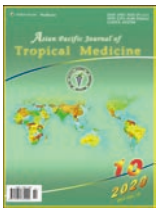

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Oxidative stress and antioxidants in diabetes mellitus

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ABSTRACT

Numerous studies have implicated oxidative stress in the development of complications of diabetes. During hyperglycemia, production of oxidant agents such as reactive oxygen species and reactive nitrogen species increases. This process, along with a decrease in the activity of antioxidant enzymes, induces oxidative stress in the body. This redox imbalance causes damage to vital biomolecules such as proteins, lipids and DNA and results in the generation of harmful products for the body. Mechanisms associated with the creation of oxidative stress conditions and subsequently complications of diabetes are explained through several pathways such as flux through the polyol pathway, intracellular production of advanced glycation end products precursors, protein kinase-C activation, and increased activities of the hexosamine pathway. On the other hand, the study of polymorphism in the antioxidant enzymes genes indicates that some of the gene polymorphisms reduce the antioxidant power of the enzymes. This article aims to review various studies to demonstrate the effect of oxidative stress on the pathogenesis of diabetes and the positive role of antioxidants on diabetic complications.

KEYWORDS: Diabetes; Antioxidants; Oxidative stress; Pathogenesis

1. Introduction

Metabolic diseases such as diabetes, cardiovascular disease and cancer are caused by a number of pathophysiological conditions in the body that are associated with a disruption of body redox balance[1]. Disturbance of redox balance and thus cellular dysfunction creates a pro-oxidative environment, meaning that there is no balance between producing reactive species such as reactive oxygen species (ROS) or reactive nitrogen species (RNS) and their elimination in the body. These conditions are called oxidative stress and finally lead to cellular and tissue damage and the onset of metabolic diseases. Therefore, in many studies aiming at preventing and treating metabolic disorders, the relationship between oxidative stress and the progression of metabolic diseases have been investigated[2,3]. There are various sources for producing free radicals, and reducing the power of free radical scavenging system in removing free radicals is one of the reasons for the increase in these reactive species, which finally leads to various metabolic disorders. Defense systems, which are responsible for the removal of free radicals in the body, include antioxidant systems such as Cu-Zn superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase[4].

Diabetes mellitus is also one of the metabolic disorders that causes severe complications such as retinopathy, neuropathy, nephropathy and cardiovascular disorders in individuals. Diabetes mellitus is a disease caused by inadequate insulin production by the pancreatic beta cells or insufficient insulin function, resulting in an increase in glucose level in the body and ultimately leading to a group of metabolic disorders in the body[2]. Diabetes is generally classified into two categories. Type 1 diabetes or insulin-dependent diabetes mellitus and type 2 diabetes or non-insulin-dependent diabetes mellitus[5]. In diabetes, hyperglycemia plays a major role in developing oxidative stress[6,7]. Several mechanisms are involved in the pathogenesis of diabetes induced by oxidative

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stress. Regarding the pathogenicity of diabetes, there is a clinical and genetic correlation between diabetes complications and oxidative stress. There is no definitive treatment for diabetes mellitus. We can only limit the progression of disease complications through medications and indeed we can control the disease to some degree[8]. Studies have shown that along with the use of commonly used drugs in the treatment of diabetes, the use of antioxidants, especially natural antioxidants, has had a significant positive effect on the disease's remedy. This article aims to review various studies to demonstrate the mechanisms that reflect the role of oxidative stress in pathogenesis of diabetes mellitus and the effect of antioxidants in treatment and prevention of the disease.

2. The diabetes epidemic and its increasing prevalence in Asia and the Pacific region

According to the International Diabetes Federation (IDF) statistics[9], the number of diabetic patients has been reported 415 million adults by year 2015 and this number has been proposed to rise to 642 million by the year 2040. It has been demonstrated that the biggest increase is in developing countries with low- and middle-income[9]. More than 60% of these patients are from Asian countries, almost one-third of them live in China. Various factors are considered to have role in the increased prevalence of diabetes including urbanization and rapid industrialization which make significant changes in lifestyle and epigenetic[10]. Lower increase of diabetes has been reported in developed countries in the Western Pacific region, including Australia and New Zealand[11]. IDF reports[11] showed that there were 138 million people with diabetes in the Western Pacific region in 2013, equivalent to 36% of the total population. Of these, China has the highest number: 113.9 million adults. After China, India is the next. Meanwhile, Tokelau, and other small countries in the Pacific Islands show a very high prevalence of diabetes. Given that obesity is the major cause of type 2 diabetes, the Pacific Island nations have been ranked high on the list of obesity and type 2 diabetes statistics[11].

South Asian countries, which include about one-fifth of the world's population, are also at high risk of developing type 2 diabetes. IDF forecasts indicate an increase in diabetes in South Asia to 120.9 million by 2030. The highest incidence of diabetes is in an Indian Ocean island, Mauritius which has the largest Asian Indian population[11].

Among the special characteristics that the people of South Asia have, the incidence of diabetes can be mentioned as abdominal obesity, higher rates of insulin resistance, early incidence of diabetes at lower BMI levels, and familial aggregation of diabetes[12]. The diabetes epidemic and its social and economic consequences in Asia and the Pacific is a worrying event worldwide. Prevention requires public health planning to provide resources and take necessary steps, such as implementing lifestyle changes at social level and providing healthy diets and sufficient mobility in the life plan[10].

3. Pathophysiology of diabetes

The intake of glucose and its consumption by muscle and fat cells are stimulated by insulin. Also glycogenolysis and gluconeogenesis in the liver tissue and lipolysis in adipose tissue are inhibited by insulin[13]. If insulin does not function properly, these processes are directed in the opposite direction. Failure to remove glucose by cells leads to an increase in extracellular glucose and a decrease in glucose levels inside the cells. Subsequently, in cells, lipolysis increases, fatty acid and diabetic ketoacidosis increase, and the synthesis of proteins and gamma globulins are reduced. Due to an increase in extracellular glucose, there may be consequences such as hyperglycemic coma and osmotic diuresis[5].

4. Complications of diabetes

Complications of diabetes include metabolic acute complications and systemic late complications which can be classified into microvascular and macrovascular degeneration complications[5]. Acute complications include hypoglycemia, hyperglycemia, hyperosmolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA). Systemic late complications include eye problems (retinopathy), foot problems, heart attack and stroke, kidney problems (nephropathy), nerve damage (neuropathy), gum disease and other mouth problems as well as related conditions like cancer and sexual problems in men and women. Retinopathy, nephropathy, neuropathy, and foot problems are considered microvascular degeneration, while cardiovascular disease, stroke and peripheral artery disease (PAD) are considered macrovascular degeneration[5,14].

5. Parameters involved in oxidative stress and diabetes mellitus

Free radicals are highly unstable and include reactive chemical units with a specific property having one or more unpaired electrons[15]. Free radicals are essential for intracellular signaling pathways and also for extracellular-signal-regulated kinase pathways that affect gene expression[16]. Various factors are the source of free radicals in cells and their surroundings, including: radiations, chemicals,

RNS, ROS, smoking, neutrophils and macrophages production and industrial effluents. Different types of ROS include superoxide anion ($O_2\cdot$), peroxyl ($RO_2\cdot$), alkoxyl ($RO\cdot$), hydroperoxyl ($HO_2\cdot$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), hypochlorous acid ($HOCl^-$), ozone (O_3), and different types of RNS include nitric oxide ($NO\cdot$), peroxynitrite (ONOO-), alkyl peroxynitrites (ROONO), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4), nitrous acid (HNO_2), nitronium anion (NO^{2+}), nitroxyl anion (NO^-), nitrosyl cation (NO^+), nitryl chloride (NO_2Cl), nitrate ($NO3^-$)[5,17].

In addition, free radicals have deleterious effects and the body uses various antioxidant systems to defend these toxic effects of free radicals. But when the balance between the amount of free radicals and the antioxidant power of the body is disrupted, the body suffers from oxidative stress. Oxidative stress, with cellular impairment, ultimately leads to cell death, and the association of oxidative stress with the pathogenesis of more than 50 diseases has been identified so far[5].

It has been shown in various studies that free radicals play an important role in damaging proteins, lipids, and DNA, resulting in various disorders such as diabetes mellitus, cancer or rheumatoid arthritis[18].

Medications are among those that may cause toxicity in tissues and organs by inducing oxidative stress[19]. Anti-inflammatory drugs such as diclofenac which causes nephrotoxicity and hepatotoxicity are one of these groups. The use of these drugs leads to an increase in hydroxylation of mediators during oxidative stress and dysfunction of mitochondria[19]. Antiretroviral drugs such as azidothymidine that have side effects such as skeletal myopathy and cardiac toxicity are another example of these drugs. Consumption of these drugs increases apoptosis and the level of ROS, which in turn the level of NOS and the expression of superoxidase dismutase/catalase are increased to protect the body against toxicity[19]. Antineoplastic drugs such as doxorubicin which cause cardiac toxicity, may lead to lipid peroxidation, mitochondrial dysfunction and apoptosis[20]. Hepatotoxicity induced by paracetamol (from analgesic drugs) is associated with an increase in proapoptotic proteins and inflammation and mitochondrial dysfunction[21]. Consumption of antineoplastic drugs such as cisplatin is associated with an increase in the amount of radical hydroxyl, hydrogen peroxide and superoxide, and a decrease in GSH-peroxidase and GSH-reductase and apoptosis[19]. Consumption of antipsychotic drugs such as chlorpromazine is also associated with the creation of singlet oxygen and superoxide against UVA/B irradiation[22]. Table 1 presents various sources of oxidative stress in diabetes.

Table 1. Sources of oxidative stress in diabetes mellitus.

Sources	Examples
Medications	Anti-inflammatory drugs such as diclofenac
	Antiretroviral drugs such as azidothymidine (AZT)
	Antineoplastic drugs such as doxorubicin
	Antipsychotic drugs such as chlorpromazine
Decreased antioxidant defense	Decrease in glutathione level
	Decrease in antioxidant systems (catalase, SOD, GPx)
	Decrease in concentration of vitamins such as vitamin E, C
	Alteration in concentrations of other antioxidants (ubiquinol, carotene, uric acid)
Alteration in enzymatic pathways	Increased polyol pathway activity
	Decreased glyoxalase pathway activity
	Alteration in mitochondrial oxidative metabolism
	Altered prostaglandin and leukotriene metabolism
Other sources	Ischaemia-reperfusion injury
	Hypoxia
	Pseudohypoxia
	Hyperglycaemia
	Autoxidation of carbohydrates
	Autoxidation of fatty acids in triglycerides, cholesteryl esters and phospholipids
	Glycation and glycoxidation

In this regards, measuring some biomarkers can show the relationship between oxidative stress and diabetes[23]. In the following, the biomarkers of oxidative stress in diabetes are reviewed.

Biomolecules and antioxidant system molecules are subjected to changes in exposure to ROS. These modified molecules are known as biomarkers associated with oxidative stress in studies[24]. In many studies, it has been shown that the concentration of biomarkers of oxidative stress in diabetes mellitus is significant. Therefore, in studies on diabetes, the levels of biomarkers related to lipid peroxidation, glycoxidation, amino acid oxidation, DNA oxidation and lipoxidation reactions are measured[25]. Generally, oxidative stress biomarkers in diabetes are as follows.

5.1. Lipid peroxidation and products of lipid peroxidation

One of the side effects of diabetes mellitus is the disorder of lipid profile, which results in increased lipid peroxidation. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are highly reactive aldehydes that are produced as a result of peroxidation of lipids. MDA is one of the oxidative stress biomarkers produced as a result of lipid peroxidation, and its measurement in plasma, serum, and many other tissues in diabetic studies is always considered[26]. One of the reasons is that oxidative damage plays an important role in the development of diabetes complications and is the increase of MDA levels in diabetic patients, especially in atherosclerosis and neural disorders[27]. Other lipid peroxidation products include hydroperoxides, conjugated dienes, F2-isoprostanes dicarboxylic acids[28].

5.2. Protein oxidation and products of protein oxidation

Proteins are critical bio-molecules that ROS cause changes in their structure and function[27]. Free radicals created by hyperglycemia react with some amino acids in proteins including cysteine, methionine and tyrosine which lead to the production of products that are important diagnostic criteria for diabetes such as glycated hemoglobin[29]. Carbonyls are important biomarkers for oxidative stress which are produced from the effect of ROS on proteins[27]. The interaction between reducing sugars or oxidized lipids and proteins or nucleic acids results in the production of advanced glycation end products (AGEs). AGEs cause changes in intracellular proteins, including proteins associated with genes regulation[30]. The interaction between plasma proteins and chlorinated oxidants results in the production of advanced oxidation protein products. Advanced oxidation protein products are part of the protein oxidation markers in chronic oxidative stress[31]. O-tyrosine, o, o'-dityrosine, 3-chlorotyrosine, 3-nitrotyrosine, dihydroxyphenylalanine, protein disulfides, methionine sulfoxide, hydroperoxides of isoleucine, leucine, valine, protein carbonyls-adipic semialdehyde and 2-oxohistidine are considered primary products of protein oxidation[32] and AGEs or pentosidine are considered secondary products of protein oxidation[30]. Fructosamine and glycated hemoglobin levels are considered nonenzymatic glycosylated proteins[29].

5.3. Levels of antioxidants e.g. vitamins and glutathione

Changes in concentration of vitamins can be good indicators for measuring diabetic disorders, because vitamins, like vitamins E, A and C are important components of antioxidant systems that eliminate oxidant agents[33].

Glutathione is a tripeptide that protects cells against free radicals due to its thiol group. It almost presents in all cells and is a significant biomarker for oxidative stress because reduction in its level in diabetes is significant[34,35]. The function of the glutathione reductase enzyme is to reduce glutathione oxide and the glutathione peroxidase enzyme is responsible for the change of peroxide to water. Oxidative stress products affect the function of these enzymes, and therefore the measurement of these enzymes is considered as diabetic index, which is widely used in studies[36].

5.4. Levels of antioxidant enzymes

The catalase enzyme is responsible for converting hydrogen peroxide (H_2O_2) into water (H_2O) and oxygen (O_2). H_2O_2 is a highly reactive molecule that results from the reactions related to energy metabolism, but its increase causes significant and irreparable damage to the cells[37]. So, the deficiency in the function of the catalase enzyme, strongly affects the balance of the antioxidant and pro-oxidant system in the cell. This is especially noticeable in pancreatic beta cells that contain large amounts of mitochondria. Therefore, the defect of this enzyme can lead to the development or spread of diabetes by damaging these cells[38].

The SOD enzyme is responsible for converting superoxide to other products with less harm for the cell, namely, molecular oxygen and peroxide (O_2 and H_2O_2). Therefore, this enzyme is considered as the first barrier against oxidative stress products and is one of the diabetic biomarkers that is highly desirable to measure its function in studies[27]. Other antioxidant enzymes include glutathione peroxidase and glutathione reductase[33].

5.5. Products of DNA oxidation

Products of DNA oxidation including modified bases, 8-oxo-2' deoxyguanosine and strand breaks are other biomarkers of oxidative stress in diabetes mellitus[39].

5.6. Nitrite concentration

Nitrite concentration is also considered as one of the biomarkers of oxidative stress in diabetes mellitus[29].

6. Polymorphisms in antioxidant genes involved in type 2 diabetes

A structural change in the mitochondrial Mn-SOD enzyme or SOD2 has been identified as a result of the presence of a polymorphism in the *A16V* gene (C/T) (rs4880). This change reduces antioxidant enzyme power to limited post-transcriptional transport and thus increases the risk of coronary artery disease and acute myocardial infarction disease. Individuals with valine variant are at risk[40]. In fact, oxidative stress can cause post-transcriptional changes in antioxidant enzymes. Some of these post-transcriptional changes in antioxidant enzymes can affect the function of the enzyme and, by reducing the antioxidant potential of the enzymes, increase the risk of a variety of diseases in a person[41]. In Table 2, the polymorphisms of a number of antioxidant genes involved in type 2 diabetes are presented.

7. Mechanisms involved in the pathogenesis of oxidative stress in diabetes mellitus

Hyperglycemia caused by diabetes involves all cells in any tissue,

Table 2. Important antioxidant gene polymorphisms in type 2 diabetes.

Enzyme	Location	Locus	Post-translational modification(s)	Polymorphisms	Disease risk	Reference
Mn-SOD (SOD 2)	Mitochondria	6q25.3	Tyrosine nitration of Tyr34, Tyr45, Tyr193	Ala16→Val	↑Carotid intimamedia thickness	[42]
Catalase	Peroxisomes	11p13	Tyrosine nitration Cys377 Chlorination	GA insertion in exon 2 G insertion in exon 2 T→G Substitution in intron 7-262C→T Substitution in exon 9	↑Diabetes mellitus ↑Homocysteine ↑Vascular oxidant stress	[43]
GPx-3	Extracellular	5q23	Not reported	Plasma7-SNP promoter haplotyope	↑Stroke ↑Cerebral venous thrombosis	[44]
GST	Intracellular (cytosolic)	17p13.1	Tyrosine nitration	M1*0 and T1*1 alleles	↑Coronary artery disease	[45]

but most cells exposed to hyperglycemia can control glucose transfer to the cell to keep glucose intolerance constant. In contrast, some types of cells are vulnerable to hyperglycemia including retinal capillary endothelial cells, mesangial cells in the kidney glomerulus, and neuronal and Schwann cells in peripheral nerves. These types of cell lack such ability. So, the complications of diabetes-induced tissue damage are actually damaging to these cells that cannot maintain a constant concentration of glucose in the cell in the face of hyperglycemia, and they are involved in the complications of diabetes[46]. It is necessary to study the mechanisms that occur inside these cells when we study the diabetes complications.

7.1. Polyol pathway flux

The aldose reductase enzyme typically converts toxic aldehydes into inactive alcohol. But in dealing with excessive glucose concentration in the cell, the aldose reductase enzyme catalyzes the conversion of glucose to sorbitol, instead of its usual function, which results in the consumption of NADPH cofactor and consequently, sorbitol is converted to fructose[47]. Reduced glutathione production is decreased due to a decrease in the amount of NADPH. Since glutathione is an important antioxidant for the cell, during this process, the sensitivity of the cell to oxidant agents increases inside the cell[48].

7.2. Intracellular production of AGE precursors

The three mechanisms associated with these products are as follows: these products alter intracellular proteins, the most effective of which are the proteins involved in regulating the transcription of the gene[49]. These AGE precursors may interfere with intercellular signaling and subsequent cellular function by exiting the cell and making changes to the extracellular matrix[50]. These AGE precursors can cause changes in circulating proteins, such as albumin, after exiting the cell and they are also attached to AGE receptors and lead to vascular damage by producing inflammatory cytokines and growth factors.

7.3. Protein kinase-C (PKC) activation

Intracellular hyperglycemia increases the production of diacylglycerol by activating the PKC isoforms. This molecule has several effects on the expression of the gene[51] which finally leads to an increase in the production of deleterious products and reduces the production of needed products in the normal functioning of the cells, for example, reduction in the synthesis of endothelial nitric oxide and increase in production of vasoconstrictor endothelin-1[52].

7.4. Increased hexosamine pathway activity

Following an increase in glucose level inside the cell, a large amount of glucose enters the glycolysis pathway. Some fructose 6-phosphate produced in the glycolysis pathway enters the signaling process which is finally converted to glucosamine-6 phosphate by the enzyme glutamine-fructose-6 phosphate amidotransferase and then is converted to uridine diphosphate (UDP) N-acetyl glucosamine and N-acetyl glucosamine are bound to the serine and threonine residues existing in the transcription factors. Finally, this glucosamine may cause pathological changes in the expression of the gene[53,54]. Hyperglycemia disrupts the gene expression of glomerular cells by the same mechanism[55,56]. It also plays a role in the production of carotid artery plaques in type 2 diabetic patients by modifying the proteins of endothelial cells[57].

Studies in this field offer a unified mechanism for all of these pathogenic pathways. All of these hyperglycemia-induced mechanisms of pathogenesis induce their own effects through a unified pathway, and this unified pathway is the source of excessive production of superoxide in the electron transport chain in the mitochondria. In all types of cells that are impaired due to hyperglycemia, there is also an increase in the production of ROS[58]. Hyperglycemia induces mitochondrial superoxide production and superoxide poly ADP-ribose polymerase (PARP). Polymerase inhibits glyceraldehyde-3 phosphate dehydrogenase (GAPDH), and inhibition of GAPDH leads to all four pathogenicity mechanisms we studied above[59]. GAPDH inhibition increases glycolytic intermediates before GAPDH, such as 3-phosphate glyceraldehyde. Glyceraldehyde 3-phosphate is the main intracellular precursor of AGE which activates the AGE path. On the other hand, the glyceraldehyde 3-phosphate activates PKC which in turn activates the classic PKC pathway. While inhibiting GAPDH, fructose 6-phosphate is another intermediate which activates the hexose amine pathway and is converted to UDP-N-acetylglucosamine (UDP-GlcNAc) along the pathway, and eventually leads to an increase in glucose. This glucose is reduced by the enzyme aldose reductase along with consumption of NADPH[50].

Increase in glucose leads to the production of ROS and breakdown

of DNA strand. DNA damage also results in the activation of PARP. The PARP then produces ADP-ribose that binds to GAPDH as well as other nuclear proteins, which inhibits GAPDH[60,61].

On the other hand, insulin resistance in adipocyte cells increases free fatty acid (FFA), and after entering the FFA into macrovascular endothelial cells and increasing the amount of them in these cells, FFA oxidation occurs in the mitochondria and ultimately leads to an increase in the production of FADH, NADH, and subsequent increase in ROS production. The effect of ROS on cellular damage is also similar to that of the hyperglycemia described above[62].

8. Role of antioxidants in treatment and prevention of diabetes mellitus

Since there is no definitive treatment for diabetes, we can only limit the progression of disease complications through medications and indeed control the disease to some degree. The sulphonyl urea and biguanide drugs can be exemplified as the most effective medications for the treatment of non-insulin dependent diabetes mellitus[8]. and since it is known that each chemical drug has its own specific side effects, recently, the use of drugs with a natural herbal source is mostly welcomed by patients and physicians. Metformin is the only conventional drug from the herbal source and *Galega officinal* is widely used in the treatment of non-insulin dependent diabetes[8].

Considering that oxidative stress is the basis of many complications of diabetes, researchers have conducted extensive research into the antioxidant effects of various substances, including natural antioxidants from plant origin, to introduce substances with better and more effectiveness in their research to control diabetes[8].

A lot of studies have shown that antioxidants such as lycopene[63], retinol, α- and γ-tocopherol, β-cryptoxanthin[64] ascorbic acid[65] α- and β-carotene, lutein and zeaxanthin[66], which are present in various plants, greatly reduce the complications of diabetes. A study showed that the aqueous extract of *Chrysobalanus icaco*, which has antioxidant properties, was able to reduce blood glucose[67]. In other studies, the effects of antioxidant phytochemicals on reduction of complications of chronic diseases such as diabetes, heart disease and obesity have been confirmed and discussed in detail[68]. Phytochemicals regulate the activity of α-glucosidase and lipase due to their antioxidant properties, and reduce glycemic levels, improve pancreatic function, and have synergistic action with hypoglycemic drugs and thus are effective in improving diabetes[68]. In fact, the overall results of various studies suggest that the use of vegetables, fruits and seeds is effective in preventing complications of diabetes due to their antioxidant properties. However, there is little evidence that the use of an antioxidant alone can have a complete therapeutic effect, but the use of antioxidants can be part of the therapeutic process[8].

On the other hand, despite such studies that suggest the use of antioxidants in the process of improving the health of people, a large clinical trials have shown that even the high levels of a type of antioxidant can be harmful[69] because antioxidant removes free radicals by giving electrons to free radicals, but antioxidant may turn into a pro-oxidant in the absence of other suitable antioxidants and not being reinstated[69]. While the various antioxidants in fruits and vegetables act as an antioxidant chain, therefore, regarding the use of antioxidants in the treatment of diseases such as diabetes, it is recommended that vegetables, fruits and herbs containing high levels of antioxidants canreplace one single antioxidant in high amounts[69].

9. Conclusions and perspectives

In this paper, studies on the role of oxidative stress in the complications of diabetes are reviewed. The results suggest that oxidant products including ROS and RNS are increased by glucose metabolism and FFA *via* multiple pathways leading to oxidation of major bio-macromolecules such as lipids, nucleic acids and proteins, as well as nephropathy, neuropathy, and cardiovascular disease. In fact, oxidative stress plays a key role in the onset and progression of the complications of diabetes. Also, the overall results of various studies suggest that the use of antioxidants, especially those with multiple antioxidant biomolecules such as vegetables, fruits and seeds is effective in preventing complications of diabetes. However, large clinical trials have shown that high level of a type of antioxidant can be harmful, because antioxidant removes free radicals by giving electrons to free radicals, then it may turn into a pro-oxidant in absence of other suitable antioxidants. Various antioxidants in fruits and vegetables act as an antioxidant chain, therefore, regarding the treatment of diseases such as diabetes, it is recommended that vegetables, fruits and herbs containing multiple molecules of antioxidants be used instead of taking only one antioxidant in high dose. In sum, cohort studies with large samples as well as systemic and meta-analysis studies are needed to clearly clarify which kinds of antioxidant compounds and conditions have positive impacts on the recovery of diabetes.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Authors' contributions

G.M. and R.M. developed the idea, selected articles and wrote the manuscript writing. Both A.H. and L.Z. developed the revised and the edited manuscript. All the authors read and approved the final draft of the manuscript. R.M. supervised the project.

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