Nature and Science

Websites:
http://www.sciencepub.net/nature
http://www.sciencepub.net

Emails:
naturesciencej@gmail.com
editor@sciencepub.net

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Examining the Role of Alpha-Lipoic Acid and Epigallocatechin-C-Gallate in Inhibiting Sugar-Induced Myoglobin Glycation: Scientific Gaps in Current Knowledge?

Mousa Numan Ahmad[1*], Amani Ibrahim Farah[1], Tareq Musbah Al-qirim[2]

[1] Department of Nutrition and Food Technology, Human Nutrition and Dietetics, The University of Jordan, Amman11942, Jordan; [2] Faculty of Pharmacy, Al-Zaytoonah University of Jordan, Amman 11733, Jordan
[*]Correspondence to: mosnuman@ju.edu.jo; mousanuman@gmail.com

Abstract: Alpha-lipoic acid (ALA) and epigallocatechin-c-gallate (EGCG) have been known to protect protein oxidation and lessen the pathogenesis of oxidative-related multiple metabolic diseases; however, understanding their role in mediating biochemical activities under glycemic pressures remains unclear. This article discusses the current literature addressing the role of ALA and EGCG in inhibiting myoglobin glycation and the formation of advanced glycation end-products (AGEs), highlights the gaps in current knowledge, and suggests future avenues of research. Glycation is a non-enzymatic reaction of free reducing sugars with free amino groups of proteins, nucleic acids, and compound lipids that eventually forms AGEs. The latter modify the structure of proteins causing altered physiological functions that may lead to a variety of pathophysiological complications mostly associated with diabetes mellitus and cardiovascular disease. This cascade of oxidative abnormalities can be lessened by antioxidants, particularly ALA and EGCG. Insight view through the studies on nutraceutical, pharmaceutical, and natural products that contain these antioxidants reveal a marked gap in knowledge that may hinder understanding of the ALA and EGCG-mediated therapeutic effects on myoglobin glycation. The sugar media and level, the EGCG concentration that sets the balance of EGCG's pro- and antioxidant activities under glycemic pressure, the reactions' sequence and duration between the glycated protein and EGCG, and the hypothesis in which ALA augments the EGCG anti-glycation effect are the five scientific gaps in current knowledge that merit further investigations. [Ahmad MN, Farah AI, Al-qirim TM. **Examining the role of alpha-lipoic acid and epigallocatechin-c-gallate in inhibiting sugar-induced myoglobin glycation: Scientific gaps in current knowledge?** *Nat Sci* 2020;18(6):17-25]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 4. doi:10.7537/marsnsj180620.04.

Keywords: Advanced glycation end-products; alpha-lipoic acid; antioxidants; epigallocatechin-c-gallate; diabetes complications; prooxidants; protein glycation.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by chronic dysglycemia resulting from defects in insulin secretion, insulin action, or both (Punthakee et al., 2018). Chronic dysglycemia is often associated with long-term micro- and macro-vascular complications, particularly retinopathy, neuropathy, cardiomyopathy, and atherosclerosis (Punthakee et al., 2018). Despite increasing knowledge of lifestyle-related risk factors, the prevalence of diabetes mellitus continues to rise globally (Chatterjee et al., 2017). The number of people with diabetes in the world has quadrupled in the past three decades; henceforth, the disease becomes the ninth major cause of death (IDF, 2017). In Jordan, the prevalence of diabetes mellitus has been increasing (WHO, 2016), a matter which necessitates appropriate preventive strategies to promote a 'diabetes-protective lifestyle' (Kolb and Martin, 2017).

The aspect of quantitative and qualitative dietary intake and pattern is an important lifestyle risk factor for the pathogenesis and progression of diabetes (Kolb and Martin, 2017). Dietary advanced glycation end products (AGEs) and in vivo–generated AGEs garnered marked attention in diabetes mellitus research (Christopher, 2017). It has been suggested that intakes of foods high in sugar and/or foods exposed to high-temperature cooking methods such as deep-frying, broiling, roasting, baking, and grilling can increase the total daily AGE intake, which remarkably contributes to the progression of diabetes and cardiovascular diseases (Baye et al., 2017). However, the exact mechanisms are not clearly understood (Ghelani et al., 2017 and 2018).

Glycation is a spontaneous non-enzymatic reaction of free reducing sugars with free amino groups of proteins, DNA, and lipids that forms Amadori products (Kim et al., 2017). The later undergo a variety of irreversible dehydration and rearrangement reactions that lead to the formation of AGEs (Chaudhuri et al., 2018). The reaction is highly accelerated in the presence of hyperglycemia and tissue oxidative stress (Kim et al., 2017). Henceforth, the AGEs' excessive formations and their accumulations in

different tissues cause long-term development of diabetic micro- and macro-vascular complications (Chaudhuri et al., 2018).

Myoglobin, a cytoplasmic hemoprotein, is one of the vital body proteins that are subject to modifications by reducing sugars, particularly glucose and fructose via Maillard reactions (Richards, 2013). It is expressed in the striated muscles and plays an important role in maintaining tissue oxygen homeostasis (Wittenberg, 2009). Besides, myoglobin acts as an intracellular scavenger of nitric oxide, regulating its level in the cardiac and skeletal muscle and thereby maintains mitochondrial respiration ((Hendgen-Cotta et al., 2014). Thus, it is a key element influencing redox pathways in cardiac muscle, aiding the functional and metabolic protection of the heart from oxidative damage (Richards, 2013).

Glycation alters the tertiary structure of myoglobin resulting in altered physiological function that may lead to a variety of pathophysiological complications associated with diabetes ((Banerjee et al., 2016; Chaudhuri et al., 2018). Myoglobin glycation also compromises its function in cardiomyocytes (Hendgen-Cotta et al., 2014). In hyperglycemia, such glycation may cause a serious threat concerning the formation of Amadori products, increasing protein carbonyls, and ultimately AGEs formation, which may further aggravate ischemia and myocardial infarction (Banerjee et al., 2016). Therefore, myoglobin is a physiologically important target for glycation research, and the inhibition of myoglobin glycation-mediated tissue damage might offer therapeutic potential for preventing or delaying the progression of diabetic complications.

Although many synthetic compounds have been proposed to inhibit and scavenge AGEs, protein glycation was not effectively suppressed by any of them in the clinical application (Abbas et al., 2016). Amino guanidine has shown a potent inhibiting power of protein glycation process and fluorescent AGEs' formation in animals and humans (Nagai et al., 2012). Nevertheless, severe adverse effects limit its clinical use (Freedman et al., 1999; Park et al., 2019). Consequently, there is an instant need to evaluate new compounds that suppress protein glycation and thus preventing diseases mediated by AGEs. Therefore, numerous natural crude plant extracts and isolated phytoconstituents evaluated for their antiglycation properties (Abbas et al., 2016). A recent literature review demonstrates that catechin isolated from green tea, as well as alpha-lipoic acid nutraceuticals, possess significant anti-glycation properties (Abbas et al., 2016).

Alpha-Lipoic Acid (ALA) is a naturally occurring dithiol that is found in animal food such as meat and liver (El Barky et al., 2017). ALA is a biologically active form that is produced endogenously by the body, and it is known as a vital cofactor for some enzymatic complexes involved in energy generation for the cell (Salehi et al., 2019). At the cellular level, ALA is reduced to dihydrolipoic acid, which plays important cellular roles, including free radical scavenging and modulating inflammatory pathways (Moura et al., 2015). The ALA effect on the formation of AGEs and protein glycation has been examined both *in vitro* and *in vivo* (Ghelani et al., 2017, Agathos et al., 2018). However, ALA has not been evaluated in myoglobin glycation induced by fructose.

Epigallocatechin-C-Gallate (EGCG) is a polyphenol found in plant-based foods and beverages such as green tea and cocoa (Chowdhury et al., 2016). EGCG has numerous health-promoting effects as being antiatherogenic, anti-inflammatory, and antioxidant (Mereles and Hunstein 2011). Green tea EGCG might ameliorate diabetes complications in which it reduces body fat, maintains cardiovascular health, and improves glucose metabolism (Chowdhury et al., 2016). Despite EGCG strongly protects biomolecules from damage, it has also prooxidant activities (Elbling et al., 2005). This article is intended to examine and analyze the current scientific literature dealing with the role of ALA and EGCG in inhibiting myoglobin glycation and the formation of AGEs, and to discuss the scientific gaps in current knowledge and suggests future research.

2. Literature Search

An up-to-date literature search was conducted on the role of ALA and EGCG in inhibiting sugar-induced myoglobin glycation and the formation of AGEs. The search was limited to the most available English publications. Relevant articles were principally identified through an online search of PubMed, Science Direct, and PsycINFO. Google Scholar and other databases were also used. The search process was performed using the following keywords or their combinations: cardiovascular complications, diabetes complications, myoglobin, antioxidants, prooxidants, protein glycation, EGCG, AGEs, and ALA. Included articles were mainly in vivo and in vitro original experimental, clinical, intervention, and cross-sectional researches in humans. Some researches in animals and review articles were also consulted. For further search accuracy, the reference lists of works were checked for additional publications from the major databases.

3. Myoglobin Glycation in Diabetes

It is well appreciated that diabetes is a major public health problem that is approaching epidemic levels globally (Zimmet, 2017). The role of lifestyle-related risk factors is very important in the pathogenesis and progression of diabetes (Kolb and

Martin, 2017). As the incidence of diabetes is associated with the dietary patterns, dietary AGEs, and *in vivo*–generated AGEs garnered most of the attention in diabetes research (Christopher, 2017). In a double-blind randomized crossover trial, subjects consumed less N-(carboxymethyl) lysine, N-(carboxyethyl) lysine and methylglyoxal-derived hydroimadazolidine during the low-AGE dietary period than the high-AGE period, confirmed by changes in urinary AGE excretion may reduce the risk of type 2 diabetes by improving insulin sensitivity (Courten et al., 2016). Besides, the glycation reaction is highly accelerated in the presence of hyperglycemia and tissue oxidative stress (Kim et al., 2017). In a sub-cohort study, Koska and colleagues (2018) reported that increased levels of several advanced glycation end products and oxidation products were associated with longer diabetes duration, and those with incident coronary vascular disease events have higher levels of 3-deoxyglucosone hydroimidazolone; a specific AGE.

Blood glucose is known to cause slow chemical modifications of vital proteins, known as protein glycation (Roy et al., 2004 and 2010). Banerjee et al. (2016) demonstrated that *in vitro* incubation of heme protein myoglobin with methylglyoxal, a reactive α-oxoaldehyde that increases in diabetic condition for 7 days, induces heme loss, changes in the tryptophan fluorescence, and decreases of the α-helicity with increased β-sheet content, while increasing the period of incubation up to 18 days, additional AGEs have been detected, and aggregation of myoglobin was evident. Furthermore, Bhattacherjee and Chakraborti (2011) reported that there are gradual changes in the structure of myoglobin after 6 days of glycation by fructose using an *in vitro* model study, concerning increased absorbance at 280 nm, enhanced the fluorescence emission, and alteration in tertiary structure. However, long-term glycation for 30 days causes AGE formation that might change the redox state of heme iron forming oxymyoglobin. Thus, myoglobin is a physiologically important target for glycation research.

Henceforth, inhibition of myoglobin glycation mediated tissue damage might offer therapeutic potential for preventing or delaying the progression of diabetic complications (Roy et al., 2004 and 2010). In streptozotocin-induced diabetic rats, aminoguanidine treatment significantly reduced cardiac fibrosis, α-smooth muscle actin, and reduces oxidative-associated cardiac fibrosis likely through AGE/ AGE receptor signaling (Magdaleno et al., 2019). Nevertheless, severe adverse effects limit its clinical use; in a double-blinded placebo randomized control trial conducted to elucidate the therapeutic potential of aminoguanidine in human diabetic nephropathy, the trial was prematurely halted due to a lake of safety issues arising from pernicious- like anemia and development of anti-nuclear antibodies adverse effects (Freedman et al., 1999). Apart from aminoguanidine, other molecules have been investigated; OPB-9195 a novel thiazolidine derivative that has been reported to prevent the progression of diabetic nephropathy by blocking the type IV collagen production and suppressing the overproduction of the growth factors in diabetic rats (Tsuchida et al., 1999). However, it has not been tested in humans, nor is there any evidence for planned clinical trials (Goh and Cooper, 2008). Consequently, there is an instant need to evaluate new compounds that suppress protein glycation and thus preventing diseases mediated by AGEs.

4. Alpha-Lipoic Acid & Protein Glycation

The effect of ALA on the formation of AGEs and protein glycation has been examined both in vitro and in vivo (Ghelani et al., 2017, Agathos et al., 2018). It has been shown that ALA has markedly inhibited the formation of fructosamine, protein carbonyls, and fluorescent AGEs using synthetic glycation in vitro model containing bovine serum albumin and glucose (Suzuki et al., 1992). In obese Zucker rats, 22 weeks of treatment of ALA markedly inhibited protein carbonyls content and enhanced insulin sensitivity in skeletal muscle (Muellenbach et al., 2009). ALA was effective at dampening the cytotoxicity of AGE bovine serum albumin against SH SY5Y cells as a target model; also, rate of lactate dehydrogenase leakage was significantly decreased, and the axonal length was significantly increased in cells treated with ALA (Niu et al., 2018).

It has been also documented by Leu et al. (2013) that ALA down regulated the receptor for AGEs expression in the human embryonic kidney cells. Moreover, in streptozotocin-induced diabetic mice, topical treatment of ALA nanoparticles markedly promoted cutaneous wound healing through down-regulated expression of the receptor for AGEs (Chen et al., 2012). Besides, Kowluru (2005) showed that AGEs-induced activation of NF-kB in retinal endothelial cells was markedly suppressed by ALA. Furthermore, Yin and colleagues (2012) demonstrated that ALA reduced the AGEs mediated formation of lipid peroxidation products in human neuroblastoma cells and rat cortical neurons. In an investigation, Ghelani et al. (2018) demonstrated that the ALA significantly inhibited glucose-induced myoglobin glycation and AGEs formation in an in vitro model. However, ALA has not been evaluated in myoglobin glycation induced by fructose.

5. Epigallocatechin-C-Gallate & Protein Glycation

As suggested by several studies that long term consumptions of EGCG that contain beverages such as green tea might ameliorate the diabetes' complications in which it reduces body fat, maintains cardiovascular

health, and improves glucose metabolism (Thielecke and Boschmann, 2009). It has been shown mentioned that tannins are 15-30 times more effective at quenching peroxyl radicals than simple phenolics using *in vitro* model (Hagerman et al., 1998)). Furthermore, EGCG could efficiently trap reactive dicarbonyl compounds under physiological conditions, thus, this will be an effective approach to reduce the formation of AGEs and the development of diabetic complications (Sang et al., 2007). Nakagawa et al. (2002) demonstrated that EGCG significantly inhibited glucose-induced protein damage in human serum albumin\glucose in vitro system, suggesting that the presence of the gallate group at the 3 position plays the most important role in the protective activity against protein glycation. Moreover, the AGE-induced tumour necrosis factor- α and cells apoptosis in human embryonic kidney cells were inhibited by EGCG (Liang et al., 2010).

Despite EGCG strongly protects biomolecules from structural damage, several investigations showed prooxidant activities for EGCG (Yiannakopoulou, 2013). In human serum albumin-glucose systems, it has been stated that low EGCG levels (0.25~10μM) can inhibit glycation-induced fluorescence (Nakagawa et al. 2002). However, high EGCG concentrations might induce prooxidative effects. In this regard, Ebling and colleagues (2005) reported that 20 μM concentration of EGCG enhanced oxidative stress and inhibit cell growth in cultured rodent macrophages and human promyelocytic cells with leukemia, but adverse effects were not reported for low EGCG concentrations (<= 10 μM). Moreover, Fujiwara et al. (2011) demonstrated that EGCG concentration (> = 50 μM) could enhance N-(carboxymethyl) lysine formation, a major antigenic AGE structure in both cell culture and glycated human serum albumin model system; on the other hand, adverse effects were not reported for low levels of EGCG (<= 10 μM). Thus, it may be hypothesized that EGCG concentrations have a critical role in which they determine the EGCG-mediated biochemical activities' outcome and provide novel data associated with EGCG's typical concentrations that could be fulfilled by oral dosing.

Regarding the reactions' sequence and duration between the glycated protein and EGCG, the latter is considered chemically labile (Wang et al., 2008). In a study, EGCG was incubated with human serum albumin HSA and glucose for two weeks (Nakagawa et al., 2002). Since Glycation is a slow process, Bhattacherjee and Chakraborti (2011) incubated horse heart myoglobin with fructose solution at 25 ◦C for up to 30 days; however, the in vivo half-life of EGCG is only around four hours (Van Amelsvoort et al., 2001). If the intact EGCG has a role in glycation, this role must be present during a short period and must include already formed glycated protein. The former studies did not demonstrate the effects of intact EGCG on the previously glycated protein.

Concerning the ALA and EGCG-mediated biochemical activities under glycemic pressure, there is inadequate information on glycation at physiologically relevant levels of glucose. Ghelani et al. (2018) incubated myoglobin under high glycemic conditions (i.e. 1 M of glucose solution) in evaluating the effect of ALA in inhibition of myoglobin glycation and AGEs formation in an in vitro model. Besides, bovine serum albumin was incubated under 30 mM glucose solution with different concentrations of EGCG (Nakagawa et al., 2002). Hence, the effects of ALA and EGCG on myoglobin glycation in mild physiologically relevant glycemic concentrations ranged from 0–100 mM.

Limited data are found related to fructose-induced myoglobin glycation. Glucose to fructose shunt via the polyol pathway is seemingly very active in diabetic conditions (Yan, 2018). In streptozotocin-induced diabetic rats, an increased retinal level of fructose, as well as apoptosis of inner retina neurons mediated by polyol pathway activity, has been reported (Asnaghi et al., 2003). Furthermore, polyol pathway metabolites in the ventricle of streptozotocin-induced diabetic rats were increased 8-fold suggesting that polyol pathway activity may be an important factor in the etiology of diabetic cardiomyopathy (Cotter et al., 1992). Thus, fructose-induced myoglobin glycation and glucose-induced myoglobin glycation are targets for future investigations.

Concerning the hypothesis that ALA augments the EGCG anti-glycation effect, Leu et al. (2013) demonstrated that the effect of EGCG combined with ALA is greater than the effect of EGCG alone in down-regulation the expression of AGEs receptor as well as in inhibition high glucose-induced tumor necrosis factor-α and interleukine-6 production in human embryonic kidney cells. Moreover, the combined pretreatment of aluminum chloride-induced neuro-toxicity exposed rats with quercetin and alpha-lipoic acid resulted in restored altered lipid peroxidation and superoxide dismutase to near-normal levels, improved the protein carbonyl, reduced glutathione, and acetylcholine esterase activities in rat brains towards normal levels (Al-Otaibi et al., 2018). In streptozotocin -induced diabetic mice, topical treatment of ALA combined with EGCG nanoparticles significantly promoted cutaneous wound healing through down-regulated expression of the receptor for AGEs compared with the effect of EGCG alone (Chen et al., 2012). Thus, the synergistic effect between EGCG and ALA in inhibiting myoglobin glycation and the formation of AGEs has not yet been evaluated.

6. Scientific Gaps in Current Knowledge

Table 1 presents the suggested scientific gaps in current knowledge concerning antiglycation effects of alpha-lipoic acid and epigallocatechin-c-gallate. For further understanding of the role of ALA and EGCG in mediating biochemical activities under glycemic pressures, five important knowledge gaps that could hinder such understanding are discussed. As for ALA and EGCG-mediated effects on protein glycation, the sugar level is the first knowledge gap. Many studies on ALA and EGCG-related glycation have been done under high glycemic conditions approaching sugar concentrations >30 mM (Nakagawa et al., 2012, Ghelani et al., 2017 and 2018). However, blood sugar concentrations among diabetic patients are between 7–10 mM (ADA, 2019). No direct evidence is found to indicate whether ALA and EGCG effects on myoglobin glycation is observed under levels of high experimental sugars being meaningful under normal or physiological conditions. It may be proposed that the effects of ALA and EGCG on myoglobin glycation in mild glycemic concentrations ranging from 0–100 mM are a physiologically relevant glycemic environment.

Table 1. Suggested scientific gaps in current knowledge concerning antiglycation effects of alpha-lipoic acid and epigallocatechin-c-gallate

Gap in knowledge	**Reference**
Sugar media and sugar concentrations	Nakagawa et al., 2012; Ghelani et al., 2018; Yan, 2018; Yuan et al., 2019
Alpha-lipoic acid and epigallocatechin-c-gallate concentrations	Elbling et al., 2005; Nakagawa et al., 2012; Agathos et al., 2018; Ghelani et al., 2018
Alpha-lipoic acid and epigallocatechin-c-gallate pro- and antioxidant activities	Elbling et al., 2005; Nakagawa et al., 2012; Agathos et al., 2018; Ghelani et al., 2018
Alpha-lipoic acid- and epigallocatechin-c-gallate - glycated protein reactions′ sequence and duration	Amelsvoort et al., 2001; Wang et al., 2008; Kim et al., 2017; Cai et al., 2018;
Alpha-lipoic acid-epigallocatechin-c-gallate synergistic antiglycation effect	Gonzalez-Perez and Gonzalez-Castaneda, 2005; Chen et al., 2011; Leu et al, 2013; Moura et al., 2015; Al-Otaibi et al., 2018

The EGCG concentration that sets the balance of EGCG's pro- and antioxidant activities under glycemic pressure is considered the second knowledge gap. On one hand, the low EGCG concentrations can inhibit glycation-induced fluorescence in human serum albumin-glucose systems (Nakagawa et al., 2012). On the other hand, high EGCG concentrations may induce prooxidative effects (Elbling et al., 2005). It may be proposed that EGCG concentrations have a critical role in which they determine EGCG-mediated biochemical activities' outcome and provide the novel data associated with the EGCG's typical concentration that could be fulfilled by oral dosing.

The reactions' sequence and duration between the glycated protein and EGCG is the third knowledge gap. As mentioned by Wang et al (2008), the EGCG is considered chemically labile, and EGCG is subject to natural decomposition and oxidation in neutral solutions. This seems to be rational to propose that the parent compounds as well their degradation products could play different roles in the protein glycation process. Glycation is a slow biochemical process that may require weeks to be generated (Kim et al., 2017). However, the in vivo half-life of EGCG is only around 4 hours (Van Amelsvoort et al., 2001; Cai et al., 2018). If the intact EGCG has a role in glycation, this role must be present during a short period and must include already formed glycated protein. The former studies did not demonstrate the effects of intact EGCG on previously glycated protein. Thus, in future studies, it is important to direct comparisons between myoglobin that is exposed to EGCG and its degradation products through glycation process and myoglobin that is shortly exposed to EGCG after glycation, focusing on the physiologically realistic effect of ingested EGCG on pre-existing glycated proteins.

The tested sugars media is the fourth knowledge gap. Most previous investigations are limited to evaluate the glucose-induced myoglobin glycation. Limited data are found in this regard related to fructose-induced myoglobin glycation. Besides, the glucose to fructose shunt via the polyol pathway as mentioned by Yuan et al., (2019) being more active in diabetic conditions causing an increased fructose concentration and thence, fructose-induced glycation contributes considerably to diabetic complications. Thus, besides glucose, it may be proposed that fructose or even other monosaccharides have vital effects on myoglobin glycation induction.

The opinion in which ALA augments the EGCG antiglycation effect is the fifth knowledge gap. Previous studies showed that ALA increases the expression of antioxidant enzymes and participates in the recycling of vitamins C and E (Gonzalez-Perez and Gonzalez-Castaneda, 2005; Moura et al., 2015). Furthermore, it has been confirmed that ALA augments

the antioxidant effects of EGCG (Leu et al., 2013). It may be proposed that a probable synergistic effect between EGCG and ALA in inhibiting myoglobin glycation and the formation of AGEs.

7. Conclusions

Taken together, ALA and EGCG are known to protect protein oxidation and lessen the pathogenesis of oxidative-related multiple metabolic diseases such as diabetes and cardiovascular disease. They have pro- and antioxidant effects; thus, understanding their role in mediating biochemical activities under glycemic pressures is still unclear. The current discussion of the role of ALA and EGCG in inhibiting myoglobin glycation and the formation of AGEs reveals five important gaps in knowledge. These gaps are the sugar media and level, the EGCG concentration that sets the balance of EGCG's pro- and antioxidant activities under glycemic pressure, the reactions' sequence, and duration between the glycated protein and EGCG, and the synergistic effect ALA in augmenting the EGCG antiglycation. The suggested five gaps in current knowledge opens new avenues of scientific ideas that merit further investigations. Furthermore, the current discussion may provide cues for designing new antioxidant-based nutraceuticals or supplements for preventing the progress of diabetic and cardiovascular complications in humans.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgment

The authors would like to thank the University of Jordan, Amman, Jordan, and Al-Zaytoonah University of Jordan, Amman, Jordan.

Corresponding Author:
Mousa Numan Ahmad,
Professor of Clinical Nutrition and Cardiometabolism,
Department of Nutrition and Food Technology,
Human Nutrition and Dietetics,
University of Jordan,
Amman 11942, Jordan
mosnuman@ju.edu.jo; mousanuman@gmail.com

References

1. Abbas, G., Al-Harrasi, A.S., Hussain, H., Hussain, J., Rashid, R. and Choudhary, M.I. Antiglycation therapy: discovery of promising antiglycation agents for the management of diabetic complications. Pharmaceutical Biology, 2016; 54: 198-206.
2. Agathos, E., Tentolouris, A., Eleftheriadou, I., Katsaouni, P., Nemtzas, I., Petrou, A., Papanikolaou, C. and Tentolouris, N. Effect of α-lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy. Journal of International Medical Research, 2018; 46: 1779–1790.
3. Al-Otaibi, S.S., Arafah, M.M., Sharma, B., Alhomida, A.S. and Siddiqi, N.J. Synergistic effect of Quercetin and α-lipoic acid on aluminium chloride induced neurotoxicity in rats. Journal of Toxicology, 2018; 2018: ID 2817036.
4. American Diabetes Association. Glycemic targets: standards of medical care in diabetes. Diabetes Care, 2019; 42: S61–70.
5. Asnaghi, V., Gerhardinger, C., Hoehn, T., Adeboje, A. and Lorenzi, M. A role for the polyol pathway in the early neuroretinal apoptosis and glial changes induced by diabetes in the rat. Diabetes, 2003; 52(2): 506–511.
6. Banerjee, S., Maity, S. and Chakraborti, A.S. Methylglyoxal-induced modification causes aggregation of myoglobin. Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy, 2016; 155: 1–10.
7. Baye, E., Courten, M.P., Walker, K.E., Ranasinha, A. Earnest, J.M. Forbes, B. and Courten, B. Effect of dietary advanced glycation end products on inflammation and cardiovascular risks in healthy overweight adults: a randomized crossover trial. Nature Scientific Reports, 2017; 7: 4123.
8. Bhattacherjee, A. and Chakraborti, A.S. Fructose-induced modifications of myoglobin: Change of structure from met (Fe3+) to oxy (Fe2+) form. International Journal of Biological Macromolecules, 2011; 48(1): 202-209.
9. Cai, Z.-Y., Li, X.-M., Liang, J.-P., Xiang, L.-P., Wang, K.-R., Shi, Y.-L., Yang, R., Shi, M., Ye, J.-H., Lu, J.-L., Zheng, X.-Q and Liang, Y.-R. Bioavailability of tea catechins and its improvement. Molecules, 2018;23(9)*: 2346.*
10. Chatterjee, S., Khunti, K. and Davies, M.J. Type 2 diabetes. Lancet, 2017; 389: 2239–2251.
11. Chaudhuri, J., Bains, Y., Guha, S., Kahn, A., Hall, D. and Bose, N. The role of advanced glycation end products in aging and metabolic diseases: bridging association and causality. Cell Metabolism, 2018; 28(3): 337–352.
12. Chen, S.A., Chen, H.M., Yao, Y.D., Hung, C.F., Tu, C.S. and Liang, Y.J. Topical treatment with antioxidants and au nano particles promote healing of diabetic wound through receptor for advance glycation end products. European Journal of Pharmaceutical Sciences, 2012; 47(5): 875–883.
13. Chowdhury, A., Sarkar, J., Chakraborti, T., Pramanik, P.K. and Chakraborti, S. Protective

role of epigallocatechin-3-gallate in health and disease: a perspective. Biomedicine & Pharmacotherapy, 2016; 78: 50–59.
14. Christopher, L.R. Perspective: The paradox in dietary advanced glycation end products research—the source of the serum and urinary advanced glycation end products Is the intestines, not the food. Advances in Nutrition, 2017; 8(5): 679–683.
15. Cotter, M.A., Cameron, N.E. and Robertson, S. Polyol pathway-mediated changes in cardiac muscle contractile properties: studies in streptozotocin- diabetic and galactose-fed rats. Experimental Physiology, 77, 1992; sp003649.
16. Courten, B., Courten, P.J.M., Soldatos, G., Dougherty, S.L., Straznicky, N., Schlaich, M., Sourris, C.K., Chand, V., Scheijen, M.J. L. Kingwell, A.B., Cooper, M.E., Schalkwijk, C.G., Walker, Z.K. and Forbes, J.M. Diet low in advanced glycation end products increases insulin sensitivity in healthy overweight individuals: a double-blind, randomized, crossover trial, American Journal of Clinical Nutrition, 2016; 103(6): 1426-1433.
17. El Barky, A.R., Hussein S.A. and Mohamed, T.M. The potent antioxidant alpha lipoic acid. Journal of Plant Chemistry and Ecophysiology, 2017; 2: 1016.
18. Elbling, L., Weiss, R. M., Teufelhofer, O., Uhl, M., Knasmuller, S., Schulte-Hermann, R., Berger, W. and Michksche, M. Green tea extract and (−)-epigallocatechin-3-gallate, the major tea catechin, exert oxidant but lack antioxidant activities. Federation of American Societies for Experimental Biology, 2005; 19: 807-810.
19. Freedman, B.I., Würth, J., Cartwright, K., Bain, R. P., Dippe, S., Hershon, K.S., Mooradian, A. D. and Spinowitz, B.S. Design and baseline characteristics for the aminoguanidine clinical trial in overt type 2 diabetic nephropathy (ACTION II). Controlled Clinical Trials, 1999; 20(5): 493-510.
20. Fujiwara, Y., Kiyota, N., Tsurushima, K., Yoshitomi, M., Mera, K., Sakashita, N., Takeya, M., Ikeda, T., Araki, T. and Nohara T. Natural compounds containing a catechol group enhance the formation of N-(carboxymethyl)lysine of the Maillard reaction. Free Radical Biology and Medicine, 2011; 50: 883–891.
21. Ghelani, H., Razmovski-Naumovski, V. and Nammi, S. Chronic treatment of (R)-α-lipoic acid reduces blood glucose and lipid levels in high-fat diet and low-dose streptozotocin-induced metabolic syndrome and type 2 diabetes in Sprague-Dawley rats. Pharmacological Research & Perspectives, 2017; 5(3): e00306.
22. Ghelani, H., Razmovski-Naumovski, V., Pragada, R. R. and Nammi, S. Attenuation of glucose-induced myoglobin glycation and the formation of advanced glycation end products (AGEs) by (R)-α-lipoic acid *in vitro*. Biomolecules, 2018; 8(1): 9.
23. Goh, S.Y. and Cooper, M.E. The role of advanced glycation end products in progression and complications of diabetes. Journal of Clinical Endocrinology & Metabolism, 2008; 93(4): 1143–1152.
24. Gonzalez-Perez, O. and Gonzalez-Castaneda, R.E. Therapeutic perspectives on the combination of alpha-lipoic acid and vitamin E. Nutrition Research, 2005; 26(1): 1–5.
25. Hagerman, A.E., Riedl, K.M., Jones, G.A., Sovik, K.N., Ritchard, N.T., Hartzfeld, P.W. and Riechel, T.L. High molecular weight plant polyphenolics (tannins) as biological antioxidants. Journal of Agricultural and Food Chemistry, 1998; 46: 1887–1892.
26. Hendgen-Cotta, U.B., Kelm, M. and Rassaf, T. Myoglobin functions in the heart. Free Radical Biology and Medicine, 2014; 7: 252–259.
27. International Diabetes Federation, IDF. Diabetes Atlas, 8th edn. Brussels, Belgium, 2017.
28. Kim, C.S., Park, S. and Kim, J. The role of glycation in the pathogenesis of aging and its prevention through herbal products and physical exercise. Journal of Exercise Nutrition and Biochemistry, 2017;21(3): 55–61.
29. Kolb, H. and Martin, S. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Medicine, 2017; 15(1): 131.
30. Koska, J., Saremi, A., Howell, S., Bahn, G., Courten, B., Ginsberg, H., Paul, J.B. and Reaven, D.P. Advanced glycation end products, oxidation products, and incident cardiovascular events in patients with type 2 diabetes. Diabetes Care, 2018; 41(3): 570-576.
31. Kowluru, R.A. Effect of advanced glycation end products on accelerated apoptosis of retinal capillary cells under *in vitro* conditions. Life Sciences, 2005; 76(9): 1051–1060.
32. Leu, J.G., Lin, C.Y., Jian, J.H., Shih, C.Y. and Liang, Y.J. Epigallocatechin-3-gallate combined with alpha lipoic acid attenuates high glucose-induced receptor for advanced glycation end products (RAGE) expression in human embryonic kidney cells. Anais da Academia Brasileira de Ciencias. 2013; 85(2): 745–752.
33. Liang, Y., Jian, J., Liu, Y., Juang, S., Shyu, K., Lai, L., Wang, B. and Leu, J. Advanced glycation end products-induced apoptosis attenuated by PPARδ activation and epigallocatechin gallate through NF-κB pathway in human embryonic

kidney cells and human mesangial cells. Diabetes Metabolism Research and Reviews, 2010; 26: 406-416.
34. Magdaleno, F., Blajszczak, C. C., Charles-Niño, C.L., Guadrón-Llanos, A.M., Vázquez-Álvarez, A.O., Miranda-Díaz, A. G. and Rincón-Sánchez, A. R. Aminoguanidine reduces diabetes-associated cardiac fibrosis. Experimental and Therapeutic Medicine, 2019; 18(4): 3125–3138.
35. Mereles, D. and Hunstein, W. Epigallocatechin3-gallate (EGCG) for clinical trials: more pitfalls than promises? International Journal of Molecular Sciences, 2011; 12: 5592-5603.
36. Moura, F.A., Andrade, K.Q., Santos, J.C. and Goulart, M.O. Lipoic acid: Its antioxidant and anti-inflammatory role and clinical applications. Current Topics in Medicinal Chemistry, 2015; 15: 458–483.
37. Muellenbach, E.M., Diehl, C.J., Teachey, M.K., Lindborg, K.A., Hasselwander, O. and Matuschek, M. Metabolic interactions of AGE inhibitor pyridoxamine and antioxidant alpha-lipoic acid following 22 weeks of treatment in obese Zucker rats. Life Sciences, 2009; 84(15-16): 563–568.
38. Nagai, R., Murray, D.B., Metz, T.O. and Baynes, J.W. Chelation: a fundamental mechanism of action of AGE inhibitors, AGE breakers, and other inhibitors of diabetes complications. Diabetes, 2009; 61(3): 549–559.
39. Nakagawa, T., Yokozawa, T., Terasawa, K., Shu, S. and Juneja, L. R. Protective activity of green tea against free radical- and glucose-mediated protein damage. Journal of Agricultural and Food Chemistry, 2002; 50: 2418–2422.
40. Niu, G., Guo, J., Tian, Y., Zhao, K., Li, J. and Xiao, Q. α-lipoic acid can greatly alleviate the toxic effect of AGES on SH-SY5Y cells. International Journal of Molecular Medicine, 2018; 41: 2855-2864.
41. Park, S., Kang, H.J., Jeon, J.H., Kim, M.J. and Lee, k. Recent advances in the pathogenesis of microvascular complications in diabetes. Archives of Pharmacological Research, 2019; 42(3): 252-262.
42. Punthakee, Z., Goldenberg, R. and Katz, P. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Canadian Journal of Diabetes, 2018; 42: S10–5.
43. Richards, M.P. Redox reactions of myoglobin. Antioxidants and Redox Signaling, 2013; 18(17): 2342–2351.
44. Roy, A., Sen, S. and Chakraborti, A.S. In vitro nonenzymatic glycation enhances the role of myoglobin as a source of oxidative stress. Free Radical Research, 2004; 38: 139–146.
45. Roy, A., Sil, R. and Chakraborti, A.S. Non-enzymatic glycation induces structural modifications of myoglobin. Molecular and Cellular Biochemistry, 2010; 338(1-2): 105–114.
46. Salehi, B., Yılmaz, B., Antika, G., Tumer, T.B., Mahomoodally, F.M., Lobine, D. and Sharifi-Rad, J. Insights on the Use of α-Lipoic Acid for Therapeutic Purposes. Biomolecules, 2019; 9(8): 356.
47. Sang, S., Shao, X., Bai, N., Lo, C.Y., Yang, C.S. and Ho, C.T. Tea polyphenol (−)-epigallocatechin-3-gallate: A new trapping agent of reactive dicarbonyl species. Chemical Research in Toxicology, 2007; 20: 1862–1870.
48. Suzuki, Y.J., Tsuchiya, M. and Packer, L. Lipoate prevents glucose-induced protein modifications. Free Radical Research Communications, 1992; 17(3): 211–217.
49. Thielecke, F. and Boschmann, M. The potential role of green tea catechins in the prevention of the metabolic syndrome - A review. Phytochemistry, 2009; 70: 11–24.
50. Tsuchida, K., Makita, Z., Yamagishi, S., Atsumi, T., Miyoshi, H., Obara, S., Ishida, M., Ishikawa, S., Yasumura, K and Koike, T. Suppression of transforming growth factor beta and vascular endothelial growth factor in diabetic nephropathy in rats by a novel advanced glycation end-product inhibitor, OPB-9195. Diabtologia, 1999; 42(5): 577-588.
51. Van Amelsvoort, J.M.M., Hof, K.H.V., Mathot, J., Mulder, T.P.J., Wiersma, A. and Tijburg, L. B. M. Plasma concentrations of individual tea catechins after a single oral dose in humans. Xenobiotica, 2001; 31: 891–901.
52. Wang, Zhou, W. and Jiang, X. Reaction kinetics of degradation and epimerization of epigallocatechin gallate (EGCG) in aqueous system over a wide Temperature range. Journal of Agricultural and Food Chemistry, 2008; 56: 8, 2694–2701.
53. Wittenberg, B.A. Both hypoxia and work are required to enhance expression of myoglobin in skeletal muscle. Focus on “hypoxia reprograms calcium signaling and regulates myoglobin expression.” American Journal of Physiology-Cell Physiology, 2009; 296: 390–392.
54. World Health Organization – Diabetes country profiles, WHO, 2016.
55. Yan L.J. Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. Animal Models and Experimental Medicine, 2018; 1(1): 7–13.
56. Yiannakopoulou, E. C. Targeting oxidative stress response by green tea polyphenols: clinical

implications. Free Radical Research, 2013; 47: 667–671.
57. Yin, Q.Q., Dong, C.F., Dong, S.Q., Dong, X.L., Hong, Y. and Hou, X.Y. AGEs induce cell death via oxidative and endoplasmic reticulum stresses in both human SH-SY5Y neuroblastoma cells and rat cortical neurons. Cellular and Molecular Neurobiology, 2012; 32(8): 1299–1309.
58. Yuan, T., Yang, T., Chen, H., Fu, D., Hu, Y., Wang, J. and Xie, X. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biology, 2019; 20: 247–260.
59. Zimmet, P.Z. Diabetes and its drivers: the largest epidemic in human? Clinical Diabetes and Endocrinology, 2017; history 3: 1.

6/13/2020