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The research and development on the antioxidants in prevention of diabetic complications

Mohammad Rahimi-Madiseh[1], Afsaneh Malekpour-Tehrani[2], Mahmoud Bahmani[3], Mahmoud Rafieian-Kopaei[1*]

[1]*Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*

[2]*Department of Social Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran*

[3]*Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*

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ABSTRACT

Diabetes mellitus can damage the eyes, kidneys, nerves and heart. Microvascular and macrovascular disorders are the leading causes of morbidity and mortality in diabetic patients. Hyperglycemia can increase the indicators of lipid peroxidation and oxidative stress in which free radicals have the main role in the pathogenesis of these complications. Therefore, antioxidants which combat oxidative stress should be able to prevent and repair free radicals induced damages. Although free radicals contribute to kidney damage, atherosclerosis, diabetes, heart disease, nephrotoxicity and hepatotoxicity; however, clinical trials do not uniquely confirm a substantial impact on diabetic damage. It seems that antioxidants in vegetables, fruits and grains help preventing diabetes complications; however, there is little evidence that taking single antioxidants such as vitamin E or vitamin C protect these complications. The findings about combination antioxidants are also complicated and not entirely clear. In this review paper we tried to present the role of oxidative stress on micro-vascular complications of type 2 diabetes mellitus. Other objective of this paper is to review the new findings about the role of various antioxidants on prevention and treatment of diabetes mellitus as well as its complications including retinopathy, nephropathy and neuropathy.

1. Introduction

The prevalence of diabetes among adults has been increased significantly worldwide. It has been predicted that the number of adults with diabetes will increase from 135 million in 1995 to 30 million in 2025. The age range of diabetic patients in developing and developed countries is between 45–64 and 63–65 years, respectively. Diabetes is the fourth leading cause of death globally and every 1 min 6 persons die from the complications of diabetes [1].

Diabetic causes arterial diseases in conjunction with neuropathy which accounts for more than 60% of all non-traumatic amputations in the United States. Diabetes mellitus and impaired glucose tolerance increase cardiovascular disease risk up to 8-fold [2]. Furthermore, new blood vessel growth is impaired in response to ischemia in diabetic patients, resulting in decreased collateral vessel formation in ischemic hearts and in non-healing foot ulcers [3].

A high-fat diet has also been shown to release free radicals and contribute to impairment of β-cell function and also damage to mitochondrial DNA. Interesting studies have shown that hyperglycemia even in non-diabetic rats can increase muscle protein carbonyl content and increase the levels of malondialdehyde and 4-hydroxynonenal, indicators of lipid peroxidation and oxidative stress. These biomarkers of insulin resistance and oxidative stress suggest that free radicals have significant role in the pathogenesis of insulin resistance and impaired insulin signaling [4]. Therefore, antioxidants which combat oxidative stress should be able to prevent and repair free radical induced damages.

Free radicals are mainly reactive oxygen species (ROS) consisting of superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO) and proxy nitrite. While on the one hand hyperglycemia increases free radical production, on the other hand it impairs the endogenous antioxidant defense system [5,6]. Antioxidant defense mechanisms include both enzymatic and nonenzymatic strategies. Common antioxidants

*Corresponding author: Mahmoud Rafieian-Kopaei, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran.
Tel/Fax: +98 33340709
E-mail: rafieian@yahoo.com
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include vitamins A, C and E, glutathione, and the enzymes superoxide dismutase, catalase, glutathione reductase and also α-lipoic acid, coenzyme Q10, several bioflavonoids, cofactors (folic acid, vitamins B1, B2, B6, B12), and antioxidant minerals (copper, zinc, selenium, and manganese) [7]. Medicinal plants are the most important source of antioxidants which seem to act on various diseases better than the above mentioned ones [8–10]. So, the aim of this study was to present the effect of oxidative stress on micro-vascular complications of type 2 diabetes. Better knowledge in this field can facilitate designing interventional studies for preventing or averting micro-vascular complications in diabetic patients. Other objective of this paper is to review the available data about the impacts of these two kinds of antioxidants on vascular complications of diabetes mellitus including retinopathy, nephropathy and neuropathy.

2. The mechanisms of diabetes induced tissue damage

Hyperglycemia, and in diabetic microvasculature, intracellular hyperglycemia, have been shown to cause tissue damage through 5 major mechanisms:

1. Increase in expression of the receptor for advanced glycation end products (AGEs) and its activating ligands;
2. Increase in intracellular formation AGEs;
3. Increase in flux of glucose and other sugars through the polyol pathway;
4. Activation of protein kinase C isoforms;
5. Overactivity of the hexosamine pathway.

All five mechanisms have been shown to be activated by mitochondrial overproduction of reactive oxygen species (ROS). In contrast, diabetic macrovascular and heart damage, are resulted from increased oxidation of fatty acids, resulting from pathway-specific insulin resistance [11].

Many cellular pathways that cause insulin resistance and diabetic complications have linked to the production of free radicals and oxidative stress. Early effects of elevated glucose may increase the presence of potentially protective pathways but prolonged exposure of elevated glucose can cause formation of ROS and can be detrimental even after glucose control. Excessive levels of free radicals cause damage to cell lipid membranes, cell proteins and nucleic acids, which finally may cause cell death [12,13]. Besides, elevation of ceruloplasmin during hyperglycemia is suggestive of elevated ROS. Oxidative stress can trigger the onset of diabetes mellitus by decreasing insulin sensitivity and damaging the β-cells of pancreas ROS can penetrate through β-cell membranes and destroy those cells [12].

Hyperglycemia can cause increased production of ROS in different cell types. For example with increase in age in type 2 DM in rat models, elevated levels of 8-hydroxydeoxy guanosine (8-OHdG) and hydroxynonenal (HNE)-modified proteins in pancreatic β-cells have been reported. Studies have shown that acute glucose surge in addition to chronic hyperglycemia can promote oxidative stress mechanisms during type 2 DM [12].

Oxidative stress and apoptotic cell death during disorders such as diabetes mellitus are significantly associated with impairment in cellular energy maintenance and mitochondrial function. ROS exposure can lead to the opening of the mitochondrial membrane permeability transition pore, reduction of mitochondrial β-nicotinamide adenine dinucleotide (NAD^+) stores, and thereby apoptotic cell injury. Free fatty acids also can lead to ROS release, mitochondrial DNA damage, and impaired pancreatic β-cell function [14].

ROS can oxidize the DNA, protein and lipid and have an important role of chronic diseases like diabetes [15]. Elevated oxidative stress in diabetics is claimed to promote the development of myocardial injury, retinopathy, nephropathy, and neuropathy. The possible mechanisms of oxidative stress in developing these complications include glucose autoxidation, decreased tissue concentration of low molecular weight antioxidants like glutathione and vitamin E, and deteriorated activation of antioxidant defense enzymes such as catalase and superoxide dismutase (SOD) [1]. Experimental and clinical studies indicate that increase in oxidative stress may be responsible for progressing risk of cardiovascular diseases in diabetic or insulin-resistant states because of elevated levels of glucose [16–18]. Common risk factors for cardiovascular diseases amongst non-diabetic, insulin-resistant, and diabetic patients are reasonable because pathologies for cardiovascular diseases amongst these three groups of patients are very similar, although the progression and severity of the pathologies are not the same. However, it is not clear whether oxidative stress is causing micro-vascular pathologies because micro-vascular pathologies are noticed only in the diabetic state and are freely associated with hyperglycemia. In contrast, microvascular pathologies such as predicate loss and meningeal expansion, which contribute to diabetic retinopathy and nephropathy, respectively, are not reported in the aging populations or insulin-resistant state in spite of the fact that they experience oxidative stress to a similar level as diabetes [19].

Thus, an increase in oxidative stress induced by free fatty acids, lipids, or other processes is not sufficient to cause micro-vascular complications of diabetes. It is still possible that oxidative stress may promote the micro-vascular pathologies although it is unlikely that micro-vessel pathologies of diabetes are initiated by oxidative stress [15].

Lastly, the damage caused by oxidative stress is likely to be tissue specific because hyperglycemia appears to increase oxidant production in many cell types and tissues that do not manifest significant pathologies [19].

3. Oxidative stress and diabetic retinopathy

Diabetic retinopathy is one of the most important causes of blindness in adults. The reasons of this complication are micro-vascular damage, swelling of blood vessels and fluid leak. If diabetic retinopathy not prevented, new vessels grow and finally retinal detachment will be occurred [20]. The occurrence of this disease depends on the duration of diabetes and rarely develops in first few years of diabetes but the incidence increases to 50% by 10 years and 90% by 25 years of diabetes. The increase in survival of diabetic patients has been lead to increase in prevalence of diabetic retinopathy. The retina has high content of polysaturated fatty acids and has the highest uptake of oxygen and also highest oxidation of glucose. As a result retina is more prone to oxidative stress. The correlation between hyperglycemia, oxidative stress and changes in the redox homeostasis is the main phenomenon in the pathogenesis of diabetic retinopathy. It has been suggested that oxidative stress contributes not only to the development of diabetic retinopathy but also in the resistance of it even

after good glycemic control. The reason that diabetic retinopathy is resistant to reverse might be due to accumulation of damaged molecules and ROS that are not easily removed [1,20] It has been shown that membrane lipid peroxidation and oxidative damage to DNA (indicated by 8-hydroxy 2deoxyguanosine:8- Hodge), the result of ROS-induced damage, are raised in the retina in diabetes [21].

Since oxidative stress shows an imbalance between excess formation and\or impaired removal of ROS, the antioxidant defense system of the cell is crucial part of the overall oxidative stress experienced by a cell [9,22]. In diabetes the activities of antioxidant defense enzymes responsible for scavenging free radicals and maintaining redox homeostasis such as SOD, glutathione reeducates, glutathione peroxidase, and catalase are decreased in retina [23]. Further, the cell is equipped with intracellular antioxidant, GSH, that is the main defense of the cell. It can act as a scavenger of ROS and modulate intracellular redox state. The level of this intracellular antioxidant is diminished in the retina in diabetes and enzymes responsible for its metabolism are compromised [24]. Not only this antioxidant defense, but also nonenzymatic antioxidants such as vitamin C, vitamin E and β-carotene that exist biologically for the redox homeostasis regulation are also decreased during oxidative stress in hyperglycemic state [25]. The high consumption of oxygen and exposure to visible light makes the retina highly susceptible to oxidative stress. Studies have consistently shown that photo-chemical injury is attributable to oxidative stress and the antioxidants like vitamin C, vitamin E and vitamin A protect against this type of injury [25]. Hence for the early detection of diabetic retinopathy and its prevention it is advisable to estimate the markers of oxidative stress. Also, the diet of these patients should contain a recommended dietary allowance of vitamins to allow the non-enzymatic and enzymatic antioxidant systems to respond to oxidative stress which is observed in diabetic patients.

4. Oxidative stress and diabetic neuropathy

More than fifty percent of all patients with diabetes develop neuropathy, a progressive deterioration of nerves that leads to peripheral and autonomic nerve dysfunction. Diabetic neuropathy is the most common cause of amputation and failure of autonomous system [26]. The lifelong chance of undergoing one or more amputation in a patient with diabetes mellitus is 15% [27]. In diabetic state, accumulation of superoxide, increase in polio–pathway activity, advanced gyration end products (AGE) accumulation, protein kinase C (PKC) activity and hexamine flux trigger progressive cellular dysfunction. In nerve, the confluence of metabolic and vascular impairment result in neuron dysfunction and loss of neurotropic support, and in long term can mediate neuron, Schwann cell and glial cell apoptosis of the peripheral nervous system [28].

Animal studies with experimental diabetes have shown that nerve growth factor (NGF), neurotrophin-3 (NT-3), colliery neutrophil factor and insulin like growth factor-I (IGF-I) have been decreased and were correlated with presence of neuropathy [29].

Hedgehog proteins are essential for development of nervous system. Desert hedgehog is found exclusively in Schwann cells and is necessary in peripheral nerve patterning. After 10 weeks of experimental diabetes, a decrease in the expression of desert hedgehog gene was found. This decrease correlates with several established physiological biochemical markers of induced diabetes, including motor and sensory nerve conduction velocities, diminish in blood flow of nerve, decreased NGF and neuropeptide levels and decreased pain threshold in response to heat [30].

To prevent or avert the complications of diabetes including neuropathy, numerous studies have been done using antioxidant agents and some of them have shown promising results. High doses of singe-antioxidant agents like vitamin E or vitamin C may disturb the antioxidant-provident balance of cell systems. It has been suggested that mixture of antioxidant therapies possibly in combination with some trace elements and vitamins that improve metabolic processes can provide a better choice for treatment. Monitoring the patients antioxidant reserves also may clear development of defects that could be diminished by changing the therapeutic antioxidant regimen [10,31]. Therefore, until we can completely control blood glucose level, therapies like antioxidants that are targeted against oxidative stress remain most promising way to prevent neuropathy and other diabetic complications.

5. Oxidative stress and diabetic nephropathy

As it was mentioned, ROS is permanently produced in physiological conditions and effectively eliminated by several intra and extracellular, antioxidant systems. Numerous studies on experimental models of both immune and nonimmune glomerular injury demonstrated ROS to be first agent in the pathogenesis of these disorders and showed that the kidney is susceptible to oxidative stress [32–36]. Hyperglycemia not only because of generation of more ROS but also because of attenuation of the scavenging enzymes is a pathogenetic factor of long-term complications of diabetes [37–41].

In order to establish a role for oxidative stress in diabetic nephropathy it has been demonstrated that oxidative stress is elevated in diabetic kidney before the clinical signs of nephropathy. The half-life of ROS is extremely short and as a result direct measurement of ROS in tissue is difficult, so the endogenous end products of ROS have been measured to address the involvement of oxidative stress in a given pathologic state [42–44]. Lipid peroxidation of unsaturated fatty acids, one of the radical reactions, has been an index of increased oxidative stress and cytotoxicity. Studies have shown that albuminuria that is a marker of glomerulopathy in diabetes has significantly higher levels of lipid peroxides in plasma, urine and renal proximal tubes [45–47] and this finding suggests that oxidative stress are increased in diabetic kidneys [48].

Moreover, 8-hydroxy deoxyguanosine(8-OHdG) which is an oxidized purine residue in DNA, has been accepted as a good marker of oxidative tissue injury. Formation of 8-OHdG was also elevated in the kidney and provided additional evidence that oxidative stress is the main cause of diabetic nephropathy [48].

Possible changes in the repair system for 8-OHdG in addition to an increased production of ROS, might play a role in such oxidative damage in the kidney of diabetic patients [49]. Typical lesions of kidney affected by diabetes are seen in glumeruli and include thickening of capillary basement membrane with mesangium expansion, resulting in diffuse, nodular glomerulosclerosis [50,51].

Expansion of the glomerular mesangium is one of the most important factors in the loss of filtration function. Glucose produced a dose-dependent increase in lipid peroxidation in

cultured meningeal cells, which is supportive of increased lipid peroxidation in diabetic glomeruli [52]. Hyperglycemia-induced oxidative stress plays a major role in expansion of extracellular matrix and glucose–induced collagen production was effectively prevented by two antioxidants, taurine and vitamin E [53]. Although increased superoxide generation in hyperglycemia is a key event in activation of other pathways, it is only a first step in generating endothelial dysfunction [54–56].

Nitric oxide (NO) plays a central role in modulating endothelial function [57,58]. Metabolism of L-arginine produces NO by nitric oxide synthase (NOS), and has three isoforms: brain (bNOS), endothelia (eNOS) and inducible type (iNOS). Hyperglycemia is a stimulating factor for inducing iNOS [59] and mitochondrial-generated superoxide can inhibit eNOS. The superoxide anion can reduce NO, thereby diminishing the efficacy of this strong endotheliom-derived vasodilator and during hyperglycemia, availability of NO is reduced [59].

When endothelial cells respond to high glucose, reactive nitrogen and oxygen species production occurs [57,60]. These reactive agents trigger DNA single-strand breakage, and as it was mentioned above, increased amounts of 8-hydroxyguanine and 8-hydroxydeoxy guanosine (markers of DNA damage due to oxidative stress) can be found in both the plasma and tissues of diabetic rats. These concentrations are correlated and can be decreased by control of hyperglycemia and by using antioxidants probucol and vitamin E [61].

As previously mentioned, convincing evidence is now available about the effect of oxidative stress in the development of diabetic complications. However, clinical trials with antioxidants, especially with vitamin E have not demonstrated any benefits [62].

It has recently been suggested that treatment with antioxidants like vitamin E is limited to scavenging already-produced oxidants and should be considered more symptomatic rather than a routine therapy for vascular oxidative stress [63]. New insights into the mechanisms leading to the oxidative stress generation in diabetes are now available and these findings have led to more assessment of new antioxidant molecules that hopefully in the future may inhibit at an early stage, the mechanism leading to diabetic complications like diabetic nephropathy [43,64,65].

6. Medicinal plants antioxidants and diabetic complications

Sustained hyperglycemia can damage the eyes, kidneys, nerves and heart and antioxidants are able to reduce the diabetes and none diabetes damages [66–68]. Microvascular (nephropathy and retinopathy) and macrovascular (atherosclerotic) disorders are the leading causes of morbidity and mortality in diabetic patients [63]. As it was mentioned there is no preventive or curative method for diabetes mellitus. Therefore, there is a need to find out reliable treatments in slowing the progression of diabetic complications. Investigations on various approaches have shown promising results [69,70] Recently some plants have shown beneficial effects not only on renal function in diabetes mellitus [71,72], but also on renal toxicities induced by some drugs or toxins [73,74].

Since time immemorial, mankind has searched for medications to cure or prevent various diseases. A 5 000 year-old Sumerian clay slab has recently discovered describing the use of medicinal plants for the preparation of drugs [75]. In the late 19th and early 20th centuries, there was a steady decline in the therapeutic use of herbal medicines. Nevertheless, currently, due to the potent side effects of modern synthetic drugs and increasing contraindications to their usage, a popular resurgence has materialized for the use of medicinal plants [76,77]. Medicinal plants, mostly with antioxidant activity, are the major source of drugs for the treatment of oxidative stress induced complications. Nowadays, about half of the available drugs are estimated to be originated from plants [78].

The rebirth of herbal medicine, particularly in developed countries, is chiefly centered on renewed interest by society and advancing scientific information regarding plants. In this context therefore, it is important that the momentum of research into medicinal plants is maintained or even escalated [76]. Hence, studies with medicinal plants have shown promising effects in several disease conditions including diabetes [4,79], hyperlipidemia [80,81], pain [82,83], amnesia [84,85] and gastrointestinal [86,87] complications. Herbal preparations also have capacities to diminish drug and none drug induced toxicities [74,88,89].

Out of the two types of diabetes, the incidence of non-insulin dependent diabetes mellitus (NIDDM) is much higher than the insulin dependent one. The sulphonyl urea and biguanide drugs are valuable treatment for hyperglycemia in non-insulin dependent diabetes mellitus, but other than having side effects, they usually are unable to lower glucose level to within normal range [77].

Even insulin therapy does not reinstate a permanent normal pattern of glucose homeostasis, and carries an increased risk of hypoglycemia and atherogenesis. Medicinal plants have the advantage of having no or only few side effects [87,90,91]. Some of them have been used in traditional medicine from ancient times. Till today metformin is the only available drug derived from a medicinal plant *Galega officina* approved for the treatment of non-insulin dependent diabetes mellitus patients [92].

There are a lot of medicinal plants with anti-diabetic property; nearly all of them possess antioxidant activities. These plants might provide useful sources for the development of new drugs useful in the treatment of diabetes mellitus and its complications [4]. Herbal medicines seem to be a reliable source for new drugs. This section of the article reviews and emphasis the beneficial effects of some medicinal plants in prevention and treatment of diabetes-associated complications [92]. Current pre-clinical and clinical studies have demonstrated that many have beneficial effects on some processes in experimental animals. Modification of risk factors in diabetes has an impressive impact on morbidity and mortality in diabetic patients [70,93].

Hyperglycemia leads to increased oxidative stress and activation of polyol pathway, which may cause inflammation and renal damage [94]. Several plant extracts with hypoglycemic properties and protective activities against diabetes complications have been identified [93]. It has been shown that metformin, a biguanide hypoglycemic compound from a herbal source (*Galega officinalis*), may be useful in the prevention of kidney injury [70,92]. Some other herbal medicines such as curcumin from *Curcuma longa*, *Panax quinquefolium*, *Vitis vinifera* and glycosides from *Stelechocarpus cauliflorus* have also been shown to prevent diabete complications [93,94]. The active phytochemicals and the mechanisms responsible for activities of several herbal medicines have been identified. Some herbal medicines have a

positive impact on glucose homeostasis in diabetic patients. These plants have compounds effective on diabetes mellitus or impaired glucose tolerance. Some plants lower blood pressure or improve the renal and cardiovascular functions, which are often seen in diabetic patients. The active agents identified in these plants include polysaccharides, flavonoids, xanthones and peptides [95,96].

Increased activities and levels of antioxidants usually reduce diabetes complications. Antioxidants usually give electrons to free radicals. People with low intake of vegetables and fruits have been shown to beat greater risk for development of diabetes complications. Although free radicals contribute to kidney damage, atherosclerosis, diabetes, heart disease, nephrotoxicity and hepatotoxicity; however, clinical trials do not uniquely confirm a substantial impact on kidney damage [9,10]. It seems that antioxidant in vegetables, fruits and grains help preventing diabetes complications; however, there is little evidence that taking single antioxidants such as vitamin E or vitamin C protect against these complications. The findings about combination antioxidants are also complicated and not entirely clear [10,97]. Natural whole products, such as vegetables and fruits, seem to act as parts of elaborate networks and therefore, no single antioxidant can do the work of the whole ones [10,77,98].

7. Conclusion

Diabetes mellitus can damage the eyes, kidneys, nerves and heart. Microvascular and macrovascular disorders are the leading causes of morbidity and mortality in diabetic patients. Hyperglycemia increases oxidative stress in which ROS has the main role in the pathogenesis of these complications. Therefore, antioxidants which combat oxidative stress should be able to prevent and repair ROS induced damages. It seems that antioxidants in vegetables, fruits and grains help preventing diabetes complications; however, there is little evidence that taking single antioxidants such as vitamin E or vitamin C protect against these complications.

Conflict of interest statement

The author declares that there is no conflict of interest.

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