdanparast et al. 2007). Some of the best examples are the ethanol fraction of *Melissa officinalis*, L (Lemon balm), which were reported to possess high inhibitory properties on AGEs formation in late glycation (Miroliaei et al. 2011). Green tea significantly decreases the level and the accumulation of AGEs, and in diabetes, it reduced the cross-linking of tail tendon collagen (Babu et al. 2008). Caffeoylquinic, *p*-coumaroylquinic, feruloylquinic, and dicaffeoylquinic acids present in coffee inhibit protein glycation and the formation of dicarbonyl compounds (Verzelloni et al. 2011). Taurine amino acid was shown to decrease acrylamide production in a potato model, implicating its use in food processing to reduce acrylamide formation (Shin et al. 2010).

Polyphenols

The anti-glycation activity of several medicinal herbs and dietary plants was similar to or even stronger than that of aminoguanidine (Ma et al. 2011). Some studies have confirmed that the anti-glycation activity compared significantly with the phenolic content of the experimental plant extracts (Peng et al. 2008). Polyphenols are the most profuse dietary antioxidants, commonly present in the cereals, seeds, fruits, vegetables, nuts, chocolates, and beverages, such as tea, coffee, and wine. They have some health benefits such as the prevention of cancer (Landis-Piwowar et al. 2007), cardiovascular disease (Vinson et al. 2006), and neurodegenerative disease. Polyphenols as groups of natural products contain several sub-groups of phenolic compounds. They are classified by the biological function, source of origin, and chemical structure.

Also, bulk amounts of polyphenols exist in plants as glycosides, with many sugar units and with sugars at various positions of the polyphenol skeletons (Tsao 2010).

On the basis of the chemical structure of the aglycones, polyphenols are divided into the following groups:

1. Phenolic acids

Phenolic acids are the most important antioxidant phytochemicals naturally present in vegetables and fruits. They are non-vitamin in nature. The biological activity of phenolic acid depends on the lipophilicity and presence of ring-substituted hydroxyl groups. Phenolic acid is present in the nonflavonoid polyphenolic compound category, which can be divided into two parts cinnamic acid and benzoic acid derivatives, based on C3–C6 and C1–C6 backbones (Fig. 3) (Tsao 2010).

Cinnamic acid

Caffeic acid (Fig. 4) is a natural cinnamic acid found in herbs and vegetables, e.g., basil, coffee, pear, oregano, and apple (Clifford 1999). Gugliucci et al. in 2009 demonstrated that caffeic acid present in *Ilex paraguariensis* extracts inhibits the formation of fluorescent AGEs in in vivo experiments (Gugliucci et al. 2009). Additionally, extracts from species *Chrysanthemum* (*C. indicum* L. and *C. morifolium* R.) confirmed the marked inhibition of the generation of AGEs and CML in in vitro experiments. Other species of *Chrysanthemum* (*C. morifolium* R.) contain flavonoid glucoside varieties, chlorogenic acid, and apigenin (Tsuji-Naito et al. 2009). Certain *trans* cinnamic acid and quinic acid combined and formed chlorogenic acid, which is present in pineapple, strawberries, and sunflower. 5-caffeoylquinic acid (5-CQA) is a commercially available chlorogenic acid and has been widely studied because of its antioxidant activity. Chlorogenic acids are metal scavengers and free radicals; they may also hinder glucose absorption and have been shown to change the gene expression of antioxidant enzymes (Fiuza

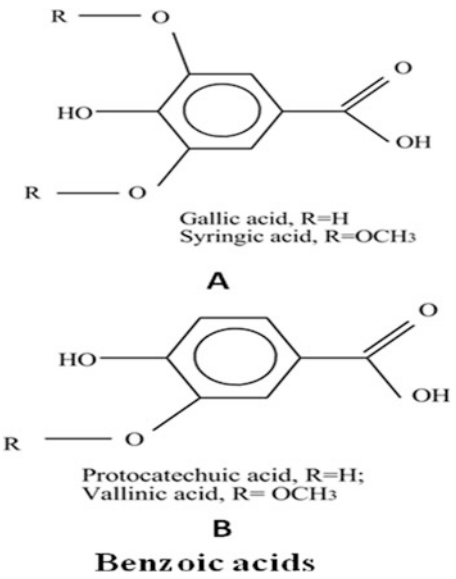

Fig. 3 Different structure(s)(A&B) of benzoic acid

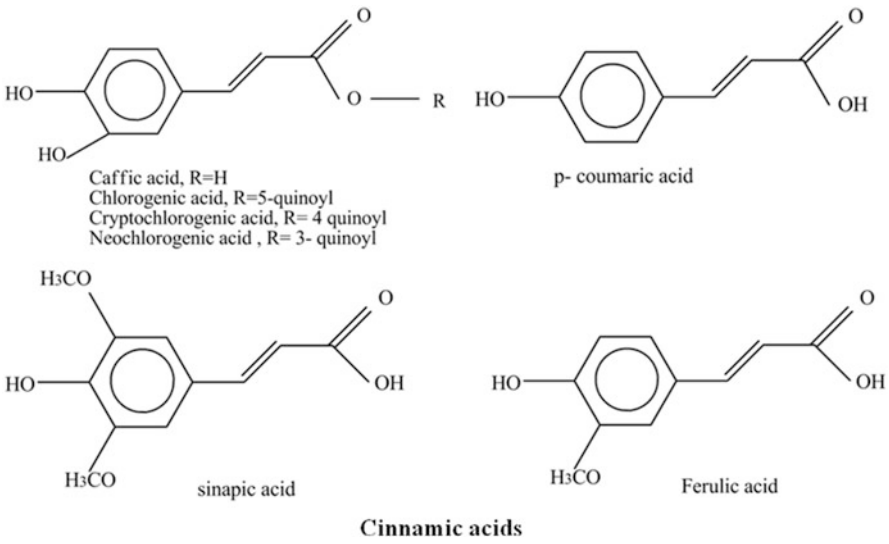

Fig. 4 Phenolic acid- different structure of cinnamic acid

et al. 2004). The chlorogenic acid fraction present in coffee has been shown to inhibit the generation of CML in a concentration-dependent manner. Moreover, polyphenols such as caffeoylquinic, dicaffeoylquinic, p-coumaroylquinic, and feruloylquinic acids contributed to more than 70% of the antioxidant property of the coffee fractions (Verzelloni et al. 2011). In particular, *Ilex paraguariensis*, like coffee, contains a high amount of caffeic acid, generally esterified as chlorogenic acid (Gugliucci et al. 2009). High amounts of chlorogenic acid were also found in *Chrysanthemum morifolium* R. (Tsuji-Naito et al. 2009). Jang et al. isolated three quinic acids derived from the leaves and stem of *Erigeron annuus.* the structure identified is 3-caffroylquinic acid, 3,5-di-*O*-caffrolyl-epi-quinic acid, and 3,5-di-*O*-caffeoylquinic acid methyl ester. The 3,5-di-*O*-caffeoyl-epi-quinic acid compound exhibited most effective activity against AGE generation and in stopping the opacification of rat lenses, whereas 3-caffeoylquinic acid was less effective. Sucrose ester and caffeoyl erigerosides were also more efficient AGE inhibitors than aminoguanidine (Jang et al. 2010).

Ferulic acid

Ferulic acid (FA) is one of the natural cinnamic acids available in food and drinks, e.g., fruits, oats, and vegetables (Wang et al. 2009). It has free radical scavenging properties of oxidized low-density lipoprotein and hydroxyl radicals (Kikuzaki et al. 2002). A few reports have shown that FA reacts with HSA and finally forms a complex structure (Kang et al. 2004). These structures have a decreased HSA α-helix structure, which has led to many other structural changes within the protein. In 2011, Miroliaei et al. published research data that demonstrated that the

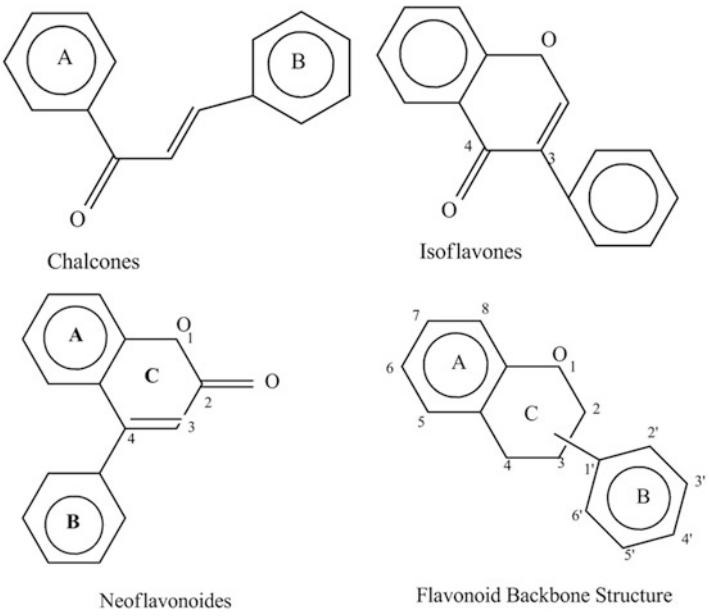

Fig. 5 Structure of various flavonoids

treatment of BSA with the herb *Melissa officinalis* L. prevents structural changes occurring because of D-glucose. The extract contains rosmarinic acid, which has the potential to prevent changes in the glycation site and after that produces a barrier for cross β-structure formation. Additionally, a research paper published by Ma et al. in 2011 showed that the isolation of rosmarinic acid from *Salvia miltiorrhiza Bge* has more inhibitory potential against AGE formation (Ma et al. 2011).

2. Flavonoids

The general structural backbone of flavonoids consists of C6–C3–C6. The two C6 units are phenolic in nature (ring A and ring B; Fig. 5). With the hydroxylation pattern and chromane ring (ring C) variation, flavonoids can be further divided into different sub-groups such as flavanones, flavonols, flavan-3-ols, flavones, and anthocyanins. In the majority of cases of flavonoids, ring B is attached to the C2 position of ring C. In some cases, ring B is attached to the C3 and C4 positions of ring C, known as isoflavones and neoflavonoids respectively. Various types of vegetables, tea, and red wine are rich in flavonoids (Terao et al. 2008). Several flavonoids are antioxidant in nature, effective in trapping free radicals and participating in balancing the overall plant cell redox homeostasis (Hernández et al. 2009). In various lipid system flavonoids show their antioxidant properties, which are helpful in preventing atherosclerosis (Terao et al. 2008). *Cuminum cyminum* (CC), commonly known as jeera, have 51.87% w/w flavonoids, which are

responsible for its antiglycation property. Researchers have revealed that streptozotocin-diabetic rats, when treated with CC, had reduced oxidative stress in the renal region and decreased AGE accumulation by enhancing the antioxidant defense and also reducing lipid peroxidation induced by free radicals. Moreover, experiments suggested that the antihyperglycemic properties of CC may be caused by the protection of surviving pancreatic β cells (Jagtar and Patil 2010).

Owing to the lack of the heterocyclic ring C, chalcones are still present in the flavonoid family (Tsao 2010). The chalcone butein, obtained from an ethyl acetate fraction of *Rhus verniciflua*, is the effective inhibitor of human ALR2 at a concentration of 0.7 μM (IC50 value). Butein also potently inhibits AGE accumulation in vitro. Some research reports say that the methylation or glycosylation of the 3′- or 4′-hydroxyl group decreases this activity, whereas the hydroxyl groups at the 3′-, 4′-, 5-, and 7-positions of flavones raise their AGE-inhibitory activities (Matsuda et al. 2003).

Dihydrochalcones are the major sub-family of flavonoids and is present in *Malus domestica* (apple trees). It is found in large amounts in immature fruits and in leaves (Pontias et al. 2008). Phloridzin and its aglycone phloretin are the simplest forms of dihydrochalcones (Williams 1964). The study by Bernonville et al. (2010) suggests the presence of the combination of phloridzin with two additional dihydrochalcones, identified alone as trilobatin and sieboldin. Phloridzin in the intestine inhibits glucose absorption and renal resorption, which ultimately results in the normalization of glucose in the blood (Herenkranz et al. 2005). On the basis of antioxidant assay results, sieboldin was much more efficient than phloridzin in the inhibition of AGE formation (Dugé de Bernonville et al. 2010).

Isoflavones

In isoflavones, ring B is attached to the C3 (Fig. 5) position of ring C. They are richly present in the leguminous family of plants (Tsao 2010). Soybeans and soy products are particularly important sources of isoflavones, which have both phytoesterogenic and antioxidant activities that may contribute to their potential cardioprotective and anticarcinogenic effects (Rimbach et al. 2008). Daidzein and genistein are two main isoflavones present in soy along with formononetin, glycetein, and biochanin (Mazur et al. 1998). Hsiesh et al. reported in 2009 that soy isoflavone administration significantly attenuates oxidative damage and improves parameters linked to aging and Alzheimer's disease (Hsieh et al. 2009).

Puerarin (daidzein-8-C-glucoside) is another isoflavone glycoside collected from the root of *Pueraria lobata* and it has a range of pharmacological effects, including anti-allergic and anti-hyperglycemic properties (Hsu et al. 2003). Moreover, puerarin has been reported to successfully inhibit AGE formation, which is a common risk factor in diabetic individuals and in neurodegenerative diseases (Kim et al. 2006). In 2010, Kim et al. demonstrated that puerarin treatment administered to mouse mesangial cells increased heme oxygenase-1 (HO-1) protein levels with

increases in dosage (Kim et al. 2010). This enzyme is also helpful in the conversion of heme to biliverdin, which is quickly metabolized to bilirubin (Alam and Cook 2003). Additionally, puerarin treatment increases the phosphorylation of the protein kinase C δ-subunit, which basically regulates the expression of HO-1, inhibiting AGE-induced inflammation in the mesangial cells of mice.

Conclusion

Overall, the research concluded that the process of glycation and AGEs were found in all types of diseases: diabetes, arthritis, and most neurodegenerative disorders. The accumulation of these AGEs present in the tissue of neurodegenerative diseases shows its involvement in these conditions. However, more research is needed to confirm this involvement. In particular, in the case of AD, only a few reports show the modification and accumulation of AGEs in senile plaque, NFTs, and cerebral amyloid angiopathy in these patients. Studies also revealed that Aβ itself glycosylated in vitro, which ultimately promotes the aggregation of Aβ. These studies raise an important question of whether AGE modification of amyloid plaque is a primary event or whether it is a secondary consequence of Aβ aggregation. However, this issue is controversial and requires more study. AGE modification is an important event that occurs in these neurodegenerative diseases. Thus, it could be involved in the early and late prognosis of AD. AGEs are believed to act as good pathogenic propagators in different diseases, particularly in diabetes and some neurodegenerative diseases. It is of great curiosity to identify antiglycative substances and their mode of action. In this book chapter, we endow examples of the anti-glycation ability of plant-derived products (Fig. 6), which directly targets the stages of glycation through different types of action, such as hypoglycemic action, the inhibition of Amadori product formation, the inhibition of AGE precursors, and the reduction of AGE cross-linking. The phenolic content of plant extract has good anti-glycation activity, although there are non-phenolic compounds, such as carotenoids, terpenes, polyunsaturated fatty acid, and melanoidins, that exhibit the great potential to reduce protein glycation. Flavonoids and isoflavones may also have the potential to inhibit glycation in neurodegenerative disease.

As discussed above, the accumulation of AGEs occurs in different neurodegenerative tissue, such as that in Alzheimer's and Parkinson's diseases, and their inhibition may be helpful in the fast treatment of neurodegenerative diseases. However, there are very few studies on the use of natural products for the cure of AD. These plant-derived compounds are attractive candidates for the evolution of a new generation of therapeutics for the treatment of different age-related consequences such as neurodegenerative disease.

Compliance with Ethics Requirements The authors declare that they have no conflicts of interest.

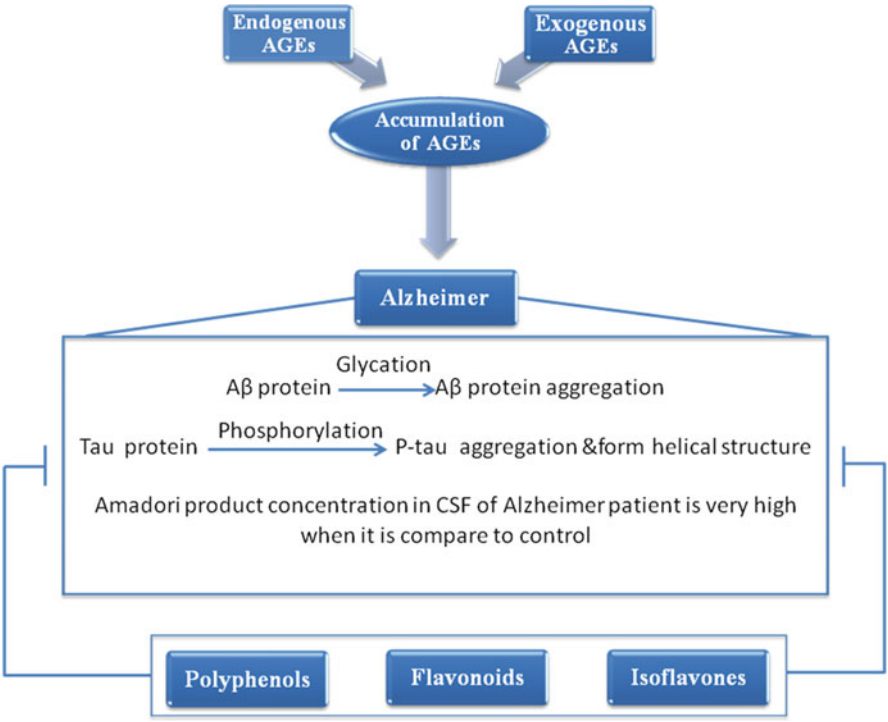

Fig. 6 In Alzheimer Aβ protein aggregates and phosphorylated P-tau protein aggregates and form helical structure. Amadori product concentration in CSF of Alzheimer patient is also high with respective to control. All these process aggravate AD, prevention of all these processes may slow down disease. Polyphenols, Flavonoids and Isoflavones have potential to stop these processes and all these plant derived product may also use for the treatment of Alzheimer disease

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