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Chapter

Antioxidants: Pharmacothearapeutic Boon for Diabetes

Varuna Suresh, Amala Reddy, Pavithra Muthukumar and Thendarl Selvam

Abstract

Glucose-induced oxidative stress can be found related to "glucose variability" and "glucose memory". The irregular low and elevated glucose conditions cause damage to endothelial cell function than a steady, constant rise in level of glucose. Activation of PKC, NADPH oxidases, and mitochondrial oxidants are some of the pathways exhibited as a result of this aggravated cellular response. Regarding glucose memory, long after the normalization elevated level of glucose in the endothelial cells of diabetic rats and culture, a existance or 'memory' of induced basement membrane mRNA is expressed. This demonstrates that glucose causes dangerous long-term effects beyond the hyperglycemia period. Oxidative stress give rise to glucotoxicity and lipotoxicity which are phenomena's related to diabetes. Following the pathogenesis of diabetes, hyperglycemia and hyperlipidemia exerts a supplementary toxic effect on the beta-cells. So, hyperglycemia can be considered as a requirement for the destructive effects of lipotoxicity. Thus glucolipotoxicity can be considered as a substitute for lipotoxicity which relates the detrimental correlation between lipids and beta-cell function. Generally, the antioxidant pharmacotherapy can be coupled with drugs to boost the natural cellular defense mechanisms as the naturally existing antioxidant components, which neutralizes free radical damage. This considers antioxidant a boon tool for pharmacotherapeutic agent.

Keywords: Hyperglycaemia, Glucose, Pharmaco therapeutic, Antioxidants

1. Introduction

Diabetes is a metabolic disorder which is characterized based on the blood glucose level over a certain interval of time. It can also be termed as a condition that impairs the ability of the body to process blood sugar. This disorder has now been a common problem irrespective of age and gender [1]. As per the statistical surveys reported the count of people effected by diabetes is increasing over the world in a quite faster rate [2]. Diabetes are of two type in which type-1 is a chronic condition in which pancreas produces very little insulin, this may be due to loss of beta cells [3]. Beta cells dysfunction results from prolonged exposure of high level of glucose. Type-2 is a condition were that affects the way the body processes blood sugar [4]. Diabetes can lead to many complications that can show severe negative impact on different organs, mainly nerves, heart, kidney, eyes and blood vessels [5].

Diabetes can cause oxidative stress which can be caused by imbalance between production and accumulation of reactive oxygen species, which can damage DNA, lipid, protein beside these it can triggers the activation of different cellular pathways. When these molecules which are having notable regulatory effects in the body if deregulated it can lead to several diabetic complication [6–8].

When there is higher concentration of reactive oxygen species in the body with a minimal amount of anti-oxidant enzymes it can cause oxidative stress [9]. Whenever an external stimuli enters the body it can lead to reduction of the amount of anti-oxidant enzymes in the body and can cause inflammation [10].

Free radicles contain unpaired electrons and therefore lack stability which in turn search for another electron to stabilize themselves resulting in process that damages DNA and other parts of human cell [11]. Antioxidants are substances that can prevent the cells from damages that can be caused by free radicles. The antioxidants which is produced by the body is called endogenous antioxidants and those which is taken from outside is called exogenous [12].

There are many health benefits for anti-oxidants and this work pay attention on the benefits shown by antioxidants against oxidative stress, how it helps to reduce the formation of reactive species and thus in preventing or treating of diabetes and related complications that is the pharmacotherapy of antioxidants in treating diabetes [13]. Pharmacotherapy can be the therapy utilizing a drug that can cause relief to a particular disease. This work focuses on the characteristics of antioxidants and the use of same in prevention of diabetes [14].

2. Effect of BETA cell dysfunction and oxidative stress on hyperglycemia and lipotoxicity

Impaired glucose utilization can lead to hyperglycaemia. Beta cell dysfunction may be due to pancreatic diseases, drugs, surgery, tumors [15]. It may result from the long duration of exposure to high glucose, beta cells are meant to be sensitive towards reactive oxygen species because they are low at antioxidant enzymes such as catalase, SOD, GPx. Thus this end up in damaging mitochondria and blunt insulin secretion [16].

There are several studies that states the negative effect of oxidative stress on cell and tissues that finally leads to the damage of the same when there is an over production of reactive species that can lead to toxic effect and can cause cytostatic effects leads to membrane damage and can initiate cell death pathway [17]. If the pancreatic beta cells are healthy they can respond to nutrients and other insulin resistance via hyper secretion of insulin. This is done to maintain the energy level but this is a long process that requires a extended time period. The beta cell cannot withstand a response that can be compensatory which results in dysfunction of beta cell and death of beta cells [18].

There are also several studies that point out the impairment in beta cells can be due to the exposure of beta cell to the high glucose, which can cause glycolytic flux and thus producing reactive oxygen species including hydrogen peroxide, hydroxyl radicles and superoxide [19]. Hydrogen peroxide can be formed form superoxide this can be catalase and GPX. Many studies including in vitro and in vivo stated the over expression of superoxide production during diabetes [20].

There are many metabolic pathway which are activated during superoxide production which include advanced glycation and products (AGEs), polyol pathway activation of protein kinase c (PKC) [21]. Conversion of glucose to sorbitol is done during hyperglycemia that can further leads to the reduction of nicotinamide

adenine dinucleotide phosphate (NADPH) and glycothione and this is the reason behind the reduction in the amount of antioxidants which in then can cause oxidative which in then can cause oxidative stress [22, 23].

In case of AGEs, adduct is formed by the reaction of amino group with glucose, which can interfere with cell integrity, and can lead to the production of reactive oxygen species [24]. During hyperglycermia there will be production of advanced glycation end product, which enhance PKC and hexosamine pathway which can lead to oxidative stress. Excess reactive oxygen species can react with nitric oxide radicle firming peroxy nitriate anion and cause tissue damage [25]. The other way of beta cell dysfunction may be due to the high glucose along with the free fatty acid whose origin can be utra-abdoman fat stores. Although the exact cause for the beta cell dysfunction is not known there are many hypothesis that have stated mitochondrial dysfunction, endoplasmic stress, and oxidative stress as the cause for the improper functioning of beta cell [26].

Other studies has pointed out that the free fatty acid can cause negative effect on functions of mitochondria leading to oxidative phosphorylation uncoupling and generation of reactive oxygen species [27]. Therefore dysfunction of mitochondria and oxidative stress can be reason for impairment of endogenous antioxidant defense. To add more to this point free fatty acid can generate reactive oxygen species and can cause fragmentation of DNA. Recent experimental studies suggest that lipotoxicity induced beta cell death may be due to the formation of hydrogen peroxide in peroxisomes [28].

Free fatty acid can activate nucleus factor kappa-β (NFK β), which allows the translocation of some into nucleus and produce cellular effect. In the case it can lead to the production of cytokines and can produce nitric acid through inducible NO synthase (iNOS) expression [29]. By this way over production of NO by iNOS takes place which can react with suoeroxide and leads to production of toxic substance peroxynitrite [30]. Thus free fatty acid can up-regulate the expression of iNOS, therefore increasing the production of NO simultaneously reducing the output insulin. Therefore all these can be brought to a conclusion that reactive oxygen species. Reactive oxygen species can increase in oxidative stress can play critical role in diabetes development [31].

3. Antioxidant and their role IN diabetes

The substances that can delay or inhibit the oxidation of other molecules are termed as antioxidants. Recently therapy using antioxidants has gained more importance in the field of medicine and can be used in treatment of several diseases including diabetes [32]. Diabetes complications can be reduced to a greater extend with the help of antioxidants is studied in many experimental works. Antioxidants can be used as a drug substrate, combined drug in the treatment focused in their antioxidant activity are also utilized in the treatment of diabetes [33].

The function of beta cell can be secured by antioxidants by fighting against oxidative stress, which tries to defend the beta cells. Thus it can diminish diabetes related complications and helps in recovering of insuli9n sensitivity. Dietary antioxidant intake can also be considered as a tool in treatment of diabetes [34]. There are several antioxidants which are present naturally and whose intake can reduce the risk of this disease. Vitamin E, vitamin C, alpha lipoic acid, selenium fall under this category. The role played by these antioxidants at a prescribed quantity will aim at reducing the risk of diabetes [35].

4. Vitamin E

It is a lipophilic antioxidant that are found in tocopherol and tocotrienol form. Vitamin E is a naturally occurring antioxidant and can help in defending the cells against oxidative stress [36]. Many studies focused on the ability of vitamin E in reducing the risk of hyperglycemia and their effect in using it as a combined drug in therapy for diabetes [37]. Hepatic lipid peroxide level is decreased in streptozotocin induced diabetes by vitamin E is shown in many experimental model studies [38].

The increase in the level of lipid peroxide can be due to the change in status of antioxidant level. Administration of vitamin E can be significantly decreased when supplemented by vitamin E. During diabetes the antioxidant enzyme such as SOD, CAT and GPX decrease [39]. Therefore the oral administration of vitamin E (440 mg/kg of body weight) once in a week for one month has shown positive results in increasing the activity of antioxidant enzyme and decreasing hyper oxide level [40].

Glucose in high concentration will get attached to hemoglobin forming glycosylated hemoglobin, which is a important marker for diabetes can be prevented using vitamin E it can also reduce HbA1C level by oxidative stress inhibition [41]. The exact way by which the glucose level is reduced using antioxidants is not so clear but it reduces the plasma glucose while increasing the metabolic of glucose in peripheral tissues. Thus antioxidants can reduce the risk of several disease including diabetes and cancer. The antioxidant activity of vitamin E which helps in curing hyperglycemia can reduce the micro-vascular and macro-vascular complications in people affected with diabetes [42].

5. Vitamin C

It is a powerful antioxidant scavengering free radicals in aqueous compartment. In aqueous state, vitamin C is a chain breaking antioxidant. The stability of cell membrane can be increased by vitamin C [43]. On a statistical survey taken from the study done in diabetic research centre, Iran, a total of 84 patients was supplemented with 500 mg or 100 mg of ascorbic acid for 6 weeks among which the patients provided with 100 mg of vitamin C shown significant reduce in blood glucose and lipid level where as the ones treated with 500 mg did not show any significant response [44]. There studies carried out showed that when vitamin C was provided in a high dose it reduced the fasting glucose level, improved hBA1 and glycemia control [45].

The risk of type-2 diabetes is found to be reduced by continuous intake of vitamin C as a dietary source in a population based study. The correct or prescribed dose (as per weight of the body) of vitamin C and vitamin E can reduce the level of blood glucose [46]. However no further increase in SOD is found when treated with vitamin C. Some studies stated that decrease in plasma vitamin C and vitamin E during diabetes can be due to increased oxidative stress [47]. Vitamin C play major role in ameliorating insulin resistance of diabetic patients and can decrease or diminish the micro albuminuria, erythrocyte sorbitol level. All these are turned to be possible by vitamin C due to their antioxidant property [48].

6. Alpha lipoic acid

The injuries in cells which is caused by free radical triggering can be treated using alpha lipoic acid. It has the ability to restore other antioxidants such as

vitamin C, vitamin E glutathione. Thus can be very useful in the effective treatment of disease related to liver, cardiovascular disease and diabetes [49].

Alpha lipoic acid is known for improving glucose metabolism in diabetes patients. This can be achieved by activating threonine, tyrosine lipid kinase in target cell which is responsible for stimulating glucose uptake. The translocation of GLUT1 and GLUT4 to plasmid membrane of adipocyte and skeletal muscle is done by alpha lipoic acid is stated in many invitro studies [50]. This can help in increasing the activity of protein in insulin signaling pathway intake of this antioxidant can reduce the glucose and cholesterol level. During diabetes it can regenerate other antioxidant including vitamin C, vitamin E and SOD. An increase of insulin stimulated glucose disposal is seen in diabetic patients when administrated with 500 mg ALA for about 10 days but no change is seen in fasting plasma glucose level. Insulin resistance can be accured by intake of this antioxidant. Plasma insulin sensitivity can be raised by the oral supplementation of ALA. ALA has the ability to scavenge the reactive oxygen species which are produced during peroxidation of lipid thus saving the cells from damage. Continuous supplementation of ALA helps in reducing hyperglycemia as well as diabetic complication including diabetic nephropathy [51].

7. Selenium

This is an antioxidant which is commonly seen in several food it exist in both organic and inorganic form, in which organic form include selenocysteine and selenomethionine and selenite and selenate falls under inorganic form. This antioxidant has major role in immune function. There are several clinical studies that proved the efficacy of selenium to treat several diseases and this power of selenium is due to its antioxidant activity [52]. Earlier selenium was considered as toxic as it caused poisoning in both human and animal but later studies proved that deficiency of the same can create numerous problems in both animal and humans. Glucose metabolism can be maintained using small concentration of selenium as it can mimic insulin action, but the exact mechanism of this mimicking is not understood, reports depicts that activation of protein which is responsible for insulin signaling cascade can be done by selenuium [53].

By activating kinases, sodium selenate and sodium selenite which are inorganic selenium are involved in insulin signaling cascade. Selenate can increase glucose uptake and are involved in insulin receptor phosporylation. Insulin like activity cab be shown by selenium is because of their glucose tolerance anf their ability to alter the gluconeogenic activity. There are studies which shows the combined treatment of selenium along with vitamin C, vitamin E and alpha lipoic acid which are studied to be useful in the management of diabetes. Therefore for the curing of diseases antioxidant based formation are commonly used now a days [54].

8. Resveratrol

It is known as polyphenolic phytoalexin that is developed in significant amounts in grapevines as a secondary metabolite in response to fungal infections and has been shown to lower the risk of cardiovascular disease. Resveratrol has been shown to have positive benefits on the onset and progression of atherosclerosis, including control of vasodilator and vasoconstrictor production, and inhibition of anti-platelet aggregation and low density lipo protein [55]. In addition, previous research has shown that resveratrol supplementation reduces plaque development in animal

brains and other neurodegenerative diseases. Oral resveratrol significantly reduced brain plaque in the hypothalamus (−90%), striatum (−89%), and medial cortex (−48%) of mice [56].

Oral doses of resveratrol in humans are thought to minimize beta amyloid plaque, which is linked to aging changes in the brain. Researchers believe that resveratrol's ability to chelate Cu++ is one mechanism for plaque eradication. It appears to be a promising bioactive natural molecule with possible applications in phytotherapy or pharmacology, based on current knowledge [57]. Moreover, diabetic rats given resveratrol (5 mg kg1 b.w. d1) orally for 30 days had significantly lower blood glucose, blood urea, serum uric acid, serum creatinine, glycosylated hemoglobin, and reduced functions of pathophysiological enzymes including aspartate transaminase (AST), alkaline phosphatase (ALP) and alanine transaminase (ALT). The antihyperglycemic properties of resveratrol are also demonstrated by improvements in plasma insulin and hemoglobin levels. According to recent studies, resveratrol can be an important therapeutic agent used to treat diabetes [58].

9. Cyanidins

They are primarily found in red-blue colored fruits, tomatoes, rice, potatoes, beans, and red wines, implying that we consume substantial quantities of these compounds on a regular basis from plant-based diets [59]. This anthocyanin was isolated from black rice, which contains high levels of cyanidin 3-glucoside, and its protective effect on insulin sensitivity was tested in cultured adypocytic cells which were exposed to tumor necrosis factor alpha (TNF-α) [60].

Adipocyte dysfunction is closely linked to the development of obesity and insulin resistance. The control of kinase expression by adypocites cells is an essential target for obesity prevention and insulin sensitivity improvement [61]. The effects of cyanidin 3-glucoside on hydrogen peroxide or TNF-induced insulin resistance were found to be dose-dependent. The intracellular development of ROS and the activation of Jun N-terminal kinases were reduced when adipocytes cells were pretreated with cyanidin 3-glucoside [62].

By controlling the glucose transporter 4 (GLUT-4) and retinol binding protein 4 systems, cyanidin 3-glucoside increases insulin sensitivity. Since retinol binding protein 4 expression is reduced in diabetic mice, cyanidin 3-glucoside lowers blood glucose levels and increases insulin sensitivity. Eventually, cyanidin 3-glucoside has been shown to protect rat brains fed ochratoxin A in a recent study [63].

Adipocyte glucose uptake and GLUT4 membrane translocation were increased by cyanidin-3-glucoside and its key intestinal metabolite protocatechuic acid, according to a study conducted [64]. There were also huge rise in nuclear PPAR activity, as well as adiponectin and GLUT4 output.It's important to note that PPAR inhibition reversed the polyphenol-induced increases in adiponectin and GLUT4, implying that PPAR is directly involved in this phase. As a result of PPAR activation, cyanidin-3-glycoside and protocatechuic acid, its key intestinal metabolite, can exert insulin-like activities, indicating a causal relationship between this transcription factor and adiponectin and GLUT4 upregulation [65].

10. Antioxidant response against oxidative stress

Beta cell dysfunction which can be caused by oxidative stress which can lead to diabetic condition is mainly due to the poor or in efficient antioxidant defense mechanism. There should be a proper balance between oxidants and antioxidant

which is required for survival of cells and thus a healthy life. The degree to which component of cells that persist in oxidative state define the redox states, whereby oxidative stress can be prevented by a reducing environment. Therefore such a reducing environment should be maintained and this can be done by antioxidant enzymes such as SOD and catalase that can be useful in removing reactive oxygen species which gives more strength to the statement that endogenous antioxidant enzymes can stand against the negative role played by reactive oxygen species. Main antioxidant enzyme that helps in minimizing the oxidative stress are SOD, catalase and GPX [66].

The antioxidant enzymes including SOD and catalase can reduce the susceptibility of pancreatic islet to oxidative stress. Catalase can protect against the expression of pro-inflammatory cytokines. Thus can also protect the pancreatic islet against hydrogen peroxide and streptozotocin and cytokine toxicity [67]. It is also noted that difference in level of mitochondrial enzyme and increment in production of beta cells can alter susceptibility to dysfunction and development of diabetes. Antioxidant such as vitamin C, alpha-lipoic acid can act as cofactor in metabolic mitochondrial energy and can reduce the level of reactive oxygen species and reactive nitrogen species in pancreatic islet cells [68].

Alpha lipoic acid can reduce oxidizing forms of antioxidant including vitamin E and vitamin C and can increase the levels of GSH by increasing cysteine uptake resulting positive therapeutic advantage in diabetes. It can also improve glucose disposal that helps in reducing body weight that will be beneficial for diabetic obese patients. Lipoic acid can reduce ubiquinone which is an important component of mitochondrial respiratory complex [69]. There are also several plants derived flavonoids that has a broad spectrum of bioactivity. They show biochemical and pharmacological characteristics which matches antioxidant properties. Some of these include quercetin ginseng, curcumin. The above mentioned flavonoid can limit the production of reactive oxygen species, regulation of cell signaling which is then can result in reducing oxidative stress and controlling diabetes [70].

Vegetables and fruits hold a very high nutritional value and there are several studies that talk about the foods that are rich in antioxidants. There are evidences that states that antioxidant rich fruits and vegetables intake can reduce the risk of type-2 diabetes. As these fruits and vegetables are rich in the antioxidant content they can contribute to the reduction of oxidative stress. Fruits and vegetables are good source of alphalinolenic acid nd omega 3 poly unsaturated fatty acid [71].

These are several medicinal plants which has been used for the treatment of type 2 diabetes for past years. There are more than 800 plants which shows antioxidant properties and thus have been using for the treatment of diabetes [72]. With the advancement in the technologies there has been a rapid increment in researching on anti-diabetic plants. Which came out with new herbs and their principles activity working in their anti-diabetic properties. There are plants by products that show anti-diabetic characteristics. Lignans, flavanoids, terpenoids are some among them [73].

11. Conclusion

Diabetes is a metabolic disorder which is caused due to impaired insulin secretion. When the beta cells are normal they respond to nutrients and insulin resistance by secretion of insulin in a higher mode which can balance the glucose intolerance. Type-2 diabetes is due to the deleterious effect of beta cells. There are many evidences which states that high level of glucose can lead to the generation of reactive oxygen species which can intern cause oxidative stress.

Therefore beta cells become worse with respect to insulin secretion. In addition to that the production of reactive oxygen species can lead to the activation of several signaling pathway. Thus low antioxidant defense can lead to oxidative stress and beta cell dysfunction. Antioxidant treatment can increase the defense capacity to fight against oxidative stress. Hydrogen peroxide molecules play roles in insulin secretion.

This paper focused on antioxidant as a therapy for the treatment of diabetes. As there is no clear evidence on how the antioxidant work on curing the disease, but all the possible mechanisms are discussed here. Evidences from the experiments shows that oxidative stress can lead to dysfunction of beta cells. Redox status change and depletion in antioxidant occur during this stress and lead to reactive oxygen species production.

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Author details

Varuna Suresh, Amala Reddy*, Pavithra Muthukumar and Thendarl Selvam
Animal Cell Culture Laboratory, Department of Biotechnology, SRM Institute of Science and Technology, Chennai, Tamilnadu, India

*Address all correspondence to: amalar@srmist.edu.in

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References

[1] Mellitus D. Diagnosis and classification of diabetes mellitus. Diabetes care. 2005 Jan 1;28 (S37):S5-10.

[2] Mellitus DI. Diagnosis and classification of diabetes mellitus. Diabetes care. 2006 Jan 1;29:S43.

[3] Bastaki A. Diabetes mellitus and its treatment. International journal of Diabetes and Metabolism. 2005 Jan 1;13(3):111.

[4] Nathan DM. Long-term complications of diabetes mellitus. New England Journal of Medicine. 1993 Jun 10;328(23):1676-85.

[5] Power AC. Diabetes mellitus. Harrison's principles of internal medicine, 16th ed. Mc Graw-Hill Medical pub. 2005:2152-80.

[6] Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress—A concise review. Saudi pharmaceutical journal. 2016 Sep 1;24(5):547-53

[7] Yang H, Jin X, Lam CW, Yan SK. Oxidative stress and diabetes mellitus. Clinical chemistry and laboratory medicine. 2011 Nov 1;49(11):1773-82.

[8] Maiese K, Chong ZZ, Shang YC. Mechanistic insights into diabetes mellitus and oxidative stress. Current medicinal chemistry. 2007 Jul 1;14(16):1729-38.

[9] CHANDRA K, SINGH P, DWIVEDI S, Jain SK. Diabetes Mellitus and Oxidative Stress: A Co-relative and Therapeutic Approach. Journal of Clinical & Diagnostic Research. 2019 May 1;13(5).

[10] Tabak O, Gelisgen R, Erman H, Erdenen F, Muderrisoglu C, Aral H, Uzun H. Oxidative lipid, protein, and DNA damage as oxidative stress markers in vascular complications of diabetes mellitus. Clinical and Investigative Medicine. 2011 Jun 1:E163-71.

[11] Fang YZ, Yang S, Wu G. Free radicals, antioxidants, and nutrition. Nutrition. 2002 Oct 1;18(10):872-9.

[12] Halliwell B, Aeschbach R, Löliger J, Aruoma OI. The characterization of antioxidants. Food and Chemical Toxicology. 1995 Jul 1;33(7):601-17

[13] Rahimi R, Nikfar S, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. Biomedicine & Pharmacotherapy. 2005 Aug 1;59(7):365-73.

[14] Johansen JS, Harris AK, Rychly DJ, Ergul A. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovascular diabetology. 2005 Dec;4(1):1-1.

[15] Mooradian AD. Antioxidants and diabetes. Nutritional Management of Diabetes Mellitus and Dysmetabolic Syndrome. 2006;11:107-25.

[16] Golbidi S, Alireza Ebadi S, Laher I. Antioxidants in the treatment of diabetes. Current diabetes reviews. 2011 Mar 1;7(2):106-25.

[17] Scott JA, King GL. Oxidative stress and antioxidant treatment in diabetes. Annals of the New York Academy of Sciences. 2004 Dec;1031(1):204-13.

[18] A Haidara M, Z Yassin H, Zakula Z, P Mikhailidis D, R Isenovic E. Diabetes and antioxidants: myth or reality?. Current vascular pharmacology. 2010 Sep 1;8(5):661-72.

[19] Rosca MG, Mustata TG, Kinter MT, Ozdemir AM, Kern TS, Szweda LI, Brownlee M, Monnier VM, Weiss MF. Glycation of mitochondrial proteins

from diabetic rat kidney is associated with excess superoxide formation. American Journal of Physiology-Renal Physiology. 2005 Aug;289(2):F420-30.

[20] Hiramatsu K, Arimori S. Increased superoxide production by mononuclear cells of patients with hypertriglyceridemia and diabetes. Diabetes. 1988 Jun 1;37(6):832-7.

[21] Hotamisligil GS. Inflammatory pathways and insulin action. International Journal of Obesity. 2003 Dec;27(3):S53-5.

[22] Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. Cardiovascular research. 1998 Mar 1;37(3):586-600.

[23] Koya D, King GL. Protein kinase C activation and the development of diabetic complications. Diabetes. 1998 Jun 1;47(6):859-66.

[24] Peyroux J, Sternberg M. Advanced glycation endproducts (AGEs): pharmacological inhibition in diabetes. Pathologie Biologie. 2006 Sep 1;54(7):405-19.

[25] Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. Cardiovascular research. 1998 Mar 1;37(3):586-600.

[26] Talior I, Tennenbaum T, Kuroki T, Eldar-Finkelman H. PKC-δ-dependent activation of oxidative stress in adipocytes of obese and insulin-resistant mice: role for NADPH oxidase. American Journal of Physiology-Endocrinology and Metabolism. 2005 Feb;288(2):E405-11.

[27] Bergman RN, Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends in Endocrinology & Metabolism. 2000 Nov 1;11(9):351-6.

[28] Kusminski CM, Shetty S, Orci L, Unger RH, Scherer PE. Diabetes and apoptosis: lipotoxicity. Apoptosis. 2009 Dec;14(12):1484-95.

[29] Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocrine reviews. 2002 Oct 1;23(5):599-622.

[30] Boden G, She P, Mozzoli M, Cheung P, Gumireddy K, Reddy P, Xiang X, Luo Z, Ruderman N. Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-κB pathway in rat liver. Diabetes. 2005 Dec 1;54(12):3458-65.

[31] Boden G. Effects of free fatty acids (FFA) on glucose metabolism: significance for insulin resistance and type 2 diabetes. Experimental and clinical endocrinology & diabetes. 2003 Jun;111(03):121-4.

[32] Thakur P, Kumar A, Kumar A. Targeting oxidative stress through antioxidants in diabetes mellitus. Journal of drug targeting. 2018 Oct 21;26(9):766-76.

[33] Koya D, Hayashi K, Kitada M, Kashiwagi A, Kikkawa R, Haneda M. Effects of antioxidants in diabetes-induced oxidative stress in the glomeruli of diabetic rats. Journal of the American Society of Nephrology. 2003 Aug 1;14(suppl 3):S250-3.

[34] Marrazzo* G, Barbagallo* I, Galvano F, Malaguarnera M, Gazzolo D, Frigiola A, D'Orazio N, Li Volti G. Role of dietary and endogenous antioxidants in diabetes. Critical reviews in food science and nutrition. 2014 Dec 2;54(12):1599-616.

[35] Cao H, Xie Y, Chen X. Type 2 diabetes diminishes the benefits of

dietary antioxidants: Evidence from the different free radical scavenging potential. Food chemistry. 2015 Nov 1;186:106-12.

[36] Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. Journal of physiology and biochemistry. 2001 Mar;57(1):43-56.

[37] Brigelius-Flohé R, Traber MG. Vitamin E: function and metabolism. The FASEB Journal. 1999 Jul;13(10): 1145-55.

[38] Niki E, Traber MG. A history of vitamin E. Annals of Nutrition and Metabolism. 2012;61(3):207-12.

[39] Fardoun RZ. The use of vitamin E in type 2 diabetes mellitus. Clinical and Experimental Hypertension. 2007 Jan 1;29(3):135-48.

[40] Tuzcu M, Baydas G. Effect of melatonin and vitamin E on diabetes-induced learning and memory impairment in rats. European journal of pharmacology. 2006 May 10;537(1-3): 106-10.

[41] Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. Diabetes care. 2000 Jun 1;23(6):733-8.

[42] Lonn E, Yusuf S, Hoogwerf B, Pogue J, Yi Q, Zinman B, Bosch J, Dagenais G, Mann JF, Gerstein HC. Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE study and MICRO-HOPE substudy. Diabetes care. 2002 Nov 1;25(11):1919-27.

[43] Linster CL, Van Schaftingen E. Vitamin c. The FEBS journal. 2007 Jan 1;274(1):1-22.

[44] Will JC, Byers T. Does diabetes mellitus increase the requirement for vitamin C?. Nutrition reviews. 1996 Jul 1;54(7):193-202.

[45] Lee DH, Folsom AR, Harnack L, Halliwell B, Jacobs Jr DR. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes?. The American journal of clinical nutrition. 2004 Nov 1;80(5):1194-200.

[46] Som S, Basu S, Mukherjee D, Deb S, Choudhury PR, Mukherjee S, Chatterjee SN, Chatterjee IB. Ascorbic acid metabolism in diabetes mellitus. Metabolism. 1981 Jun 1;30(6):572-7.

[47] Gaede P, Poulsen HE, Parving HH, Pedersen O. Double-blind, randomised study of the effect of combined treatment with vitamin C and E on albuminuria in type 2 diabetic patients. Diabetic Medicine. 2001 Sep;18(9): 756-60.

[48] Young IS, Torney JJ, Trimble ER. The effect of ascorbate supplementation on oxidative stress in the streptozotocin diabetic rat. Free Radical Biology and Medicine. 1992 Jul 1;13(1):41-6.

[49] Packer L, Witt EH, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. Free radical biology and medicine. 1995 Aug 1;19(2):227-50.

[50] Budin SB, Othman F, Louis SR, Bakar MA, Radzi M, Osman K, Das S, Mohamed J. Effect of alpha lipoic acid on oxidative stress and vascular wall of diabetic rats. Rom J Morphol Embryol. 2009 Jan 1;50(1):23-30.

[51] Vallianou N, Evangelopoulos A, Koutalas P. Alpha-lipoic acid and diabetic neuropathy. The review of diabetic studies: RDS. 2009;6(4): 230.

[52] Dkhil MA, Zrieq R, Al-Quraishy S, Abdel Moneim AE. Selenium nanoparticles attenuate oxidative stress and testicular damage in

streptozotocin-induced diabetic rats. Molecules. 2016 Nov;21(11):1517.

[53] Reddi AS, Bollineni JS. Selenium-deficient diet induces renal oxidative stress and injury via TGF-β1 in normal and diabetic rats. Kidney international. 2001 Apr 1;59(4):1342-53.

[54] Asemi Z, Jamilian M, Mesdaghinia E, Esmaillzadeh A. Effects of selenium supplementation on glucose homeostasis, inflammation, and oxidative stress in gestational diabetes: Randomized, double-blind, placebo-controlled trial. Nutrition. 2015 Oct 1;31(10):1235-42.

[55] Truong VL, Jun M, Jeong WS. Role of resveratrol in regulation of cellular defense systems against oxidative stress. Biofactors. 2018 Jan;44(1):36-49.

[56] Tian X, Liu Y, Ren G, Yin L, Liang X, Geng T, Dang H, An R. Resveratrol limits diabetes-associated cognitive decline in rats by preventing oxidative stress and inflammation and modulating hippocampal structural synaptic plasticity. Brain research. 2016 Nov 1;1650:1-9.

[57] Zhang H, Zhang J, Ungvari Z, Zhang C. Resveratrol improves endothelial function: role of TNFα and vascular oxidative stress. Arteriosclerosis, thrombosis, and vascular biology. 2009 Aug 1;29(8):1164-71.

[58] Schmatz R, Perreira LB, Stefanello N, Mazzanti C, Spanevello R, Gutierres J, Bagatini M, Martins CC, Abdalla FH, da Silva Serres JD, Zanini D. Effects of resveratrol on biomarkers of oxidative stress and on the activity of delta aminolevulinic acid dehydratase in liver and kidney of streptozotocin-induced diabetic rats. Biochimie. 2012 Feb 1;94(2):374-83.

[59] Lee JS, Kim YR, Song IG, Ha SJ, Kim YE, Baek NI, Hong EK. Cyanidin-3-glucoside isolated from mulberry fruit protects pancreatic β-cells against oxidative stress-induced apoptosis. International Journal of Molecular Medicine. 2015 Feb 1;35(2):405-12.

[60] Suantawee T, Thilavech T, Cheng H, Adisakwattana S. Cyanidin Attenuates Methylglyoxal-Induced Oxidative Stress and Apoptosis in INS-1 Pancreatic β-Cells by Increasing Glyoxalase-1 Activity. Nutrients. 2020 May;12(5): 1319.

[61] Qi SS, He J, Yuan LP, Le Wu J, Zu YX, Zheng HX. Cyanidin-3-glucoside from black rice prevents renal dysfunction and renal fibrosis in streptozotocin-diabetic rats. Journal of Functional Foods. 2020 Sep 1;72: 104062.

[62] Rahman S, Mathew S, Nair P, Ramadan WS, Vazhappilly CG. Health benefits of cyanidin-3-glucoside as a potent modulator of Nrf2-mediated oxidative stress. Inflammo pharmacology. 2021 Mar 19:1-7.

[63] Speciale A, Canali R, Chirafisi J, Saija A, Virgili F, Cimino F. Cyanidin-3-O-glucoside protection against TNF-α-induced endothelial dysfunction: involvement of nuclear factor-κB signaling. Journal of agricultural and food chemistry. 2010 Nov 24;58(22):12048-54.

[64] Yu L, Zhang SD, Zhao XL, Ni HY, Song XR, Wang W, Yao LP, Zhao XH, Fu YJ. Cyanidin-3-glucoside protects liver from oxidative damage through AMPK/Nrf2 mediated signaling pathway in vivo and in vitro. Journal of Functional Foods. 2020 Oct 1;73:104148.

[65] Edirisinghe I, Burton-Freeman B. Anti-diabetic actions of Berry polyphenols–Review on proposed mechanisms of action. Journal of Berry Research. 2016 Jan 1;6(2):237-50.

[66] Pamplona R, Costantini D. Molecular and structural antioxidant defenses against oxidative stress in animals. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2011 Oct;301(4):R843-63.

[67] Djordjevic A, Spasic S, Jovanovic-Galovic A, Djordjevic R, Grubor-Lajsic G. Oxidative stress in diabetic pregnancy: SOD, CAT and GSH-Px activity and lipid peroxidation products. The Journal of Maternal-Fetal & Neonatal Medicine. 2004 Dec 1;16(6):367-72.

[68] Marangon K, Devaraj S, Tirosh O, Packer L, Jialal I. Comparison of the effect of α-lipoic acid and α-tocopherol supplementation on measures of oxidative stress. Free Radical Biology and Medicine. 1999 Nov 1;27(9-10):1114-21.

[69] Smith AR, Shenvi SV, Widlansky M, Suh JH, Hagen TM. Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress. Current medicinal chemistry. 2004 May 1;11(9): 1135-46.

[70] Goraca A, Piechota A, Huk-Kolega H. Effect of alpha--Lipoic acid on LPS-induced oxidative stress in the heart. Acta physiologica Polonica. 2009 Mar 1;60(1):61.

[71] Kaneto H, Kajimoto Y, Miyagawa JI, Matsuoka TA, Fujitani Y, Umayahara Y, Hanafusa T, Matsuzawa Y, Yamasaki Y, Hori M. Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. Diabetes. 1999 Dec 1;48(12):2398-406.

[72] Saleh NS, Allam TS, El-Rabeai RM, El-Sabbagh HS. Protective Effect of Some Egyptian Medicinal Plants Against Oxidative Stress in Rats. Alexandria Journal for Veterinary Sciences. 2018 Jul 1;58(1).

[73] Chandran R, Abrahamse H. Identifying plant-based natural medicine against oxidative stress and neurodegenerative disorders. Oxidative Medicine and Cellular Longevity. 2020 Sep 15;2020.