ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

An Overview On Anti-Ages Therapy: Mini Review

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Abstract
Non-enzymatic glycosylation is glycation between protein and reducing sugar transforming into the formation of advanced glycation end products (AGEs). Many of the epidemiological studies have demonstrated a strong correlation between the formation of AGEs with the pathogenesis of several chronic complications like inflammation, diabetes, nephropathy, retinopathy, neuropathy, atherosclerosis, and cancer. Besides, considering AGEs as lethal components, there are still very fragmentary research on the discovery and development of AGEs inhibitors. One of the causes may be the lack of awareness about the importance of anti-AGEs in the said disorders. The discovery and investigation of compounds with an AGEs inhibitor activity may offer a potential therapeutic approach for the prevention of such several pathogenic complications. The present review summarizes research on anti-AGEs products in chronic complications likeinflammation, atherosclerosis, diabetes, cancer and several other disorders.
Keywords: Glycation, Advanced glycation end products (AGEs), Diabetes mellitus, Natural Products, AGEs Inhibitors

An Introduction to advanced glycation end products

Glycation reaction initiates with spontaneous non-enzymatic reaction of aldehyde / carbonyl group of reducing sugars (glucose/ fructose/ pentose/ galactose/ mannose/ ascorbate/ xylulose) or other carbonyl compounds with free amino groups of proteins (predominantly the ε-amino group of lysine and guanidine group of arginine (Baynes et. al.,(1) and Cheng et. al., (1989; 2003. lipids and nucleic acids. The reaction is named as glycation reaction / Maillard reaction (Mailllard, 1912). The glycation reaction is slow and reversible in its early stages and is significant for slow turnover proteins. Glycation of histones due to persistent hyperglycemia results in histone-histone and histone-DNA cross-linking in chromatin by compromising the electrostatic interactions, that affect the dynamic architecture of chromatin. Histone proteins are highly prone to glycation due to their basic nature and long half-lives, but the exact role of histone glycation in the epigenetics of cancer is still in the veil. Contrary to the genetic causes of cancer, a possible reversal of glycation-mediated epigenetic modifications might open a new realm for therapeutic interventions (Rehman.S.et.al.,(2020).The glycation reaction comprises of two stages, the early and late Maillard reactions. In early stage, aldehyde group of reducing sugar (Kato, et.al., (2011); Kawakishi et. al (1991) and amino group of proteins react to form Schiff base. The later is unstable and rearranges to form more stable keto- amine compounds, known as Amadori compounds. Amadori compounds are the precursors of heterogeneous group of compounds known as advanced glycation endproducts (AGEs). The late stage involves processes such as complex oxidation reactions, dehydrogenation and condensation as well as inter- and intra- molecular cross linking of proteins and the formation of fluorescent proteins which contain AGEs. Amadori products can be chemically reverted to their original forms while AGEs are more permanent and irreversible modifications of proteins. AGEs are often fluorescent, yellowish-brown insoluble adducts which accumulate on long-lived proteins thereby compromising their physiological functions by inactivating them or modifying their biological activities leading to various complications. AGEs modifications result in pathological changes of proteins like enzyme deactivation of superoxide dismutase (Taniguchi, (2005), activation of aldose reductase (Srivastava,1989), increased basement membrane permeability (Cochrane (1995), decreased insulin binding to insulin receptors and increased atherogenicity of low density lipoprotein (LDL) (Lyons, (1992) further leading to several complicated diseases. There are many evidences that Maillard reactionis not only implicated in diabetic complications but also in the development of age- related diseases like atherosclerosis (Bucciarell et al, (2002); Baynes et.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

al., (2002), inflammation, (Basta, 2002), neurodegenerative disorders (Sasaki et. al, (1998), dialysis related amyloidis, Alzheimer's disease, end stage renal disease (ESRD), rheumatoid arthritis, liver cirrhosis (Sebekova et. al.,(2002), and cancer (Stopper et. al.,(2003) (Huttunen et. Al., (2002); Kuniyasu et. al.,(2002).

Hyperglycemia is associated with enhanced glyco-oxidized and oxidized Low- Density Lipoprotein (LDL) possessing greater atherogenicity and decreased the ability to regulate HMG-CoA reductase (HMG-R). Although aminoguanidine (AG) prevents the AGE-induced protein cross-linking due to its anti-glycation potential, it exerts several unusual pharmaco-toxicological effects thus restraining its desirable therapeutic effects. HMG-R inhibitors/ statins exhibit a variety of beneficial impacts in addition to the cholesterol-lowering effects. Current article appraises the pathological AGE-RAGE concerns in diabetes and its associated complications, mainly focusing on thephenomenon of both circulatory AGEs and those accumulating in tissues in diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy, discussing the potential protective role of HMG-R inhibitors against diabetic complications.(Nabi et. al.,(2019).

AGEs can interact with specific cell surface receptors and hence alter cell intracellular signaling, gene expression, the production of reactive oxygen species and the activation of several inflammatory pathways. High levels of AGEs in diet as well as in tissues and the circulation are pathogenic to a wide range of diseases. With respect to mobility, AGEs accumulate in bones, joints and skeletal muscles, playing important roles in the development of osteoporosis, osteoarthritis, and sarcopenia with aging. This report covered the related pathological mechanisms and the potential pharmaceutical and dietary intervention strategies in reducing systemic AGEs. (Chen et. al.,(2018)

Non enzymatic glycosylation (NEG) can generate advanced glycation end products (AGEs) and its intermediates α-dicarbonyl compounds, which contribute to the risk of diabetes. This study investigated the anti-glycation mechanisms and structure-activity relationship of (+)-catechin (CC) and (-)-epicatechin (EC). The results showed that the

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effect of CC on inhibiting AGEs was significantly better than that of EC ($p < 0.05$). By exploring the mechanism, It is found that there was no significant difference in the ability of CC and EC to capture α-dicarbonyl compounds. But CC was found to be more efficient than EC to inhibit RO, OH and CHO radicals generation, which may be the primary reason that CC was more effective than EC on AGEs inhibition. What's more, CC showed better inhibitory effect on β-glucosidase that was close to the molecular docking study. These result provides a theoretical foundation for development of different structure of procyanidins as natural AGEs inhibitors in food and medicine.(Chenet.al., 2019)

Non-enzymatic glycation of proteins plays a significant role in the pathogenesis of secondary diabetic complications via the formation of advanced glycation end products (AGEs) and increased oxidative stress. Methylglyoxal (MG), a highly reactive dicarbonyl of class α-oxoaldehyde that generates during glucose oxidation and lipid peroxidation, contributes to glycation. The experiment results validate structural modifications, increased oxidative stress and AGEs formation. Thus, we can conclude that IgG-AGEs and Fib-AGEs formed during MG induced glycation of IgG and fibrinogen could impede normal physiology and might initiates secondary complications in diabetic patients.

AGEs-induced pathogenesis of diabetic and vascular complications is greatly influenced by the function of HMG-CoA reductase (HMG-R) an enzyme reckoned for endogenous cholesterol production and lipid homeostasis. Based on the above description, targeting hyperglycaemia, cholesterol homeostasis, the formation of AGEs, oxidative stress, and AGEs-RAGE-associated signalling has now been established as promising therapeutic target in the management of DN. Although the implication of aminoguanidine, standard inhibitor of in-vitro AGEs formation (Nabi et al. 2018), has showed various adverse effects in different experimental settings i.e. cell culture, animal models studies and human clinical trials in diabetic kidney disease (Bolton et al. 2004, Nabiet al. 2019b), the development of anti-AGE therapeutic approach remains open for the management of DN. Ezetimibe (EZ) is well reckoned for its pleiotropic pharmacological actions i.e. diminishing the circulatory lipid levels via inhibition of intestinal cholesterol absorption, maintaining redox balance, and inflammatory markers in diabetic and ASCVD patients (Sarigianni et al. 2010, (Giugliano et al. 2018).

EZ markedly improved the altered biochemical markers of diabetes mellitus (DM) (FBG,HbA1c, insulin, microalbumin, and creatinine) and cardiovascular disease (in-vivo lipid/lipoprotein level and hepatic HMG-CoA reductase activity) along with diminished plasma carboxymethyl-lysine (CML) and renal fluorescent AGEs level. Gene expression study revealed that EZ significantly down-regulated the renal AGEs-receptor (RAGE), nuclear factor-jB (NFjB-2), transforming growth factor-b (TGF-b1), and matrix metalloproteinase-2 (MMP-2) mRNA expression, however, the neuropilin-1 (NRP-1) mRNA expression was up-regulated.(Chang R.et.al., (2003).

The unavoidable glycation reaction is the major cause of diabetes and metabolic disorders. The glycation reaction is enhanced in case when the glycating agent is reactive carbonyl species (RCS) like, methylglyoxal (MG). The impact of RCS may result into the diabetes mellitus and its secondary complications along-with its role in cancers too. This reaction can be discontinued by using natural product inhibitors or by chemically synthesized drugs, like aminoguanidine (AG). However, AG is reported to be nephrotoxic (toxic to kidneys) at a concentration of 10 mM or more and has therefore serious health concerns. In the present study, bio conjugation of AG was done with the gold nano particles (Gnps) to mitigate its toxic effect and upsurge the efficacy of AG on RCS induced glycation. The AG-Gnps formed was characterized by UV-Vis. spectroscopy and it reveals a peak at 529 nm corresponding to AG-gold nano particles. The particle size of the AG-Gnp was found to be 12 nm in TEM while in DLS it was found to be 54.07 nm. The fluorescence studies in combination with GK-peptide and δ- Glu assay support the inhibition of AGEs by AG-Gnps. Based on the idea of gold nano- particle synthesis, it is anticipated,the toxicity of numerous drugs used at high doses can be diminished with additional efficiency (Haliwell,et.al., (2007).

Receptor for AGEs

AGEs mediate their effects by a receptor-dependent pathway in which they bind to a specific cell surface associated receptor known as the receptor for AGEs (RAGE). RAGE, a membrane receptor of the immunoglobulin super family, is linked to serine/threonine protein kinases (Schmidt et. al., (2000), Huttunen et. al, (2000) RAGE on binding to ligands i.e AGEs activates the key cell signaling pathways and thus, result in reprogramming of cellular properties. RAGE-mediated signaling pathways are

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

associated with cell survival, proliferation, migration, and invasion, lysis of stroma, angiogenesis, and the generation of oxidative stress (Taguchi et.al,,(2000) Kuni yasu et. al.,(2003) ,Sasahira et.al.,(2007); Kuniyasu et.al.,(2003). RAGE enhances the cellular processes associated with cancer progression (Taguchi et. al,.(2000) Kuniyasu et. al., (2003).Nε-carboxy-ethyl-lysine (CEL) and Nε-carboxy-methyl-lysine (CML), which are the physiological ligands of RAGE, are also the two main AGEs found in blood plasma and tissues. Other examples include Pentosidine, Methylglyoxal, Pyraline, 3- deoxyglucosone (3DG), cross-linked AGEs, GOLD (Glyoxal-derived lysine dimer , 1,3- di(N-lysino-imidazolium salt), MOLD (Methylglyoxal-derived lysine dimer , 1,3-di(N- lysino)-4-(methyl-imidazolium salt) , DOLD (3-deoxyglucosone derived lysine dimer, 1,3-di(N-lysino)-4-(2,3,4-trihydroxybutyl)imidazolium salt),etc. Moreover, AGEs can also act as cross-linkers between proteins, and result in the production of proteinase-resistant aggregates (Byun et. al., (2017).

Pathological outcomes of AGEs accumulation

Study of glycation is very important because the end products of glycation, known as AGEs, are associated with a number of diseases. AGEs having implications in metabolic disorders and increased AGE levels have been associated in many micro vascular diabetic complications (Genuth et al., 2015; Monnier et al., 2013), including retinopathy (Nagarajet et. al., 2012; Genuth et al., 2005), nephropathy (Yamamotoet et. al., 2005; Makita et al., 1991), and neuropathy (Sugimoto et. al., 2008; Araszkiewicz et al., 2011; Vouillarmet et al., 2013). Furthermore, the immune suppressed state observed in patients with diabetes mellitus may be related to an excess of glycated immunoglobulins with disrupted functionality (Raghav et. al., 2017). Increasing evidence points to a role for AGEs in the development of diabetes mellitus associated co- morbidities including non-alcoholic steatohepatitis (Hyogo & Yamagishi, 2008), osteoporosis (Wang et al., 2002), and polycystic ovarian syndrome (Merhi, 2014). Higher values of circulating CML levels and skin AGEs have been observed in patients with peripheral vascular disease and diabetes mellitus as compared to patients without diabetesmellitus (Raposeiras-Roubin et al., 2015; Bos et al.,2011); Arsov et al., 2014; de Vos etal., 2014). AGEs accumulation has been associated with specific cardiac pathologies including congestive heart failure (Hartog et al., 2007), arrhythmias (Raposeiras-Roubinet et. al., 2012), and CAD (Kilhovd et al.,1999) in patients with diabetes mellitus.

Anti-AGE therapies

Protein glycation and formation of AGEs have been reported to play an important role in the pathogenesis of various diseases like diabetes, rheumatoid arthritis, osteoporosis, and ageing (Kuniyasu et. al., (2002). Thus, the intermediates and precursorsof AGEs are the most desired sites for compounds aimed to reduce the detrimental consequences of protein glycation both in vitro and in vivo. Additionally, Aminoguanidine (AG) is an archetype therapeutic agent for the prevention of formation of AGEs. It reacts rapidly with alpha, beta-dicarbonyl compounds such as MG, GO, and 3-DG to prevent the formation of AGEs. The adduct formed are substituted 3-amino-1, 2,4-triazine derivatives (Sasahira et. al., (2007). The notion that accumulation of AGEs is a risk factor for disease succession has been substantiated by inhibition of vascular complications in experimental diabetes by AG. However, the clinical trials on AG were stopped because of safety concerns, as it was found to be nephrotoxic at a concentrationat which it inhibited the formation of AGEs. On the other hand, the Pyridoxamine (PM),a vitamin B6 metabolite, has proven to be a potent inhibitor of the formation of AGEs in in vitro and animal experiments (Taguchi et. al.,(2000). This effect of PM is mostprobably due to blockage of the oxidative degradation of the glucose derived Amadori intermediates or due to quenching of the dicarbonyl compounds.(Kuniyasu et. al.,(2002). It inhibits the progression of renal disease and decreases hyperlipidemia and apparent redox imbalances in type 1 diabetic rats. Similarly, Naloxone, made up of the baine that is obtained from plant Papaver somniferous (Kuniyasau et.al., (2003) inhibits the formation of AGEs and is purported to have therapeutic potentials in patients with diabetes and age-related diseases (Kikuchi et. al. (2003).Similarly, there are various other medicinal plants which might have anti-glycation potential. Another compound Benfotiamine, a pro-drug of thiamine monophosphate, has AGE-lowering properties without decreasing early glycation adducts (Byun et.al.,(2017). Benfotiamine, as well as thiamine, have been reported to reduce diabetic nephropathy and retinopathy in experimental animal models (Genuth et.al.,(2005). Benfotiamine has been shown to rectify multiple pathways of biochemical dysfunction, and its major intrusion in AGEs formation in vivo is by preventing dicarbonyl formation (Nagaraj et.al., (2012). Administration of benfotiamine to type 2 diabetic patients, on a high AGE content diet, reduced circulating

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AGE levels and markers of oxidative stress**.** Genuth et. al. (2005)**.**There is a need to use various inhibitors to decrease the concentration of AGEs, based on their ability of inhibition of AGEs formation during in vitro incubation of proteins with glucose. Both natural as well as synthetic compounds have been evaluated as inhibitors against the AGEs formation (Peng et. al., 2010). In the field of anti-AGE therapy, Amino guanidine is the first compound used as an anti-AGE medicine and is extensively studied both in vitro and in vivo (Genuth et. al.(2005). It is also known to be anucleophile trap for carbonyl intermediary compounds and decreases nephropathy and retinopathy. While Pyridoxamine, a vitamin B6 derived compound, prevents intermediary Amadori protein degradation into AGE proteins. It blocks the oxidation of Amadori intermediates. Experiments on guinea pigs have evidenced that Pyridoxamine prevents AGEs formation by antagonizing the effects of angiotensin II, decreases hyperlipidemia, prevents renal hypertrophy, and decreases retinal vascular lesions and salt retention(Monnier.et.al.(2013).Similarly, Benfotiamine, a lyposoluble thiamine (vitamin B1) derived compound, increases the activity of transketolase, a speed limiting enzyme present on the non-oxidative branch of the pentose phosphate pathway thus, prevents both intracellular AGEs formation as well as Hexoseamine pathway and DAG-PKC pathway activation. Metformin is an antidiabetic drug used to increase insulin sensitivity. It is more effective in inhibiting late glycation and AGEs formation (post Amadori) than early glycation products. Genistein, member of the isoflavonoid family and a tyrosine kinase inhibitor, possess chemoprotectant activities against cancers and cardiovascular diseases. It is reported to be a potent α-glucosidase inhibitor**.** LR compounds (LR 74, LR 90,etc) are known to be potent chelators of Cu^{++} and are more potent than Aminoguanidine.(Hyogo H.,(2008)

AGE-breakers

AGE-breakers are medicines that inhibit the formation of AGEs or break established AGE cross-links between proteins. Pyridinium, 3-[2-(methylsulfonyl) hydrazino] carbonyl]-1-[2-oxo-2-2-thienyl) ethyl]-chloride (TRC4186) has demonstrated AGE-breaking activities in vitro and improvement in the endothelial and myocardial function in animal models of diabetes mellitus with reduction of AGEs accumulation in tissues over time. Alagebrium (ALT-711) breaks the abnormal crosslinks formed by collagen by being a low-affinity inhibitor of thiamine diphosphokinase (TDPK) Raposeiras-Roubin et. al. (2015)**.**

Hyperglycemic condition in diabetes accelerates formation of advanced glycation end products (AGEs) that are formed as a result of series of reaction between reducing sugars and proteins. Accumulation of AGEs has been implicated in development of insulin resistance as well as in the pathogenesis of diabetic complications. The principal mechanism by which AGEs render harmful effects is through interaction with cell bound receptors. Certain receptors like AGE-R1 are involved in degradation of AGEs, while certain other receptors like receptor for AGE (RAGE) bring about counter effects exacerbating the situation. Accumulation of diverse AGEs, synergistically down regulate AGE-R1 while up regulate RAGE causing vicious cycle leading to enhanced formation and further accumulation of AGEs. The formation of heterogeneous AGEs, importance of detection and quantification of AGEs, biological degradation of AGEs via different receptors, AGE-RAGE and its role in proinflammatory signaling has been well discussed, AGE mediated diabetic vascular complications such as nephropathy, retinopathy, neuropathy, cardiovascular and cerebro-vascular diseases and finally the biological inhibition of AGEs is discussed along with chemical inhibitors for AGEs and natural products in AGE inhibition as a measure for the prevention of diabetic complications.(Bhat.et.al., (2017)

Role of natural products in the inhibition of AGEs

Previously, it is explored that different inhibitors such as nanoparticles, drugs, andnatural products have been participated actively to impair the wound healing by glycationprocess. The structurally modified human serum albumin (HSA) with AGEs has been reactivated with the treatment of gold nano particle while the zinc oxide nano particlewas proposed as an antiglycation agent for neurodegenerative diseases (Seneviratne et al.,2012). Nowadays, researchers are taking tremendous interest to unrevealed the role of natural compounds as an inhibitor of AGEs, as they might offer therapeutic potential in delaying or preventing the onset of diabetic complications. In addition, previously published data suggested that the daily intake of natural AGEs inhibitors might play a preventive role in the progression and development of lifestyle-related diseases including diabetes mellitus, and its secondary complications (Sadowska-Bartosz

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et al., 2015). The plant extracts and their purified compounds endow with unrestrained opportunities for new drug discoveries because of the consummate availability of chemical diversity (Cos et.al., 2006). According to the World Health Organization (WHO), about 80% of the worldwide population relies on traditional medicine for their common healthcare requirements (WHO, 2004). The utility of herbal medicines in Asia represents a comprehensive history of human relations with the environment. The plants used as traditional medicine may have various important secondary metabolites that can be used to treat as well as communicable diseases (Duraipandiyan et al., 2006). Plants produces a variety of natural compounds that may possess anti-microbial, anti-diabetic, anti- allergic, anti-pyretic or anti-cancer activities. The natural compounds bearing hetero atoms may have capability to generate single electron species and thereby initiates chain of reaction, leading to lipid peroxidation, and DNA damage etc (Deavall et al., 2014). Anti-oxidant compounds have high oxidative potential than the drug designed as chain inhibitor of free radical induced breakdown. The compounds with antioxidant property usually break the chains formed during the propagation process by providing a hydrogen atom or single electron to the free radical and receive excess energy. It has been suggested that the fruits, vegetables, and herbal plants contain a large variety of phytochemicals which acts as a main source of antioxidant and having a property against the formation of ROS. Various compounds such as peptides, glycopeptides, alkaloids, triterpenoids, amino acids, lipids, polysaccharides, steroids, flavonoids, phenolics, xanthone, and inorganic salts are designated as antidiabetic phytocompounds. The role of herbal products is not only restricted to dietary uses, but it has also a divergent role in the medication of several diseases. Herbal medicine, sometimes known as phytomedicine or botanical medicine, utilizes different parts of the plants, such as its flowers, fruits, seeds, leaves, berries, bark, and roots (Zuckerman et al., 2002). Various categories of anti- diabetic drugs are present in the market, which includes insulin analogues, sulphonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, thiazolidiones, α- glucosidase inhibitors, etc, (Li et al., 2017). The alternative treatment as herbal medicines draws the attention of many researchers. Several herbs are known to reduce blood glucose level, therefore the possibility of having better glycaemic control or being less dependent on insulin injections by taking herbal medicines is incontestably appealing. However, the selection of herbs might depend on some factors that are based on the stage of progression of diabetes, types of co-morbidities, availability, affordability, and safety profile of the herbs. Preclinical studies have crossed the doorstep of the bench to bedside of the patients. Several clinical studies in diabetic patients have been conducted in recent years, which showed that medicinal plants, such as Scoparia dulcis (Senadheera et al; 2015), Cinnamomum cassia (Anderson et al; 2016), Ficus racemosa bark (Karim et al., 2013), and Portulaca oleracea L. seeds have anti-diabetic activity. The utilization of α- glucosidase inhibitor for diabetes, suppresses carbohydrate digestion and thereby decelerating the process of glucose assimilation further resulting in a significant reduction of postprandial plasma glucose and insulin level with a significant reduction of HbA1c. There is extensive use of α-glucosidase inhibitor in the management of T2DM, for example, acarbose, voglibose, miglitol, etc (Laar et al., 2005). Several investigations are ongoing in the search of potential natural compounds for the effective treatment of diabetes. Moreover, several herbs, such as cinnamon, China aster, mistletoe fig, and bitter oleander are reported to exhibit inhibitory action on α-glucosidase. Besides, the inhibitionof α-amylase has also been associated with anti-hyperglycaemic actions of medicinal herbs like Camellia sinensis, Aloe vera, basil, etc (Etxeberria et al., 2012). In addition, the polyphenol rich herbs showed the inhibitory effect on α-glucosidase and α-amylase, and these herbs include jute and soybean. These herbs have an additional benefit in managing diabetes and hypertension due to inhibitory activities on angiotensin convertingenzyme (Oboh et al., 2012). Other herbs that showed potential in treating diabetes includeolive leaves, which reduce the digestion and absorption of starch, and the black seed, which inhibits the sodium-dependent glucose transport (Figure 1).

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

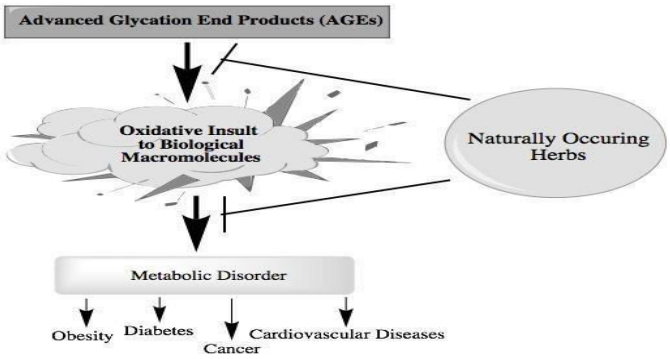

Figure 1: Antiglycation end products (AGEs) and metabolic disorders induced oxidative stress in major pathological conditions and strategies for their prevention and therapy

Naturally occurring phenolic compound against AGEs

Several reports disclosed that few polyphenol compounds possess antioxidant and physiological activities. It is well known that the spontaneous post-translational modification of proteins or amino acids have been carried out in the presence of reducing sugar as well as di-carbonyl compounds including GO, MG, and 3DG. It has also been discussed by initial studies that polyphenol compounds showed anti-glycation activity by suppressing the formation of MG, which is an absolute precursor for AGEs. Several polyphenol natural products have antioxidant properties and are known as influential candidate against the formation of AGEs (Yeh et al., 2017). Since the oxidative stress formation is the intermediate stage of glycation therefore, it has suggested that the polyphenols have antioxidant property, and can also inhibit AGEs formation (Sasaki et al., 2014).

Naturally occurring vitamins against AGEs

The vitamins and other nutrients, including minerals are known as potential inhibitor against AGEs and its different adducts. Recently, Abdullah et al. performed an in vitro study, which disclosed that the vitamin B3 inhibits the modification of HSA by MG (Abdullah et al., 2017). Another in vitro study by Vinson et al. suggested that the vitamin C and E inhibits the protein glycation and other AGEs biomarkers (Vinson et al., 1996). Apart from that, other nutrients and minerals present in vegetables and fruits are reported as natural AGE inhibitors in T2DM and its secondary complications (Asif., 2011).

Naturally occurring flavonoid compounds against AGEs

Flavonoids are considered as potential candidates in drug discovery due to their valuable antioxidant activity. Since the process of oxidation reaction is directly involved in the formation of AGEs, therefore the flavonoid compounds were evaluated against AGEs (Wu et. al., 2005). Nymphaea species containing high amount of flavonoids or bioactive compounds is the most fascinating species used as traditional medicine for a long time (Neha et al., 2013). This review is focused on the property of Nymphaea species and its ability to inhibit the progression of glycation reaction. Advanced glycation end products (AGEs) are implicated in the pathology of Alzheimer's disease (AD), as they induce neuro degeneration following interaction with the receptor for AGE (RAGE). This study aimed to establish a mechanistic link between AGE-RAGE signaling and AD pathology. AGE-induced changes in the neuro2a proteome were monitored by SWATH- MS. Western blotting and cell-based reporter assays were used to investigate AGE- RAGE regulated APP processing and tau phosphorylation in primary cortical neurons. Selected protein expression was validated in brain samples affected by AD. The AGE- RAGE axis altered proteome included increased expression of cathepsin B and asparagine endopeptidase (AEP), which mediated an increase in Aβ1–42 formation and tau phosphorylation, respectively. Elevated cathepsin B, AEP, RAGE, and pTau levels were found in human AD brain, coincident with enhanced AGEs. This

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

study demonstrates that the AGE-RAGE axis regulates Aβ1–42 formation and tau phosphorylation via increased cathepsin B and AEP, providing a new molecular link between AGEs and AD pathology.[5,6]The formation and accumulation of advanced glycation endproducts (AGEs) have been implicated in the pathogenesis of many chronic diseases, such as aging, Alzheimer's disease, diabetes and diabetic complications. The present study was aimed to investigate the inhibitory effects of the extracts from nine microalgae on the formation of AGEs by using in vitro models and identify key antiglycation constituents of the microalgae This is the first report on the antiglycation activity of fucoxanthin. The findings of the present study have not only identified a promising inhibitor of AGE formation, but have also identified a valuable natural source of this phytochemical which possesses great potential to be developed as functional food ingredients and pharmaceutical products to help reduce health risks associated withAGEs.(Sun et.al.,(2018). The p Ka values for the different peptides are predicted with great accuracy as well as the ability of the studied molecule in acting as an efficient inhibitor of the formation of AGEs which constitutes a useful knowledge for the development of drugs for fighting Diabetes, Alzheimer and Parkinson diseases. Finally, the bioactivity scores for the Mirabamides A–H are predicted through different methodologies.(Frau.et.al (2018). The non-enzymatic glycosylation is a very common phenomenon in the physiological conditions which is mediated by distinct chemical entities containing reactive carbonyl species (RCS) and participates in the modification ofvarious macromolecules particularly proteins. To date, various carbonyl species, i.e., glucose, fructose, D-ribose and methylglyoxal have been used frequently to assess the in- vitro non-enzymatic glycosylation. It is evident a significant modification in 2'- Deoxyribose-glycated BSA which was confirmed through increased hyper chromicity, keto amine moieties, carbonyl and hydroxymethyl furfural content, fluorescent AGEs, altered secondary structure conformers (α helix and β sheets), band shift in the amide-I region and diminished free lysine and free arginine content. The results of the performed study can be implied to uncover the phenomenon of serum protein damage caused by 2'- Deoxyribose leading towards diabetic complications and the number of AGE-related diseases.(Rafi et.al., (2020).The influence of advanced glycation end products (AGEs) in the biological processes contribute to the life-changing complications such as progressionof cancer, diabetes and other chronic disorders. The receptor of AGEs while interacting with its ligands causes a never-ending irregularity in the cell-signaling communication. Hence, AGEs are considered as an important link between progression and contribution to cancer. This study focuses on the presence and/or absence of oxidative and glycative stress in the serum samples of various cancer patients.our result successfully assisted the presence of AGEs in all the cancer patient's sera though it is not clear which specific cancer is more potent to AGEs (Khan et. al.,(2020). To inhibit the AGEs development is supposed to show part in the inhibition of diabetic problems. Study of dietary bioactive combinations with antiglycation properties delivers future views for inhibition or mediation associated to AGEs complications. Many studies show the possibility of dietary constituents to stop AGE development. Therefore, search for natural compounds able to prevent glycation and have the potential therapeutic ability to inhibit diabetes and age associated diseases (Khan.et.al.,(2020). AGEs are clearly implicated in the pathogenesis of diabetes complications, their potential involvement during malignanttumor development, progression and resistance to therapy is an emerging concept. Meta- analysis studies established that patients with diabetes are at higher risk of developing cancer and show a higher mortality rate than cancer patients free of diabetes. In this review, we highlight the potential connection between hyperglycemia-associated AGEs formation on the one hand and the recent evidence of pro-tumoral effects of MGO stress on the other hand. The marked interest in anti-glycation compounds in view of their strategic use to treat diabetic complications but also to protect against augmented cancer risk in patients with diabetes (Bellier et.al.,(2019). Advanced glycation end products (AGEs) are generated by non enzymatic modifications of macromolecules (proteins, lipids, and nucleic acids) by saccharides (glucose, fructose, and pentose) via Maillard reaction. The formed AGE molecules can be catabolized and cleared by glyoxalase I and II in renal proximal tubular cells. AGE-related diseases include physiological aging, neurodegenerative/neuroinflammatory diseases, diabetes mellitus (DM) and its complications, autoimmune/rheumatic inflammatory diseases, bone-degenerative diseases, and chronic renal diseases. AGEs, by binding to receptors for AGE (RAGEs), alter innate and adaptive immune responses to induce inflammation and immunosuppression via the generation of proinflammatory cytokines, reactive oxygen species (ROS), and reactive nitrogen intermediates (RNI). These pathological molecules cause vascular endothelial/smooth muscular/connective tissue-cell and renal

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mesangial/endothelial/podocytic-cell damage in AGE-related diseases. In the present review, we first focus on the cellular and molecular bases of AGE–RAGE axis signaling pathways in AGE-related diseases. Then, we discuss in detail the modes of action of newly discovered novel biomolecules and phytochemical compounds, such as Maillard reaction and AGE–RAGE signaling inhibitors. These molecules are expected to become the new therapeutic strategies for patients with AGE-related diseases in addition to the traditional hypoglycemic and anti-hypertensive agents. We particularly emphasize the importance of "metabolic memory", the "French paradox", and the pharmacokinetics and therapeutic dosing of the effective natural compounds associated with pharmacogenetics in the treatment of AGE-related diseases.(Shen et.al.,(2020). Glycation, the non- enzymatic reaction of sugars with proteins or nucleic acids to form early glycation (Amadori or fructosamine) products, is a key molecular basis of diabetic complications. Inhibiting the process of non-enzymatic protein glycation is one of the key strategies to prevent glycation-mediated diabetic complications. The present study focuses on the anti-glycation activity of 18 drugs, commonly used for the treatment of gastrointestinal, central nervous system, inflammatory diseases, bacterial infections, and gout. This study identifies nimesulide and phloroglucinol dihydrate as new inhibitors of in-vitro protein glycation for further investigations as potential anti-diabetic agents (Rasheed.,et.al. (2018). Seed extract of fenugreek had both anti-glycation and glycation reversing activities in BSA-glucose glycation model. Glycation reversing activity of fenugreek seedextract is a novel finding having therapeutic potentials. Thus, findings of this study indicate usefulness of fenugreek seed in managing AGEs associated pathologies in diabetes (Abeysekera et. al.(2018). Mushroom irradiation has been considered a sustainable process to generate high amounts of vitamin D2 due to the role of this vitamin for human health and of the global concerns regarding its deficient or inadequate intake. These results open up a new area of investigation aimed at selecting mushroom species with high nutraceutical benefits for irradiation in order to maintain their potential properties to inhibit oxidative and glycation processes responsible for human diseases.(Gallotti et.al (2020). Cocos nucifera Linn., an important source of phenolic compounds and a native plant of tropical countries, widely distributed in the Northeast and North of Brazil. Antiglycation activity represented by (BSA) – glucose/fructose, Collagen – glucose/fructose and BSA-Methylglyoxal (MG) assays, using aminoguanidine (AG) as a positive control, and cytotoxic effects toward macrophages. The identification of non-toxic antiglycation agents holds great promise in the development of alternative therapies for diseases, such as diabetes and their complications and is not often, reported in the literature.(Oliveria.et.al(2021).Bauhinia forficata Link., a cerrado native plant, is used as a complementary treatment for Type 2 DM (T2DM). Several studies involving this plant have shown that it has prominent potential to combat hyperglycemia and oxidative stress. The objective was suggestive the phytochemical constitution of fractions of ethanol extract of B. forficata leaves using HPLC-ESI-MS/MS, and evaluates their activities in enzymatic assays to evaluate their inhibitory potential against α-amylase, α- glucosidase and lipase, as well as their antioxidant and anti-glycation capacities. In addition, it has also been evaluated the cytotoxic effects of these fractions using rodents macrophages and erythrocytes. The ETOAC e ButOH fractions showed high polyphenols concentrations, having been determined 11 flavonoids, including the kaempferitrin, the phytomarker of B. forficata Link. In addition, all fractions presented higher antioxidant and antiglycation activities and prominent capacities to digestive enzymes inhibition. On the other hand, in the cellular assays, none fractions showed cytotoxic and hemolytic effects, able to combat the ROS production in macrophages. Thus, this study presented new results on the biological activities of this plant, contributing to the understanding of the action and effectiveness of its use in the management of diabetes mellitus and its complications.(Franco et.al.,(2020). One of current studies show that the natural flavonoid compounds (Q) quercetin and CH(chrysin) have direct vasculo protective effects on isolated thoracic aorta from MetS rats. This is demonstrated by the compounds' ability to ameliorate the exaggerated vasoconstriction and attenuated vasodilation typical of MetS vascular dysfunction. This effect can be attributed to the compounds' ability to reduce AGE production as well as the concomitant protein oxidation products. In addition, there is significant dependence on NO-mediated mechanisms and, in the case of Q, antioxidant activity, which contribute to the vascular protection.(Ahmad.et.al., (2020).This study explain the antiglycation inhibitory ability of chemical constituents can be used for above latediabetic complications (Khan.et.al.,(2021).

Glycation has been involved in Schiff base reaction lead to hyperglycemia at cellular level. The current study aimed to identify the bioactive compounds from selected folkloric plants for their

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antiglycation and antioxidant potential. Methanol extracts demonstrated the highest activities, therefore, it was further fractionated using n-hexane, dichloromethane, ethyl acetate, and methanol solvents to isolate the non polar compoundsfrom the Hordeum vulgare. The findings of many studies established the role of Biochanin A and Vit E from H. vulgare as potent antiglycation agents (Asif et.al., (2020).

Plant-based polyphenolics have been reported to bestow health benefits when consumed, which are partially ascribed to their antioxidant activity. Yet, many current in vitro chemical assays to characterize antioxidant potential do not truly reflect the physiologicalproperties of food antioxidants in vivo. Many of the studies employed biological approaches, including a cellular antioxidant activity (CAA) and protein glycation assays, to offer an improved picture of antioxidant potential of phenolic extracts from Georgia peach cultivars. The phenolic extracts from two peach varieties, showing contrasting antioxidant capacities according to hydrophilic-oxygen radical absorbance capacity (H- $ORAC_{FL}$) and ferric reducing antioxidant power (FRAP) assays, exhibited significant differences in two biological tests when the assays were performed on a fresh weight basis. The procyanidins fraction displayed notable antioxidant capacity, when compared to other phenolic classes in the peach extract, in these two biologically relevant assays.(Liao.et.al.(2020). Plants studied in this review inhibit glycation in several possible mechanisms. Some of these plants inhibit the production of shiff base and amadori products. The others inhibit the generation of amadori products in the advanced phase. Some others blocked the aggregation of AGEs and some plants have antioxidant activity and reduce AGEs formation by preventing oxidation of amadori product and metal-catalyzed glucoxidation (Dil.et.al.,(2019).The non-enzymatic interaction of sugar and protein resulting in the formation of advanced glycation end products responsible for cell signaling alterations ultimately leads to the human chronic disorders such as diabetes mellitus, cardiovascular diseases, cancer, etc. Studies suggest that AGEs upon interaction with receptors for advanced glycation end products (RAGE) result in the production of pro-inflammatory molecules and free radicals that exert altered gene expression effect. To date, many studies unveiled the potent role of synthetic and natural agents in inhibiting the glycation reaction at a lesser or greater extent. This review focuses on the hazards of glycation reaction and its inhibition by natural antioxidants, including polyphenols (Khanam et.al.,(2020).

Summary & Conclusion

The preclinical and clinical studies demonstrated strong involvement of AGEs inseveral diseases. As such, inhibition of AGE formation, antagonizing/suppression of expression of RAGE is the viable targets in the treatment of such diseases. Glycation of proteins leads to formation and accumulation of toxic AGEs which can permanently alter the structure and function of body proteins (Kikuchi S.et.al(2003). AGE inhibitors and AGE breakers can decrease the glycation process by binding with sugars/proteins.(K. (Byun. et.al.,(2017).

Along with the synthetic inhibitors, many inhibitors from natural sources like plant extracts are being one such compound is Curcumin [1,7-bis(4-hydroxy-3- methoxyphenyl)-1,6-heptadiene-3,5-dione], known for its anticancer, antiviral, antioxidant, anti-infectious and anti-inflammatory properties.(Yamamoto Y, et al. (2005).It reduces serum AGE levels. Decreases lipid peroxidation and regulates anti-oxidant enzymes. Resveratrol (3,4,5-trihydroxystilbene), a natural phytesterogen found ingrapes, is known to inhibit AGEs-induced proliferation and collagen synthesis activity in vascular smooth muscle (Wang X, et al. (2002).Various plant derived products have beenshown to possess hypoglycemic, hypolipidemic as well as antioxidant propertie. (Kilhovdet.al)(2007).Some important compounds such as phenolics, oligo, and polysaccharides(Taguchiet.al.,2000),carotenoids,unsaturatedfattyacids.(Kuniyasu,et.al.,20 03) and many others have been reported to possess anti-glycating activity. Thus, the dailyconsumption of dietary components, mainly from plant sources which have an antioxidant effect, is considered to be of potential benefit for prevention of diabetes and other complications.(Bhawal.et.al., 2005).

In the light of human diseases, AGEs are believed to be major pathogenic propagators in many diseases, especially in diabetes and its complications. Therefore, it is of great interest to identify anti-glycative substances and to examine their mode of action.This mini-review describes various approaches that have been undertaken to solve the problems associated with AGEs by searching for molecules that inhibit their formation. These findings led us to ascertain the antiglycation effects of several compounds. We believed that AGEs inhibition by AGE inhibitors and AGE breakers may form the basis for future

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intervention strategies in individuals. At present, it is the need of time to isolate and develop new compounds from different sources (natural or synthetic) to control several chronic diseases.

Acknowledgements

The authors acknowledge the financial supported from Indian Council of Medical Research (ICMR), New Delhi [Project No.45/1/2019/MP/BMS] and Integral University, Lucknow-226026 for bench facility to one of us (NI). The papers communication no. (IU/R&D/2021/-MCN0001087)

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