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Review Article

A Review on Oxidative Stress and Role of Antioxidants in Diabetes Mellitus

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Abstract

Diabetes is a wide spread systemic disease affecting a significant proportion of the population worldwide. There is increasing evidence that increased production and/or ineffective scavenging of Reactive Oxygen Species (ROS) may play a critical role in chronic diseases. Highly reactive ROS determines chemical changes in virtually all cellular components, leading to lipid peroxidation. Production of ROS and disturbance in antioxidant defense system in diabetic objects have been reported. Therefore, it seems reasonable that antioxidants can play an important role in the improvement of diabetes. There are many studies on the effects of antioxidants in the modulation of diabetes. The aim of this review was to summarize the central role of oxidative stress in the pathogenesis of diabetes and the prospective role of antioxidants to overcome lipid peroxidation through their free radicals scavenging properties.

Keywords: Oxidative stress; Antioxidants; Diabetes mellitus

Introduction

Diabetes Mellitus (DM) is a chronic disease characterized with either insulin deficiency or insulin resistance. Insulin is a hormone which is secreted by beta cells in the Langerhans Islets of pancreas and playing a role in carbohydrate metabolism regulation in association with glucagon. Regarding the insulin's effects on carbohydrates, almost in all tissues (except brain), insulin increases the facilitated diffusion of glucose into cells and shows an effect to reduce the blood glucose levels. Insulin secretion is related with increasing glucose level. It has been shown that it is closely related with intracellular enzymes and has a stimulating effect on transcription of glucokinase, pyruvate kinase, phosphofructo kinase and fructose-2,6 biphosphatase that are glycolytic and an inhibitory effect on transcription of phosphoenolpyruvatecarboxykinase that is gluconeogenetic. Besides being the primary regulator of carbohydrate metabolism, insulin also has an important effect on lipid and protein metabolisms that are interrelated with carbohydrate metabolism [1].

Types of diabetes mellitus

Diabetes mellitus has two broad categories defined as type1 (T1DM) and type2 (T2DM). Both types problems are the same, people suffer from diabetes mellitus needing to use external insulin usage for their life, T1DM divided two subunits. The first one is immunologic type T1DM, it is characterized pathologically by pancreatic beta cells destruction, and the second one is named idiopathic T1DM, is characterized with insulin deficiency, and in this type pancreatic beta cell destruction does not occurred. Type II diabetes (Non-Insulin dependent) is due to insulin secretory defect and insulin resistance. Gestational diabetes mellitus is any form of intolerance to glucose with onset or first recognition of pregnancy [2]. Both types of diabetes mellitus complications are classified as acute and chronic complications. Acute metabolic complications; diabetic ketoacidosis, ketoacidosis coma, hyperosmolar non-ketosis coma, lactic acidosis coma and hyperglycemia coma as a result of treatment complication. Diabetic effect of different tissues and organs are classified into chronic diabetic complication as neuropathy, nephropathy, and retinopathy, and macrovascular complications as atherosclerosis, paresis, myocardial infarction and gangrene. In general, complications of diabetes mellitus can be categorized into metabolic acute complications and systemic late complications [3,4].

Oxidative stress and antioxidants

Oxygen is one of the important components of life. However in some circumstances, this oxygen may be a killer of cells when it generates reactive species that causes necrosis, organ damage [5] and ultimately the cell death (Table 1). Reactive nitrogen and carbon species also cause oxidation by the generation of certain mechanism that interferes with the normal physiological processes inside the cell [6]. Oxidative stress can be defined as a disturbance in the balance between oxidants and antioxidants due to different factors such as aging, drug actions and toxicity, inflammation and/or addiction [7]. It is in general, excess formation or/and insufficient removal of highly reactive molecules. Oxygen is highly reactive specie that has the ability to become part of potentially harmful and damaging molecules; free radicals. Oxidative stress causes healthy cells of the body to lose their function and structure by attacking them. It is when the antioxidant level is limited that this damage can become

Table 1: Oxidative stress induced organ damage [5].

Lungs	Asthma, chronic bronchitis
Kidneys	Glomerulonephritis, chronic renal failure
Joints	Arthritis, rheumatism
Brain	Alzheimer's disease, parkinson's disease, memory loss, depression, stroke
Eyes	Cataract, retinal diseases
Fetus	Preeclampsia, IU growth restriction
Heart vessels	Arteriosclerosis, hypertension, ischemia, cardiomyopathy, heart failure
Multiorgans	Cancer, diabetes, inflammation, infection, aging

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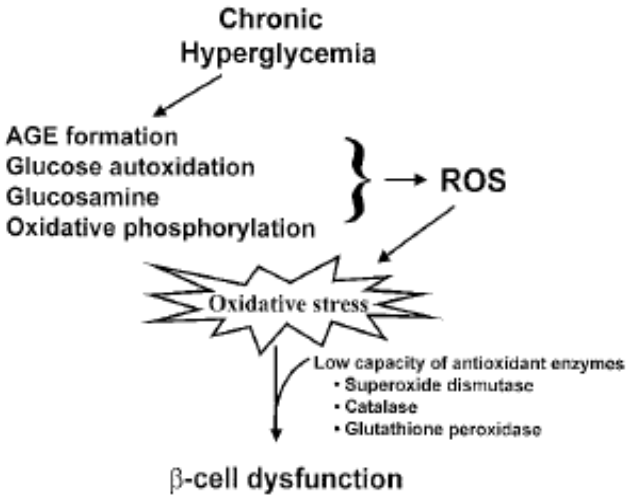

Figure 1: Oxidative stress in diabetes [13].

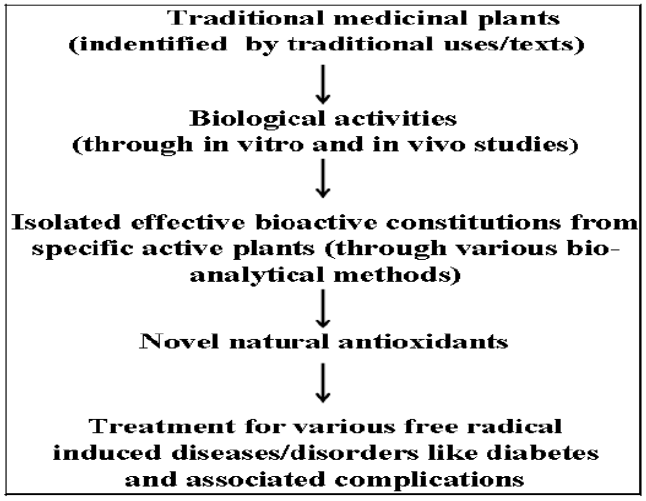

Figure 2: Medicinal plants and their uses as natural antioxidants [25].

debilitating and cumulative leading to several diseases [8].

Antioxidants are natural substances that may prevent or delay some types of cell damage. Antioxidants are found in many foods, including fruits and vegetables. There are several nutrients in food that contain antioxidants. Vitamin C, vitamin E, and beta carotene are among the most commonly studied dietary antioxidants. There are several species or molecules, endogenous (internally synthesized) or exogenous (consumed), that plays a role in antioxidant defense and may be considered as biomarkers of oxidative stress. Antioxidants can be divided as either chain breaking antioxidants or preventive antioxidants, based on their mechanism of action [9]. Different types of biological antioxidants include glutathione, vitamin C and E, cystine, and many others. Also, many plant-derived substances are known as phytonutrients or phytochemicals that possess antioxidant properties. Phenolic compounds such as flavonoids are such chemicals. These are found in several fruits, vegetables and green tea extracts.

Factors affecting oxidative stress in diabetes mellitus

Oxidative stress is increased in diabetes because of multiple factors. Among these factors, glucose autoxidation which is a dominant factor leading to the production of free radicals. Other factors include cellular oxidation/reduction imbalances and reduction in antioxidant defenses including decreased cellular antioxidant levels and a reduction in the activity of antioxidant enzymes that dispose of free radicals. Moreover, levels of some pro-oxidants such as ferritin and homocysteine are elevated in diabetes. Another important factor is the interaction of Advanced Glycation End Products (AGEs) with specific cellular receptors called AGE Receptors (RAGE). Elevated levels of AGE are formed under hyperglycemic conditions. Their formation is initiated when glucose interacts with specific amino acids on proteins forming a compound that then undergoes further chemical reactions. Glycation of protein alters protein and cellular function, and binding of AGEs to their receptors can lead to modification in cell signaling and further production of free radicals [10].

It is believed that oxidative stress plays important role in the development of vascular complications in diabetes particularly type 2 diabetes [11]. ROS level elevation in diabetes may be due to perturbations in antioxidant defense system. The variation in the levels of antioxidant enzymes makes the tissues susceptible to oxidative stress leading to the development of diabetic complications [12,13] (Figure 1). According to epidemiological studies, diabetic mortalities can be explained by an increase in vascular diseases other than hyperglycemia [11].

Oxidative stress and diabetic complications

Many evidences from experiments have given link between diabetes and oxidative stress by measuring various biomarkers that include DNA damage biomarkers and lipid peroxidation products. It is believed that in the onset and progression of late diabetic complication, free radicals have got a major role due to their ability to damage lipids, proteins and DNA [14]. A variety of pathological conditions are induced by oxidative stress such as Rheumatoid arthritis, Diabetes mellitus and cancer [15]. Biomarkers of oxidative stress in diabetes mellitus include proteins, lipids, and vitamins, enzymatic and non-enzymatic antioxidants [16-20].

Antioxidant Vitamins

Oxidative stress, the prevalence of oxidant factors over antioxidant mechanisms, plays a central role in the pathogenesis and progression of diabetes and its complications. Hence, it is likely that a substance known to reduce oxidative stress *in vivo* would reduce progression of cell damage in clinical diabetes. α-Lipoic acid has been reported to have a number of potentially beneficial effects in both prevention and treatment of oxygen-related diseases: for example, the enhancement of glucose utilization in type II diabetes [21] and the reduction of the development of diabetic complications [22]. Research on this compound is now lively in view of these potential benefits in diabetes [16]. observed that α-lipoic acid may reduce some oxidative stress in diabetes by alleviating lipid peroxidation through scavenging of free radicals, or by increasing the activities of antioxidant enzymes which then detoxify free radicals. The role of α-lipoic acid in the modulation of glutathione may be significant in the restoration of cell redox status and minimization of cell damage due to reactive oxygen species.

Several studies have reported that antioxidant vitamins and

supplements can help lower the markers indicative of oxidant stress and lipid peroxidation in diabetic subjects and animals. A number of authors have demonstrated that vitamin C and E and beta-carotene are decreased in diabetic patients and experimental animals [10,23]. The most frequently studied antioxidant vitamins are C and E. Vitamin E is a lipophilic antioxidant that interferes with the chain reaction of lipid peroxidations. Vitamin C is a hydrophilic molecule that can scavenge radicals, among them the hydroxyl radical. It is likely that vitamins C and E act in a synergistic manner, vitamin E primarily being oxidized to the tocopheroxyl radical and then being reduced back to tocopherol by vitamin C and glutathione. Vitamin C is the strongest physiological antioxidant acting in the organism's aqueous environment. It has been shown to be an important antioxidant, to regenerate vitamin E through redox cycling, and to raise intracellular glutathione levels. Thus vitamin C plays an important role in protein thiol group protection against oxidation [23]. In contrast to vitamin A, which is a group of unsaturated nutritional organic compounds, the vitamin C and E combination can also be safely used in high doses to help prevent diabetes and cardiovascular disease. However there is one report that shows a high vitamin C intake from supplements is associated with an increased risk of cardiovascular disease mortality in postmenopausal women with diabetes [24].

Plant Antioxidants

Recently, there has been a considerable interest in finding natural antioxidants from plant materials to replace synthetic ones [25] (Figure 2). Data from both scientific reports and laboratory studies show that plants contain a large variety of substances that possess antioxidant activity [26]. Phytochemicals with antioxidant effects include some cinnamic acids, coumarins, diterpenes, flavonoids, lignans, monoterpenes, phenylpropanoids, tannins and triterpenes [27]. Natural antioxidants occur in all higher plants and in all parts of the plant (wood, bark, stems, pods, leaves, fruit, roots, flowers, pollen, and seeds) [26]. Injury of plant cells, as well as mammalian cells, is associated with the activation of lipoxygenases, which catalyze the formation of hydroperoxides of polyunsaturated fatty acids; hydroperoxide radicals may react with fatty acids to produce dioxoenes, which are regarded as plant defense compounds. The occurrence of oxidative mechanisms in plants may explain why an abundance of antioxidant compounds have been identified in plant tissue [27]. Therefore it seems that plants particularly those with high levels and strong antioxidant compounds have an important role in improvement of disorders involving oxidative stress such as diabetes mellitus.

The complications in the existing diabetic treatment have led to the employment of natural resources either as a food supplement or as a medicinal formulation, as alternatives to the synthetic drugs. Indian traditional medicine formulates several herbs and is used in the treatment of various diseases since time immemorial [28]. Though they have proved effective, more recently, a huge amount of research has been underway to explain their effectiveness [29]. The expert committees of the World Health Organization (WHO) also advocate the use of herbal medicines over the drugs currently available for treatment of diabetes, as they have the potential not only to reduce the hyperglycemic state but also to reduce the secondary complications associated with it [30].

In this regard, banana (a member of Musaceae family) pseudostem, consumed as a vegetable in India, is recommended for diabetics in the Indian traditional medicine system (Ayurveda). In a previous study by [31], they established that the ethanol extract of banana pseudostem as a potent antihyperglycaemic agent and the most prevailing compounds identified by Gas Chromatography-Mass Spectrometry (GC-MS) were phytosterols. The identification of bioactives in ethanol extract and its *in vivo* antidiabetic effects remain to be elucidated.

Also, [32] suggested that administration of ethanol extract of banana pseudostem (EE) and its isolated compounds, stigmasterol and β-sitosterol, are potential antidiabetic herbal remedies in the management of diabetes and its associated complications. They restored the β-cells thereby stimulating them to produce insulin. The improved levels of insulin also positively promoted the activities of the glucose utilization and the glycogen storage pathways indicated by the measurement of insulin levels and also by the antihyperglycaemic effects, as well as the analysis of various metabolic enzymes involved in the pathways.

Plant polyphenols are among the most abundant phytochemicals present in the human diet. Polyphenols are the secondary metabolites synthesized by plants as part of their defense mechanism for survival during adverse conditions and to provide resistance against microbial infections [33]. Based on the large quantity of data available through clinical and epidemiological studies, polyphenols have received considerable interest for their presumed role in the prevention of various degenerative diseases [34,35]. Antidiabetic effect is one of the most intensely studied biological roles of polyphenols [35,36]. Grapes and their products, including red wine, are largely consumed dietary components all over the world. The observation of a lower incidence of coronary heart disease despite a high-fat diet in the French population, commonly referred to as the "French paradox", has also been attributed to a copious consumption of red wine made from grapes. This has stimulated interest in investigating whether grape polyphenols may offer consequential health benefits, including improved insulin sensitivity [37,38].

Plant based active components have a better complimentary potential to act against a number of free radical mediated diseases such as cancer and diabetes. Among those, polyphenols appear to be appropriate nutraceuticals and supplementary treatment option for various aspects of diabetes mellitus due to their biological properties. Phenolic acids constitute about one third of the total polyphenolic component in the diet and is categorized to two main classes, hydroxyl benzoic acid derivatives and hydroxyl cinnamic acid derivatives.

Supplementation with certain phytochemicals such as polyphenols or natural plant foods rich in these phytochemicals may be effective in improving human glucose and lipid disorders. Capsaicin, which is primarily contained in chili, exerts multiple pharmacologic and physiologic effects, such as analgesia, and anticancer, anti-inflammation, antioxidant and anti-obesity activities [39]. Moreover, capsaicin contained in chili may also reduce postprandial blood glucose and improve insulin resistance, although it did not prove to alter fasting plasma glucose in healthy humans in clinical trial [40,41]. Capsaicin may exert the above effects through the release of neuropeptides, such as substance P, calcitonin gene related peptide,

and other neurokinins from sensory nerve terminals [42].

Dietary factors play a key role in the development of various human diseases, including cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia thrombosis, hypertension and diabetes [43]. Medicinal plants continue to provide valuable therapeutic agents, in both modern medicine and in traditional system. The doubts about the efficacy and safety of the oral hypoglycemic agents have prompted a search for safer and more effective drugs in the treatment of diabetes [44]. In spite of the fact that insulin has become one of the most important therapeutic agents known to medicine, researchers have been making efforts to find insulin substitutes from synthetic or plant sources for the treatment of diabetes. Many herbs have remained as an alternative to conventional therapy especially in poor areas where insulin is not readily available [45].

Allium species such as onions and garlic are used as foodstuff, condiment, flavoring, and folk medicine. Garlic has attracted particular attention of modern medicine because of its widespread health use around the world, and the cherished belief that it helps in maintaining good health, warding off illnesses and providing more vigor. The biological responses of garlic have been largely attributed to reduction of risk factors for cardiovascular diseases and cancer, stimulation of immune function, enhanced detoxification of foreign compound, hepatoprotection, antimicrobial effect and antioxidant effect [43].

Onion was also a popular folk remedy. It is rich in flavonoids such as quercetin and sulfur compounds, such as allyl propyl disulfide that have perceived benefits to human health [46]. In addition, onion and garlic are rich in sulfur containing compounds mainly in the form of cysteine derivatives, *viz*. S-alkyl cysteine sulfoxides which are decomposed the enzyme alliinase into a variety of volatile compounds such as thiosulfinates and polysulfides during extraction. These compounds possess antidiabetic, antibiotic, hypocholesterolaemic, fibrinolytic, and various other biological effects. In addition to volatile substances in alliums, there are nonvolatile sulfur-containing peptides and proteins which have been shown to have potential health benefits [47,48]. El-Demerdash et al., showed that garlic and onion juices exerted antioxidant and antihyperglycemic effects and consequently may alleviate liver and renal damage caused by alloxan-induced diabetes in experimental animals.

Free radicals are reactive chemical species which are formed in normal physiology but becomes deleterious when they not quenched by antioxidant systems. A critical balance exists between Reactive Oxygen Species (ROS) production and antioxidant defense mechanisms [49]. Disturbances in this balance termed as oxidative stress seen in diabetes results in enhancement of lipid peroxidation causing cellular damage [50]. The lack of an effective antioxidant system in β-cells renders them susceptible to oxidative damage than other cell types [51]. Recently plant based therapies gains importance as they have been shown to regulate the oxidative complications of Diabetes mellitus [52].

Nigella sativa commonly named as black seed or black cumin is an annual herb incorporated in diets and everyday lifestyles to promote health and to treat diseases. Pharmacological and toxicological studies on Thymoquinone (TQ), the bioactive constituent of the essential oil of black seed shows diverse pharmacological properties such as anti-diabetic [53], antioxidative [54] and neuroprotective [55]. Sankaranarayanan and Pari suggested that administration of TQ to diabetic rats for 45 days significantly reversed the damage associated with diabetes [56]. They indicated that TQ exerts a protective action on pancreatic beta cell function and overcomes oxidative stress through its antioxidant properties. TQ administration significantly improved glycemic and antioxidant status in diabetic rats by enhancing insulin production and secretion from remnant beta cells of pancreas in streptozotocin nicotinamide induced diabetic rats. In addition, it protects tissues from peroxidative changes through its antioxidant properties.

Clove oil reportedly modulated physiological responses in streptozotocin-induced diabetic rats [57,58]. Food seasoning spice mixtures improved glucose metabolism and lipid profile in fructose fed hyperinsulinemic male Wistar rats [59]. The reduced plasma glucose and insulin levels, together with the favorable lipid profile, were possibly brought about through improved insulin-sensitizing actions of the active constituents. The spices improved the biomarkers of oxidative stress in the tissues of fructose-fed insulin-resistant rats [60]. Also, culinary herb and spice extracts inhibited protein glycation *in vitro* and the most potent inhibitors were extracts of cloves, ground Jamaican allspice, and cinnamon [61]. Insulin-like biological activity of clove and other culinary or medicinal plant aqueous extracts were also proven *in vitro* [62]. Moreover, dietary supplementation with cloves reduced tissue injuries, especially in the lens and cardiac muscles, and to a lesser extent in the liver but not the kidneys. Additionally, the cloves treatment significantly reduced blood sugar increases and lipid peroxidation in streptozotocin-induced diabetic rats by restoring the antioxidant enzyme levels. Cloves inhibited hyperglycaemia-induced oxidative tissue damage and cataract formation in the eye lens [63].

Rosemary, *Rosmarinus officinalis* L. (Labiatae), is an evergreen perennial shrub grown in many parts of the world [64]. It has been reported to possess a number of therapeutic applications in folk medicine in curing or managing of a wide range of diseases such as Diabetes mellitus, respiratory and gastrointestinal disorders, and inflammatory diseases [65,66]. The water decoction of rosemary leaves has been traditionally used to treat diabetic patients without much scientific evidence of its utility. Rosemary has been widely accepted as one of the species with the highest antioxidant [67]. It has long been recognized as having antioxidant molecules, such as rosmarinic acid, carnasol, and rosmaridiphenol which are found in ethanol-soluble fraction [67,68]. Hypoglycemic and hepatoprotective properties of the *Rosemarinus officinalis* have been reported by different research groups [69]. Rosemary extract was found to be a promising therapeutic agent for the treatment of diabetic-related diseases [70,71]. While, authors observed that the aqueous extract of *Rosmarinus officinalis* exhibited hypoglycaemic, antioxidant effects, in addition to improving renal function and reducing renal damage in diabetic rats because it contains a number of biologically active compounds, include antioxidants carnosic acid and rosmarinic acid in addition to other compounds such as ursolic acid, betulinic acid, rosmaridiphenol, and rosmanol.

Conclusion

In conclusion, this review emphasized the role of oxidative stress in Diabetes mellitus and the role of antioxidants in ameliorating the disturbance induced by free radicals. Oxidative stress has been demonstrated to play important role during diabetes, including impairment of insulin action and elevation of the complication incidence. Increase in the levels of oxygen and nitrogen free radicals is closely related to lipid peroxidation, non-enzymatic glycation of proteins and oxidation of glucose which contributes toward diabetes mellitus. Plants contain a large variety of substances that possess antioxidant activity. Therefore, antioxidant vitamins and phytonutrients could be used as a potential natural therapy to reduce oxidative stress and alleviates diabetic complications.

References

1. Unal D, Kara A, Aksak S, Altunkaynak BZ, Yıldırım S. Insulin hormone: Mechanism and effects on the body and relationship with central nervous system. Dicle MedJ. 2012; 39: 310-315.
2. American Diabetes Association. Diagnosis and classification of diabetes. Diabetes Care. 2004; 27: 5-10.
3. Wallace JI. Management of diabetes in elderly. Clin Diabetes. 1999; 17: 1.
4. Harsh M. Textbook of Pathology. fourth ed. Jaypee publishers. 2002.
5. Nosratola D, et al. Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency. Kidney Int. 2003; 63: 179-185.
6. Weseler AR, Bast A. Oxidative stress and vascular function: implications for pharmacologic treatments. Curr Hypertension Rep. 2010; 12: 154-161.
7. Sies H. Oxidative Stress. Elsevier, Florida. 1985.
8. Johansen JS, Harris AK, Rychly DJ, Ergul A, et al. Oxidative stress and the use of antioxidants in diabetes. Cardiovas. Diabetol. 2005; 4: 5.
9. Somogyi AO, Rosta K, Pusztai P, Tulassay Z, Nagy G. Antioxidant measurements. Physiol Meas. 2007; 28: 41-55.
10. Penckofer S, Schwertz D, Florczak K. Oxidative stress and cardiovascular disease in type 2 diabetes: the role of antioxidants and prooxidants. J CardiovascNurs. 2002; 16: 68-85.
11. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. IJBS. 2008; 4: 89-96.
12. Lipinski B. Pathophysiology of oxidative stress in diabetes mellitus. J Diabetes its Complications. 2001; 15: 203-210.
13. Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H. Perspectives in Diabetes. Glucose Toxicity in β-Cells: Type 2 Diabetes, Good Radicals Gone Bad, and the Glutathione Connection. Diabetes. 2003; 52: 581-587.
14. Ayepola OR, Brooks NL, Oguntibeju OO. Oxidative Stress and Diabetic Complications: The Role of Antioxidant Vitamins and Flavonoids. 2014.
15. El Faramawy SM, Rizk RA. Spectrophotometric studies on antioxidants-doped liposomes. J Am Sci. 2011; 7: 363-369.
16. Maritim AC, Sanders RA, Watkins JB. Effects of α-lipoic acid on biomarkers of oxidative stress in streptozotocin-induced diabetic rats. J Nutr Biochem. 2003; 14: 288-294.
17. Patricia PM. Reactive species and diabetes: counteracting oxidative stress to improve health. Curr Opin. Pharmacol. 2009; 9: 771- 779.
18. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ. Med J. 2012; 12: 5-18.
19. Patel H, Chen J, Das KC, Kavdia M. Hyperglycemia induces differential change in oxidative stress at gene expression and functional levels in HUVEC and HMVEC. Cardio vasc Dialectol. 2013; 12: 142-146.
20. Tiwari BK, Pandey KB, Abidi AB, Rizvi SI, et al. Markers of oxidative stress during diabetes mellitus. J Biomarkers. 2013.
21. Packer L. α-Lipoic acid: a metabolic antioxidant which regulates NF-kappa B signal transduction and protects against oxidative injury. Drug Metab Rev. 1998; 30: 245-275.
22. Morcos M, Borcea V, Isermann B, Gehrke S, Ehret T, Henkels M et al. Effect of α-lipoic acid on the progression of endothelial cell damage and albuminuria in patients with diabetes mellitus: an exploratory study. Diab Res ClinPract. 2001; 52: 175-183.
23. Nazirogilu M, Butterworth P. Protective effects of moderate exercise with dietary vitamin C and E on blood antioxidative defense mechanism in rats with streptozotocin-induced diabetes. Can J Appl Physiol. 2005; 30: 172-185.
24. Lee DH, Folsom AR, Harnack L, Halliwell B, Jacobs DRJ. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? Am J ClinNutr. 2004; 80: 194-200.
25. Khan AN, Khan RA, Ahmad M, Mushtaq N. Role of antioxidant in oxidative stress and diabetes Mellitus. J Pharmacognosy and Phytochemistry. 2015; 3: 217-220.
26. Chanwitheesuk A,Teerawutgulrag A, Rakariyatham N. Screening of antioxidant activity and antioxidant compounds of some edible plants of Thailand. Food Chem. 2005; 92: 491-497.
27. Larkins, Nicholas, Wynn S. Pharmacognosy: Phytomedicines and their mechanisms. Vet Clin North Am Small AnimPract. 2004; 34: 291-327.
28. Ramith R, Prithvi SS, Farhan Z, Lakshmi VR, Nagendra MNP. Inhibitory effect of banana (Musa sp. var. Nanjangud rasa bale) flower extract and its constituents Umbelliferone and Lupeol on α-glucosidase, aldose reductase and glycation at multiple stages. Afr J Bot. 2014; 95: 54-63.
29. Syed IR, Neetu M. Traditional Indian Medicines Used for the Management of Diabetes Mellitus. J Diabetes Res. 2013.
30. World Health Organisation (WHO). WHO Expert Committee on Diabetes Mellitus: second report, World Health Organ Technical Report Series. 1980; 646: 1-80.
31. Ramith R, Prithvi SS, Farhan Z, Nagendra MNP. Investigation of antihyperglycaemic activity of banana (Musa sp. var. Nanjangud rasa bale) pseudostem in normal and diabetic rats. J Sci Food Agric. 2015; 95: 165-173.
32. Ramu R, Shirahatti PS, Nayakavadi S, Vadivelan R, Zameer F, Dhananjaya BL, et al. Effect of a plant extract enriched in Stigmasterol and β-Sitosterol on glycaemic status and glucose metabolism in alloxaninduced diabetic rats. Food Funct. 2016; 7: 3999-4011.
33. Williamson G. Possible effects of dietary polyphenols on sugar absorption and digestion. MolNutr Food Res. 2013; 57:48-57.
34. Arts ICW, Hollman PCH. Polyphenols and disease risk in epidemiologic studies. Am J ClinNutr. 2005; 81: 317-325.
35. Pandey KB, Rizvi SI. Recent advances in health promoting effect of dietary polyphenols. Curr Nutr Food Sci. 2012; 8: 254-264.
36. Anhea FF, Desjardinsb Y, Pilona G, Dudonneb S, Genovesec MI, Lajoloc FM, et al. Polyphenols and type 2 diabetes: a prospective review. Pharma Nutr. 2013; 1: 105-114.
37. Pinent M, Blay M, Blade MC, Salvado MJ, Arola L, Ardevol A. Grapeseed-derived procyanidins have an antihyperglycemic effect in streptozotocin-induced diabetic rats and insulinomimetic activity in insulin-sensitive cell lines. Endocrinology. 2004; 145: 4985-4990.
38. Terra X, Montagut G, Bustos M, Lopiz N, Ardevol A, Blade C, et al. Grape-seed procyanidins prevent low grade inflammation by modulating cytokine expression in rats fed a high-fat diet. J Nutr Biochem. 2009; 20: 210-218.
39. Zhu Z, Luo Z, Ma S, Liu D. TRP channels and their implications in metabolic diseases. Pflugers Arch. 2011; 461: 211-223.
40. Ahuja KD, Robertson IK, Geraghty DP, Ball MJ. Effects of chili consumption on postprandial glucose, insulin and energy metabolism. Am J ClinNutr. 2006; 84: 63-69.

41. Ahuja KD, Robertson IK, Geraghty DP, Ball MJ. The effect of 4-week chilli supplementation on metabolic and arterial function in humans. Eur J ClinNutr. 2007; 61: 326-333.

42. Hoover DB. Effects of capsaicin on release of substance P-like immunoreactivity and physiological parameters in isolated perfused guinea-pig heart. Eur J Pharmacol. 1987; 141: 489-492.

43. Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: a review. Nutr J. 2002; 1: 1-14.

44. Reaven E, Wright D, Mondon CE, Solomon R, Ho H, Reaven GM. Effect of age and diet on insulin secretion and insulin action in the rat. Diabetes. 1983; 32: 175-180.

45. Sanchez FD, Game MJ, Jimenez I, Zarzuelo A. Hypoglycemic activity of Juniperus ''Berries''. Plant Medicine. 1994; 60: 197-200.

46. Griffiths G, Trueman L, Crowther T, Thomas B. Onions: a global benefit to health. Phytotherapy Res. 2002; 17: 603-615.

47. Augusti KT. Therapeutic values of onion (Allium cepa L.) and garlic (Allium sativumL.). Ind J Exp Biol. 1996; 34: 634-640.

48. El-Demerdash FM, Yousef MI,Abou El-Naga NI. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food Chem Toxicol. 2005; 43: 57-63.

49. Halliwell B, Whiteman M. Measuring reactive species and oxidative damage *in vivo* and in cell culture: how should you do it and what do the results mean? Br J Pharmacol. 2004; 142: 231-255.

50. Dalle-Donne I, Rossi R, Colombo R, Giustarini D, Milzani A. Biomarkers of oxidative damage in human disease.Clin Chem. 2006; 52: 601-623.

51. Rashidi A, Kirkwood TBL, Shanley DP. Metabolic evolution suggests an explanation for the weakness of antioxidant defences in beta-cells. Mech Ageing Dev. 2009; 130: 216-221.

52. Kim SH, Hyun SH, Choung SY. Antidiabetic effect of cinnamon extract on blood glucose in db/db mice. JEthnopharmacol. 2006; 104: 119-123.

53. Kanter M. Effects of Nigella sativa and its major constituent, thymoquinone on sciatic nerves in experimental diabetic neuropathy. Neurochem Res. 2008; 33: 87-96.

54. Ismail M, Al-Naqeep G, Chan KW. Nigella sativa thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. Free RadicBiol Med. 2010; 48: 664-672.

55. Al-Majed AA, Al-Omar FA, Nagi MN. Neuroprotective effects of thymoquinone against transient forebrain ischemia in the rat hippocampus. Eur J Pharmacol. 2006; 543: 40-47.

56. Sankaranarayanan C, Pari L. Thymoquinone ameliorates chemical induced oxidative stress and β-cell damage in experimental hyperglycemic rats. Chem Biol Int. 2011; 190: 148-154.

57. Nangle MR, Gibson TM, Cotter MA, Cameron NE. Effects of eugenol on nerve and vascular dysfunction in streptozotocin-diabetic rats. Planta Medica. 2006; 72: 494-500.

58. Zari TA, Al-Attar AM. Effects of ginger and clove oils on some physiological parameters in streptozotocin-diabetic and non-diabetic rats. J Medi Sci. 2007; 7: 267-275.

59. Rajamani S, Suganthi R, Ravichandran MK, Anuradha CV. Food seasoning spices mixture improves glucose metabolism and lipid profile in fructose-fed hyperinsulinemic rats. J Med Food. 2005; 8: 502-507.

60. Suganthi R, Rajamani S, Ravichandran MK, Anuradha CV. Effect of food seasoning spices mixture on biomarkers of oxidative stress in tissues of fructose-fed insulin-resistant rats. J Med Food. 2007; 10: 149-153.

61. Dearlove RP, Greenspan P, Hartle DK, Swanson RB, Hargrove JL. Inhibition of protein glycation by extracts of culinary herbs and spices. J Med Food. 2008; 11: 275-281.

62. Broadhurst CL, Polansky MM, Anderson RA. Insulin-like biological activity of culinary and medicinal plant aqueous extracts *in-vitro*. J AgrFood Chem. 2002; 48: 849-852.

63. Shukri R, Mohamed S, Mustapha NM. Cloves protect the heart, liver and lens of diabetic rats. Food Chem. 2010; 122: 1116-1121.

64. Al-Sereiti MR, Abu-Amer KM, Sen P. Pharmacology of rosemary (Rosmarinus officinalis Linn.) and its therapeutic potentials. Indian J Exp Biol. 1999; 37: 124-130.

65. Erenmemisoglu A, Saraymen R, Ustun H. Effect of Rosmarinus officinalis leaves extract on plasma glucose levels in normoglycaemic and diabetic mice. Die Pharmazie. 1997; 52: 645-646.

66. Kultur S. Medicinal plants used in Kirklareli Province (Turkey). J Ethnopharmacol. 2007; 111: 341-364.

67. Yesil CO, Bedir E, Vardar-Sukan F. *In vitro* antioxidant activities of Rosmarinus officinalis extracts treated with supercritical carbon dioxide. Food Chem. 2007; 101: 1457-1464.

68. Cheung S, Tai J. Anti-proliferative and antioxidant properties of rosemary Rosmarinus officinalis. Oncol Rep. 2007; 17: 1525-1531.

69. Najla O. Antidiabetic and renoprotective effects of water extract of Rosmarinus officinalis in streptozotocin-induced diabetic rat. Afr J Pharm Pharmacol. 2012; 6: 2664-2669.

70. Header E, ElSawy N, El-Boshy M, Basalamah M, Mubarak M, Ben Hadda T. POM Analyses of Constituents of Rosmarinus officinalis and Their Synergistic Effect in Experimental Diabetic Rats. J Bioanal Biomed. 2015; 7: 18-23.

71. Esterbauer H, Schaur R Jr, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Rad Biol Med. 1991; 11: 81-128.

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