Chapter 14

Antioxidant -Rich Natural Products and Diabetes Mellitus

Ayodeji B. Oyenihi, Nicole L. Brooks,
Oluwafemi O. Oguntibeju and Guillaume Aboua

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/57192

1. Introduction

Diabetes mellitus (DM) is one of the most common metabolic disorders worldwide with an estimated 143 million people suffering from the disease [1]. This number may double by 2030 [2]. Although understanding of the pathophysiological processes involved in DM has increased, with great feats achieved in the management of DM, yet serious diabetic complications still confront patients and physicians [3]. Diabetes mellitus is characterized by chronic hyperglycemia (very high blood glucose levels) and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in insulin secretion or insulin action [4-5]. On the basis of aetiology and clinical presentation, DM is classified into two; type 1 diabetes mellitus also called insulin-dependent diabetes mellitus (IDDM) and type 2 which is the non-insulin dependent diabetes mellitus (NIDDM). The effects of DM include long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, livers, hearts, and blood vessels [6].

In the treatment of diabetes, many oral hypoglycemic agents like sulfonylureas, meglitinides, thiazolidines, D-phenylalanine and α-glucosidase inhibitors are used in addition to insulin treatment action along with appropriate diet and exercise [5]. However, none can be termed as an ideal one, due to their toxic side effects and sometimes diminution in response after prolonged use [7]. The limitations and side effects associated with existing synthetic oral hypoglycemic agents had necessitated the search for newer drugs. As a result, natural agents from plants and plant products have been the alternative target to source for new antioxidant and antidiabetic agents based on their traditional use.

2. Hyperglycemia and oxidative stress

A relationship has been established between hyperglycemia, oxidative stress and numerous pathways which can lead to the development of diabetic complications. Four of these pathways are very important: activation of protein kinase C isoforms, increased hexosamine pathway flux, increased advanced glycation end-product (AGE) formation [8-9], and increased aldose-reductase pathway flux [10]. Oxidative stress has been implicated to play a central role in these pathways. Oxidative stress occurs as a result of excessive formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) collectively described as free radicals. Free radicals are highly unstable and have the ability to attract electrons from macromolecules such as carbohydrates, protein, lipid and DNA [11]. Excessive ROS can cause structural deterioration and instability of the macromolecules, consequently affecting proper cellular signaling pathways, gene regulation and function [12]. Although, the human system has check-in mechanisms to deal with oxidative damage and free radical formation through endogenous and exogenous antioxidants, however, when the rate of formation of ROS overwhelms the detoxifying ability of the antioxidants, oxidative stress can occur [11, 13-14].

The increase in oxidative stress in diabetes mellitus could be attributed to elevated blood glucose levels, which upon auto-oxidation generates free radicals and damages the cell membrane through peroxidation of membrane lipids [15] and protein glycation [16]. Chronic hyperglycemia results in oxidative stress via auto-oxidation of glucose in the presence of transition metals [17]; decreased activities of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase [18]; increased oxidative phosphorylation [19], glycosylation of proteins [17]; and activation of the hexosamine pathway [20]. Hyperglycemia-induced oxidative stress has been demonstrated to result in beta cell dysfunction and death [21-22], as well as in fibrosis of pancreatic islets [23-24]. It has also been established that hyperglycemia increases mitochondrial ROS production, which could represent a key event in the development of diabetic complications [19, 25].

Hyperglycemia has been reported to induce oxidative insult and apoptosis in diabetic liver and renal tubular cells [26-27]. Hyperglycemia leads to increased levels of ROS and D-glucose which has been shown to be capable of inducing apoptosis through the activation of Bax-caspase pathway [28]. Caspases are a family of cysteine proteases known to be the effectors of apoptosis. Upon activation of Bax by free radicals, caspases are activated, which alter mitochondrial function by reducing the electrochemical gradient across the mitochondrial membrane leading to the release of mitochondrial cytochrome C into cytoplasm [28-29]. Studies had shown that movement of Bax into the mitochondrial membrane is accompanied by a significant increase in the activities of caspase-3 and caspase-9 [30-32].

3. Levels of antioxidant action

The antioxidants acting in the defense systems act at different levels such as preventive, radical scavenging, repair and de novo, and the fourth line of defense, i.e., the adaptation.

According to Lobo *et al.* [33], the first line of defense is the preventive antioxidants, which suppress the formation of free radicals. Although the precise mechanism and site of radical formation in vivo are not well elucidated yet, the metal-induced decompositions of hydroperoxides and hydrogen peroxide must be one of the important sources. To suppress such reactions, some antioxidants reduce hydroperoxides and hydrogen peroxide beforehand to alcohols and water, respectively, without generation of free radicals and some proteins sequester metal ions. Glutathione peroxidase, glutathione-s-transferase, phospholipid hydroperoxide glutathione peroxidase (PHGPX), and peroxidase are known to decompose lipid hydroperoxides to corresponding alcohols. PHGPX is unique in that it can reduce hydroperoxides of phospholipids integrated into biomembranes. Glutathione peroxidase and catalase reduce hydrogen peroxide to water.

The second line of defense is the antioxidants that scavenge the active radicals to suppress chain initiation and/or break the chain propagation reactions. Various endogenous radical-scavenging antioxidants are known: some are hydrophilic and others are lipophilic. Vitamin C, uric acid, bilirubin, albumin, and thiols are hydrophilic, radical-scavenging antioxidants, while vitamin E and ubiquinol are lipophilic radical-scavenging antioxidants. Vitamin E is accepted as the most potent radical-scavenging lipophilic antioxidant.

The third line of defense is the repair and de novo antioxidants. The proteolytic enzymes, proteinases, proteases, and peptidases, present in the cytosol and in the mitochondria of mammalian cells, recognize, degrade, and remove oxidatively modified proteins and prevent the accumulation of oxidized proteins.

The DNA repair systems also play an important role in the total defense system against oxidative damage. Various kinds of enzymes such as glycosylases and nucleases, which repair the damaged DNA, are known [33].

There is another important function called adaptation where the signal for the production and reactions of free radicals induces formation and transport of the appropriate antioxidant to the right site [34].

4. Antioxidants and diabetes mellitus treatment

The human system employs the use of endogenous enzymatic and non-enzymatic antioxidant defense systems against the onslaught of free radicals and oxidative stress [35-36]. Enzymatic antioxidants include superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase. Non-enzymatic antioxidants include vitamins A, C, and E, glutathione, alpha-lipoic acid, carotenoids, and coenzyme Q. Other antioxidants include biflavonoids, minerals (copper, zinc, manganese, and selenium), and cofactors (folic acid, vitamins B1, B2, B6 and B12). These antioxidants work synergistically with each other using different mechanisms against different free radicals and stages of oxidative stress [37]. Hyperglycemia has been reported to impair the endogenous antioxidant defense systems in many ways during diabetes in addition to generating free radicals [18, 38]. The involvement of hyperglycemia-mediated oxidative damage in diabetes mellitus has led to the hypothesis that drugs that

improve glycemic index and/or oxidative stress will be beneficial in the treatment of diabetes mellitus and its complications.

Majority of the drugs currently used in the treatment of diabetes mellitus have antioxidant activities in addition to their primary pharmacological activity. For example, aminoguanidine has been shown to exhibit free radical scavenging properties and inhibit lipid peroxidation [39-43] although clinical trials were discontinued in Europe and in the United States due to its long term toxicity. Troglitazone lowered hydroperoxides and decreased SOD activity in type 2 diabetic rats [44]. Glibenclamide, a sulphonylureas in addition to its glucose lowering effect possesses antioxidant properties due to its ability to restore liver catalase and superoxide dismutase in diabetic rats [45]. Also, repaglinide used in the treatment of type 2 diabetes mellitus exhibited antioxidant properties and inhibited protein peroxidation by upregulating glutathione reductase and glutathione levels in diabetic rabbits in addition to its insulin releasing effects [46].

Several *in vivo* studies have been carried out to ascertain the effects of antioxidants on experimental diabetic models [47-53]. Most of these studies reported the beneficial role of antioxidants against specific biomarkers of oxidative stress and provided the foundation for clinical trials embarked on later [54-60]. Majority of the studies were not designed specifically to assess the effects of antioxidant use in diabetic patients and none has been carried out yet on antioxidant-rich plant products despite the large evidence supporting its use. Medicinal plants and antioxidant-rich plant products definitely hold promise in this area in the near future.

5. Role of flavonoids in diabetes mellitus

The presence of polyphenolic compounds such as flavonoids, phenols, flavonols, and proanthocyanidins in plants is associated with the antioxidant and antidiabetic potentials [61]. A number of studies have reported on the beneficial effect of flavonoids in diabetes mellitus [62-63]. Examples of flavonoids include quercetin, rutin, diosmin, luteolin, lycopene, catechins and cinnamic acids.

5.1. Quercetin

Quercetin (3,3',4',5-7-penta- hydroxyflavone), belongs to the class flavonol, a member of the flavonoid family and is widely distributed in plants. Quercetin and rutin are the flavonoids most abundantly consumed in foods [64]. Sources of quercetin include brassica green vegetables, carrots, berries, onions, apple, legumes, green tea, citrus fruits, red wines etc [65]. Quercetin has been shown to prevent oxidative stress [66] by different mechanisms, including scavenging free radicals [67], inhibiting xanthine oxidase [68], lipid peroxidation, and chelating metal ions [69]. Quercetin is a powerful antioxidant, proven by *in vitro* [70] and *in vivo* studies [71]. Quercetin ameliorated the damage caused by oxidative stress in pancreatic tissues in rats, by directly quenching lipid peroxides and indirectly enhancing the production of endogenous antioxidants [72].

http://dx.doi.org/10.5772/57192

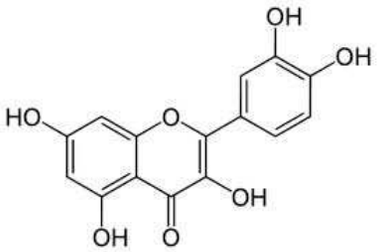

Figure 1. The chemical structure of quercetin.

Quercetin reduces intestinal glucose absorption by inhibiting GLUT 2 in CaCo-2 intestinal cells [73-74]. Quercetin has been extensively investigated in diabetic rat models in recent times. It decreases the fasting blood glucose and improves glucose tolerance [75]; protects against oxidative damage and preserves pancreatic beta cell integrity [76]. Kobori *et al.* [77] reported that quercetin alleviated diabetic symptoms and liver injury in diabetic patients. Quercetin blocks tyrosine kinase thereby interfering with insulin signaling and the propagation of the biological actions of the hormone [78-79]. Quercetin elevated insulin secretion in insulin-secreting cell line induced by glucose and glibenclamide [80] by mediating ERK1/2 pathway [81]. Insulin resistance was improved in genetically obese Zucker rats upon administration of quercetin [82]. Quercetin also reduced maltose-induced postprandial hyperglycemia in type 2 diabetic patients by inhibiting intestinal alpha glucosidase activity [83]. Several mechanisms of action of quercetin in diabetes have been postulated and those included: decreases lipid peroxidation, increases antioxidant enzymes activity like superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase [76]. Other mechanisms are inhibition of insulin-dependent activation of phosphoinositol-3 kinase (PI-3K) [84], increase adiponectin levels [85], and decrease the intestinal maltose activity [27].

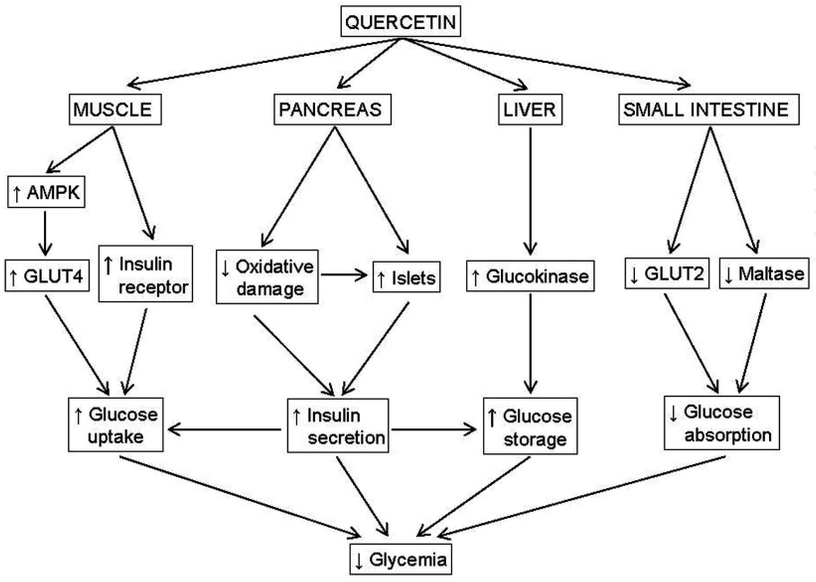

Figure 2. Proposed mechanisms for anti-diabetic effects of Quercetin. Reproduced from Portillo *et al.,* (2011).

5.2. Rutin

Rutin {2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[α-Lrhamnopyranosyl-(1→6)-β-D-gluco pyranosyloxy]-4*H*chromen-4-one} is abundantly present in onions, apples, tea and red wine [86]. The name rutin originated from the plant *Ruta graveolens*. Rutin exhibits multiple pharmacological activities including antibacterial, antitumour, antidiabetic, antiinflammatory, antidiarrhoeal, antiulcer, antimutagenic, myocardial protecting, vasodilator, immunomodulator and hepatoprotective activities [87]. It is a potent antioxidant and anti-inflammatory agent that has the potential to provide a lot of health benefits [88].

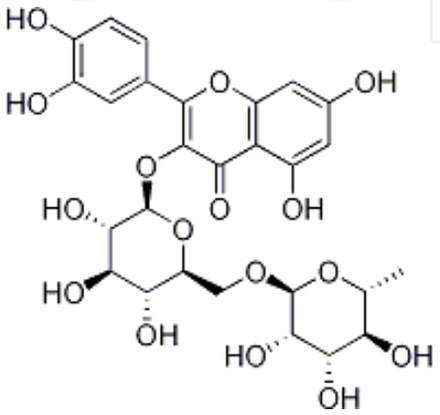

Figure 3. The chemical structure of rutin.

Rutin by its ability to scavenge free radicals and to inhibit lipid peroxidation, prevents streptozotocin-induced oxidative stress and protects pancreatic beta cells resulting in increased insulin secretion and decreased blood glucose levels. Rutin effectively reduced the increased levels of thiobarbituric acid reactive substances and hydroperoxides in the diabetic state *in vivo* [89] and *in vitro* [90]. Rutin reduces hyperglycemia and dyslipidemia while inhibiting the progression of liver and heart dysfunction in diabetic rats [91]. It also significantly decreases elevated reactive oxygen species while increasing endogenous antioxidant enzymes in kidney of diabetic rats and may consequently control or prevent the development of diabetic nephropathy [92]. When Rutin supplementation tablets (500mg) was administered simultaneously with their regular medication for 60 days to patients with type 2 diabetes mellitus, the hypertension, total cholesterol and low-density lipoproteins (LDL) were markedly attenuated. Rutin also decreased the levels of fasting blood glucose, systolic and diastolic blood pressure and improved lipid profiles in the diabetic subjects [93]. Rutin found in *Morus alba* leaves, possesses significant, dose-dependent antidiabetic activity in a type 2 diabetic rat model [94].

5.3. Diosmin

Diosmin (3′,5,7-trihydroxy-4′-methoxyflavone 7-rutinoside) is a naturally occurring flavonoid glycoside that can be isolated from various plant sources or derived by dehydrogenation of the corresponding flavanone glycoside Hesperidin, that is abundant in the pericarp of various citrus fruits [95]. Diosmin was first isolated in 1925 from *Scrophularia nodosa.* Diosmin is

http://dx.doi.org/10.5772/57192

considered to be a vascular-protecting agent used to treat chronic venous insufficiency, hemorrhoids, lymphedema, and varicose veins. Diosmin exhibits anti-inflammatory, antioxidant, and anti-mutagenic properties [95-97]. Clinical studies have demonstrated that diosmin can be used to treat venous leg ulcers and hemorrhoids [98]. Also, its anti-inflammatory and anti-apoptotic activity has been demonstrated in neuronal cells [99].

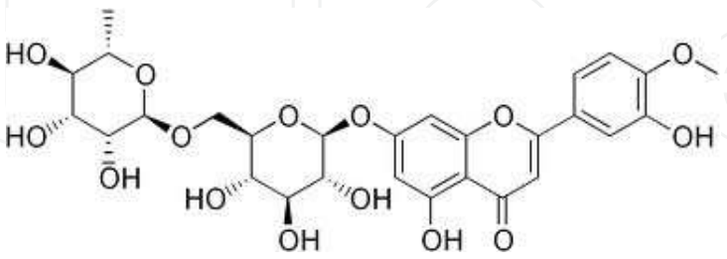

Figure 4. The chemical structure of diosmin.

Diosmin was found to be capable of normalizing capillary filtration rate and prevent ischemia in diabetics [100-101]. Diosmin has been shown to improve factors associated with diabetic complications. A decrease in hemoglobin A1c as well as an increase in glutathione peroxidase was observed in type 1 diabetic patients after an intervention with a diosmin-containing flavonoid mixture [102]. Diosmin and hesperidin are known to lower hepatotoxicity induced by carbon tetrachloride (CCl_4) and lipopolysaccharides (LPS), minimize oxidation stress caused by nicotine, reduce blood sugar and cholesterol, and inhibit carcinogenesis of the bladder and colon [31, 103-106]. Administration of diosmin for 45 days significantly lowered plasma glucose level, increased the activities of hepatic key enzymes such as hexokinase and glucose-6-phosphate dehydrogenase in addition to decreasing glucose-6-phosphatase and fructose-1,6-bisphosphatase concentrations in streptozotocin-nicotinamide treated rats exhibiting its antihypeglycemic properties [107]. Diosmin lowered plasma glucose and increased plasma insulin levels in diabetic rats by ameliorating the oxidative stress induced by streptozotocin and nicotinamide. Activities of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione s-transferase), vitamin C, vitamin E and reduced glutathione were increased while lipid peroxidation was reduced in liver and kidney of diabetic rats upon treatment with diosmin. Diosmin was also recently reported to possess antihypertensive property by increasing the activities of antioxidant enzymes,, reducing reactive oxygen species and normalizing marker enzymes in serum and tissues (liver, kidney, heart, aorta) when rats were made hypertensive by deoxycorticosterone acetate (DOCA) salt [108].

5.4. Luteolin

Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a flavonoid widely distributed in the plant kingdom including several such as *Reseda luteola L.*, *Achillea millefolium L*, *Chamomillae requtita*, *Cynara scolymus*, *Thymus vulgaris*, *Limonium sinuatum* [109]. Luteolin has a variety of pharmacological activities, including anti-mutagenic, anti-tumorigenic [110], anti-inflammatory [111], anti-hypertensive [112], and anti-oxidative [113] properties. It is thought to play an important role in the human body as an antioxidant, a free radical scavenger, an agent in the prevention of

inflammation, a promoter of carbohydrate metabolism, and an immune system modulator [114]. The antioxidant activity of luteolin and its glycosides has been associated with their capacity to scavenge reactive oxygen and nitrogen species [115-116], to chelate transition metals that may induce oxidative damage through the Fenton reaction [117] to inhibit prooxidant enzymes [118] and to induce antioxidant enzymes [119-120]. The antioxidant activity of luteolin has been investigated *in vitro* and *in vivo* [121-122].

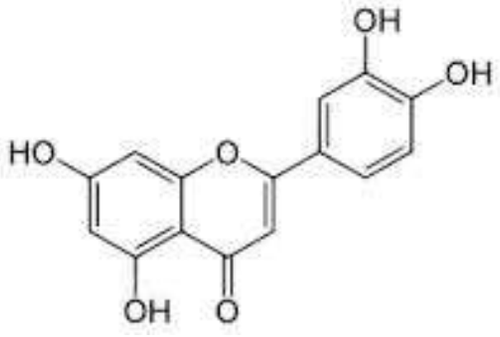

Figure 5. The chemical structure of luteolin.

The antidiabetic property of luteolin was reported by Zarzuelo *et al* [123] where a significant decrease in glycemia levels (> 50%), a 2.5-fold increase in insulin blood levels, elevated pancreatic insulin and DNA content were observed. Luteolin is reported to inhibit alpha-glucosidase and alpha-amylase suggesting that it can suppress postprandial hyperglycemia in patients with non-insulin dependent diabetes mellitus [124]. Recently, luteolin was found to influence insulin action and production of adipokines/cytokines in adipocytes by activating the PPARγ pathway suggesting its role in preventing insulin resistance and type 2 diabetes mellitus [125].

5.5. Lycopene

Lycopene is a carotenoid present in tomatoes (*Lycoperisicon esculentum*). It can be found in many fruits and vegetables like water melon, pawpaw and pink grape fruit. Lycopene is a potent antioxidant according to *in vitro* and human studies, inactivating hydrogen peroxide and nitrogen dioxide [126] and reducing the susceptibility of lymphocyte DNA to oxidative damage [127]. The presence of many conjugated double bonds in lycopene may account for its antioxidant properties [128]. Lycopene quenches singlet oxygen and traps peroxyl radicals [129]. The singlet quenching ability has been reported to be twice as high as that of beta carotene and 10 times higher than that of alpha tocopherol and butylated hydroxyl toluene (BHT) [130-132]. Lycopene is also a potent neuroprotective [133], anti-proliferative, anti-cancer [134], anti-inflammatory [135] and hypocholesterolemic agent [136]. The mechanisms of action against reactive species for lycopene has been proposed to be by adduct formation, electron transfer to radicals and allylic hydrogen attraction [137-141].

http://dx.doi.org/10.5772/57192

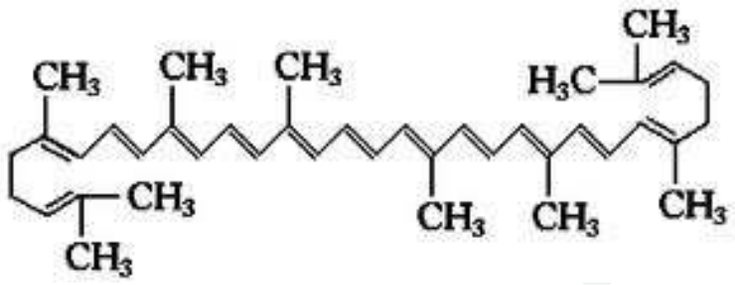

Figure 6. The chemical structure of lycopene.

Lycopene values in serum were found to be significantly lower in patients suffering from type-2 diabetes and impaired glucose metabolism [142-143]. Also, according to data from phase I of the Third National Health and Nutrition Examination Survey (1988-1991), lycopene was found to be inversely related to fasting serum insulin suggesting a possible role for lycopene in the pathogenesis of insulin resistance and diabetes [144]. Lycopene was also found to be useful in the management of neuropathy, a complication of diabetes mellitus, by attenuating cold allodynia and thermal hyperalgesia in streptozotocin induced diabetic rats [145].

5.6. Catechins

Tea (*Camellia sinensis* L) is the most widely consumed beverage in the world, next to water [146-147]. Tea contains catechins, polyphenolic compounds belonging to the flavonoid family. The most important catechins in green tea are: epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG) and epicatechin (EC) [148]. The antioxidant properties of catechins have been well documented [149-155]. The mechanisms of action of catechins may include free radical scavenging [149-150, 152-153], chelating metal ions to form inactive complexes [150, 152, 156-157], transferring electrons rapidly to ROS induced radical sites on DNA [158] and forming stable semi-quinone free radicals [150]. Catechins also increase the body's endogenous antioxidants to reduce oxidative damage and decrease lipid peroxidation biomarkers in several tissues in rats [158]. Apart from their antioxidant properties, catechins are also anti-carcinogenic, anti-tumorigenic, anti-mutagenic, anti-proliferative, anti-inflammatory, anti-allergic, anti-hypertensive and chemopreventative [159].

In diabetes mellitus, the effects of catechins *in vitro* and *in vivo* studies were investigated [160-163]. In rat models of diabetes, catechins have been demonstrated to have ameliorative effects on biomarkers of oxidative stress on diabetic erythrocytes [164] and on erythrocyte Na/H antiport [165].

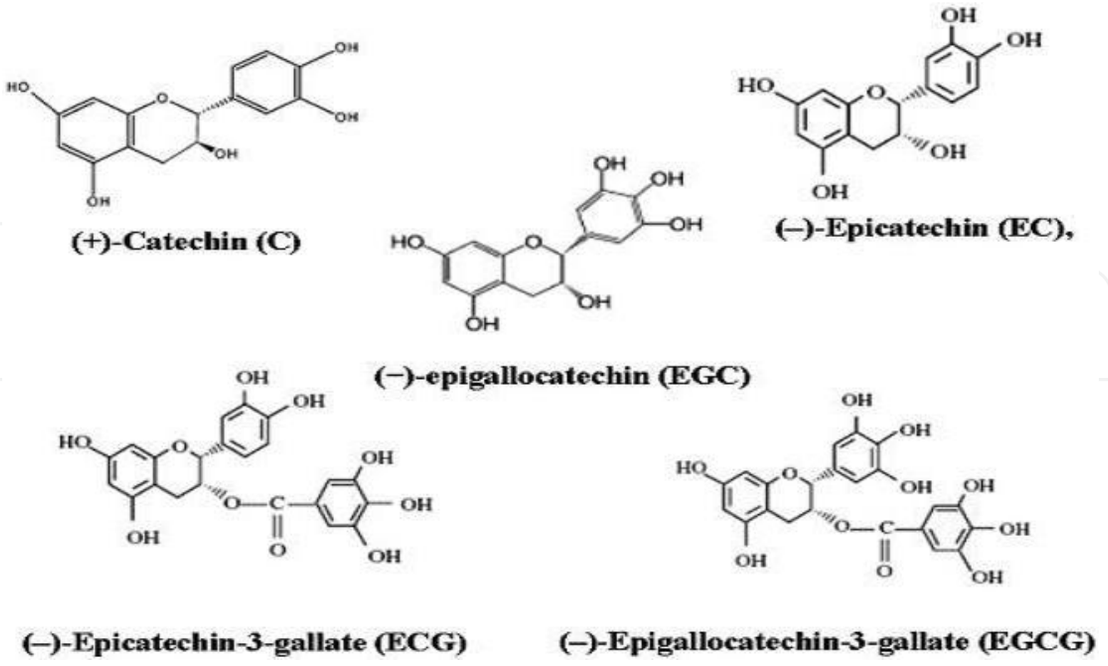

Figure 7. The chemical structure of catechins

5.7. Cinnamic acids

Cinnamon, used extensively since ancient times in food as a herb or spice, has been shown to ameliorate the symptoms of metabolic syndromes, such as insulin resistance and elevated levels of glucose and lipids [166]. Cinnamon bark contains cinnamic acid, cinnamaldehyde and cinnamic alcohol [167]. Cinnamic acid has been reported to exhibit several pharmacological properties including hepatoprotective [168], antioxidant [169] and anti-diabetic properties [170].

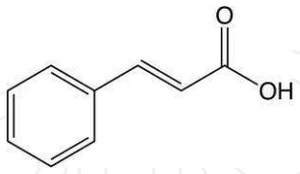

Figure 8. The chemical structure of cinnamic acid.

Cinnamic acid was recently reported to be capable of preventing advanced glucated end-products (AGEs)-mediated diabetic complications. It inhibited the formation of AGEs in a bovine serum albumin (BSA)/fructose system, as well as reduced the levels of fructosamine, the formation of N-(carboxymethyl) lysine (CML) and the level of amyloid cross beta-structure [167]. Sinapic acid is a 4-hydroxy-3, 5-dimethoxy cinnamic acid derivative. It is widely distributed in edible plants such as cereals, nuts, oil seeds and berries [171]. Sinapic acid is a potent antioxidant [172]. Sinapic acid possesses potential anti-hyperglycemic effects, through an increase in insulin production associated with a subsequent increase in the activity of

http://dx.doi.org/10.5772/57192

glcolytic enzyme, hexokinase and decrease in the activity of gluconegoenic enzymes, glucose-6-phosphatase and fructose-1, 6-bisphosphatase [173].

6. Selected antioxidant-rich natural plants with antidiabetic potentials

6.1. *Sclerocarya birrea*

Sclerocarya birrea (Family : Anacardiaceae) is a medium-size-to-large deciduous tree widely used for the treatment of proctitis, dysentery, and diarrhea in South Africa and Africa at large and its antimicrobial and antiparasitic properties has been documented [174-175]. *Sclerocarya birrea* is widely used as traditional remedy against diabetes in Africa [176] and has a significant hypoglycemic effect [177]. The methanolic extracts of different parts of the tree such as the leaves, fruit juice, roots and stem-bark has antioxidant properties [61] due to high contents of flavonoids and polyphenolic compounds.

Figure 9. *Sclerocarya birrea* plant

6.2. *Prosopis glandulosa*

Prosopis glandulosa (Family: Fabaceae) commonly known as Honey mesquite is a small to medium height tree or shrub that is thorny and branching near the ground found mostly in southern parts of India. The bark and leaves are used by the tribes and native medical practitioners to treat various ailments such as leprosy, dysentery, bronchitis, asthma, leucoderma, piles, and tremors of the muscles, tumors, eye diseases and rheumatism [178]. It is commonly found in the dry, arid regions of the northern and north-western Cape of South Africa. Literature studies have indicated that the plant contains flavan-3-ol dimer, mesquitol [179-180] and catechin [181]. Phytochemical screening of leaves from *Prosopis glandulosa* indicates the presence of alkaloids, glycosides, flavonoids, phenolic compounds, steroids and terpenoids [182].

Figure 10. *Prosopis glandulosa* plant

6.3. *Tamarindus indica*

Tamarindus indica Linn (Family: caesalpiniaceae) is a plant that grows naturally in tropical and subtropical regions and has become an important plant for food, herbs in many parts of the world [183]. Literature studies reported *Tamarindus indica* as a traditional medicine for the management of diabetes mellitus in human and experimental animals [184-185]. Siddhuraju [183] reported the potential antioxidant activity of *Tamarindus indica* seeds isolating the antioxidant components 2-hydroxy-30,40-dihydroxyacetophenone, methyl 3,4- ihydroxybenzoate, 3,4-dihydroxyphenylacetate and oligomeric proanthocyanidins. Phenolic compounds such as procyanidin B2, epicatechin, procyanidin trimer, procyanidin tetramer, procyanidin pentamer, procyanidin hexamer, polymeric tannins, polymeric tannins are also present in the seeds of *Tamarindus indica* [186]. It has been postulated that the antidiabetic property of *Tamarindus indica* observed in experimental animals may be due to the presence of the antioxidant-rich compounds [187].

Figure 11. Tamarindus indica plant

http://dx.doi.org/10.5772/57192

7. Conclusion

The pathophysiology of most of the diseases affecting mankind today (*diabetes mellitus* inclusive) seems to have a common denominator, namely oxidative stress. Although, it is a wide topic with several theories, mechanisms, sites and targets of action, reactive oxygen species (ROS) have been implicated in the management of many diseases. As a result, antioxidants have received overwhelming attention in recent years with many outstanding achievements. Most therapeutic agents and drugs are either antioxidants or act primarily to prevent the formation of excess ROS. Therefore it is not surprising to note that natural products with antioxidant properties from plant origin are again gaining prominence in research circles all over the world.

Currently, a lot of therapeutic agents with different modes of action have been designed to combat hyperglycemia; the efficacy and effectiveness of these agents are limited due to several reasons. Individual agent with particular mechanism of action can only act on part of the pathogenic process and only to a partial extent [188-189]. Also, several defects in the pathophysiology of diabetes remain unresolved, and therefore, result in the inability to single out a drug target to focus on as human systems are too interwoven and complex to be fully understood through conventional experimental protocols [190]. However, combination of natural products and phytomedicines from different plants present in most traditional medicines appears to take a different, more holistic approach. These medicinal preparations contain a variety of natural products that act synergistically on a variety of targets through different mechanisms fighting the disease in a more efficient manner. Consequently, the conventional, unidirectional therapeutic method in the management of diabetes seems to be gradually replaced by a more holistic, multidimensional approach

Author details

Ayodeji B. Oyenihi[1], Nicole L. Brooks[2], Oluwafemi O. Oguntibeju[3] and Guillaume Aboua[4]

1 Department of Biochemistry, School of Life Sciences, University of KwaZulu-Natal, Durban, South Africa

2 Department of Wellness Sciences, Faculty of Health & Wellness Sciences, Cape Peninsula University of Technology, Bellville, South Africa

3 Oxidative Stress Research Centre, Departments of Biomedical Sciences, Faculty of Health and Wellness Sciences, Cape Peninsula University of Technology, Bellville, South Africa

4 Department of Biomedical Sciences, Faculty of Health and Wellness Sciences, Cape Peninsula University of Technology, Bellville, South Africa

References

[1] King H, Aubert R.E, and Herman W.H. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21(9):1414-1431.

[2] Harris M.I, Flegal K.M, Cowie C.C, Eberhardt M.S, Goldstein D.E, Little R.R, Wiedmeyer H.M, and Byrd-Holt D.D. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care. 1998;21:518-524.

[3] Tiwari A.K., and Rao J.M. Diabetes mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospects. Current Science. 2002;83(1): 30-37.

[4] Jayakar B. and Suresh B. Antihyperglycemic and hypoglycemic effect of Aporosa lindleyana in normal and alloxan induced diabetic rats. Journal of Ethnopharmacology. 2003;84: 247-249.

[5] Bastaki S. Diabetes mellitus and its treatment. International Journal of Diabetes and Metabolism 2005;13:111-134.

[6] Bennett P.H and Knowler W.C. Definition, diagnosis and classification of Diabetes Mellitus and glucose homeostasis: Joslin's Diabetes Mellitus. In: Kahn CR, WEIR GC, KING GL, JACOBSON AM, MOSES AC, SMITH RJ editors. Lippincott, Williams and Wilkins 2005: 331-339.

[7] Chattopadhyay R.R. A comparative evaluation of some blood sugar lowering agents of plant origin. Journal of Ethnopharmacology. 1999;67:367–372.

[8] Vlassara H and Palace M.R. Diabetes and advanced glycation endproducts. Journal of Internal Medicine. 2002;251:87-101.

[9] Peppa M, Uribarri J, and Vlassara H. The role of advanced glycation end products in the development of atherosclerosis. Current Diabetes Reports. 2004;4: 31-36

[10] Rolo A.P and Palmeira C.M. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. Toxicology and Applied Pharmacology. 2006;212:167-178.

[11] Valko M., Leibfritz D., Moncola J., Cronin M.T.D., Mazura M., and Telser J. Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry and Cell Biology. 2007;39:44–84.

[12] Pop-Busui R, Sima A, Stevens M. Diabetic neuropathy and oxidative stress. Diabetes/Metabolism Research and Reviews. 2006;22:257-273.

[13] Ridnour L.A., Thomas D.D., Mancardi D., Espey M.G., Miranda K.M., Paolocci N., Feelisch M., Fukuto J., and Wink D. A. The chemistry of nitrosative stress induced by nitric oxide and reactive nitrogen oxide species. Biological Chemistry. 2004;385:1-10

[14] Halliwell B. Free radicals and antioxidants - quo vadis? Trends in Pharmacological Sciences. 2011;32:125-130.

[15] Baynes J.W and Thorne S. Role of oxidative stress diabetic complications: a new perspective on an old paradigm. Diabetes, 1999;48: 1-9.

[16] Baynes W. Chemical modification of protein by lipids in diabetes. Clinical Chemistry and Laboratory Medicine 2003;41: 1159-1165.

[17] Wolff S.P., Bascal Z.A. and Hunt J.V. "Autoxidative glycosylation": free radicals and glycation theory. Progress in Clinical and Biological Research. 1989;304:259-75.

[18] Blakytny, R. and Harding, J. J. Glycation (non-enzymic glycosylation) inactivates glutathione reductase. Biochemical Journal, 1992;288:303-7.

[19] Nishikawa T., Edelstein D., Du X. L, Yamagishi S., Matsumura T., Kaneda Y., Yorek M.A, Beebe D., Oates P.J., Hammes H.P., Giardino I. and Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 2000;404:787-90.

[20] Kaneto H., Xu G., Song K., Suzuma K., Bonner-Weier S., Sharma A. and Weier G. C. Activation of the hexosamine pathway leads to deterioration of pancreas b-cells function through the induction of oxidative stress. Journal of Biological Chemistry. 2001;276:31099-31104.

[21] Donath M. Y.; Gross D. J.; Cerasi E. and Kaiser N. Hyperglycemia-induced b-cell apoptosis in pancreatic islets of Psammomys obesus during development of diabetes Diabetes. 1999;48:738-44.

[22] Robertson R.P, Harmon J, Tran P.O, Tanaka Y, and Takahashi H. Glucose toxicity in beta cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. Diabetes. 2003;52:581–587.

[23] Hayden M.R. Islet amyloid and fibrosis in the cardiometabolic syndrome and type 2 diabetes mellitus. Journal of the Cardio-metabolic Syndrome. 2007;2:70-5.

[24] Hong O., Lee S., Rhee M., Ko S., Cho J., Choi Y., Song K., Son H. and Yoon K. Hyperglycemia and hyperinsulinemia have additive effects on activation and proliferation of pancreatic stellate cells: possible explanation of islet-specific fibrosis in type 2 diabetes mellitus. Journal of Cell Biochemistry. 2007;101:665-75.

[25] Kiritoshi S, Nishikawa T, Sonoda K, Kukidome D, Senokuchi T, Matsuo T, Matsumura T, Tokunaga H, Brownlee M and Araki E. Reactive oxygen species from mitochondria induce cyclooxygenase-2 gene expression in human mesangial cells: potential role in diabetic nephropathy. Diabetes. 2003;52 :2570–2577.

[26] Stitt-Cavanagh E., MacLeod L, and Kennedy C.R.J. The Podocyte in Diabetic Kidney Disease. The ScientificWorld JOURNAL. 2009;9:1127–1139.

[27] Kim Y.J, Kim Y.A, Yokozawa T.. Pycnogenol modulates apoptosis by suppressing oxidative stress and inflammation in high glucose-treated renal tubular cells. Food and Chemical Toxicology. 2011;49:2196–2201.

[28] Green D.R and Reed J.C. Mitochondria and apoptosis. Science 1998;281:1309–1312.

[29] Liu X, Kim CN, Yang J, Jemmerson R and Wang X. Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome C. Cell. 1996;86:147–157.

[30] Fraser A. and Evans G. A. license to kill. Cell. 1996;85:781–784.

[31] Yang J, Liu X, Bhalla K, Kim C.N, Ibrado A.M, Cai J, Peng T.I, Jones D.P and Wang X. Prevention of apoptosis by Bcl-2: release of cytochrome c from mitochondria blocked. Science. 1997;275:1129–1132.

[32] Nakagami H, Morishita R, Yamamoto K, Taniyama Y, Aoki M, Yamasaki K, Matsumoto K, Nakamura T, Kaneda Y and Ogihara T. Hepatocyte growth factor prevents endothelial cell death through inhibition of bax translocation from cytosol to mitochondrial membrane. Diabetes. 2002;51:2604–2611.

[33] Lobo V. Patil A. Phatak A. and Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy Reviews. 2010;4:118–126.

[34] Niki E. Antioxidant defenses in eukaryotic cells. In: Poli G, Albano E, Dianzani MU, editors. Free radicals: From basic science to medicine. Basel, Switzerland: Birkhauser Verlag;. 1993;365–73

[35] Harris, E.D. Regulation of antioxidant enzymes. Journal of Nutrition. 1992;122:625-626.

[36] Jacob R.A. The integrated antioxidant system. Nutrition Research. 1995;15:755-766.

[37] Maritim A, Sanders R, Watkins J.I. Effects of alpha-lipoic acid on biomarkers of oxidative stress in streptozotic-induced diabetic rats. Journal of Nutrition and Biochemistry. 2003;14(5):288-294.

[38] Saxena A.K, Saxena P, Kale R.K and Baquer N.Z. Impaired antioxidant status in diabetic rat liver: Effect of vanadate. Biochemical Pharmacology. 1993;45:539–542.

[39] Biegelsen E.S and Vita J.A. Human studies of antioxidants and vascular function. In: Keaney Jr. JF, editor. Oxidative stress and vascular disease. Dordrecht: Kluwer Academic Publishers: 1999;213-243.

[40] Gaziano J.M. Antioxidants and cardiovascular disease. In: Keaney Jr. JF, editor. Oxidative stress and vascular disease. Dordrecht: Kluwer Academic Publishers: 1999;245-258.

[41] Kern T.S, Tang J, Mizutani M, Kowluru R.A, Nagaraj R.H, Romeo G., Podesta F., and Lorenzi M. Response of capillary cell death to aminoguanidine predicts the develop-

ment of retinopathy: comparison of diabetes and galactosemia. Investigative Ophthalmology and Visual Science. 2000;41: 3972-3978.

[42] Dobsak P., Courderot-Masuyer C., Siegelova J, Svacinova H., Jancik J.,Vergely-Vanriessen C., Rochette. Antioxidant properties of aminoguanidine: a paramagnetic resonance test Scripta Medica (BRNO). 2001;74 (1): 45–50.

[43] El-Shazly A.M, Mahmoud A.M, and Darwish N.S. Potential prophylactic role of aminoguanidine in diabetic retinopathy and nephropathy in experimental animals. Acta Pharmaceutica. 2009;59: 67–73.

[44] Fukui T, Noma T, Mizushige K, Aki Y, Kimura S, and Abe Y. Dietary troglitazone decreases oxidative stress in early stage type II diabetic rats. Life Sciences. 2000;66:2043–2049.

[45] Elmali E, Altan N, and Bukan N. Effect of the Sulphonylurea glibenclamide on liver and kidney antioxidant enzymes in streptozocin-induced diabetic rats. Drugs. 2004;5:203–8

[46] Gumieniczek A, Hopka H, Rolinski J, Bojarska-Junak A. Antioxidative and anti-inflammatory effects of repaglinide in plasma of diabetic animals. Pharmacology Research 2005;

[47] Mekinova D, Chorvathova V, Volkovova K, Staruchova M, Grancicova E, Klvanoca J, and Ondreicka R. Effect of intake of exogenous vitamins C, E and beta-carotene on the antioxidative status in kidneys of rats with streptozotocin-induced diabetes. Nahrung. 1995;39(4):257-261.

[48] Kocak G, Aktan F, Canbolat O, Ozogul C, Elberg S, Yildizoglu-Ari N, and Karasu C. Alpha-lipoic acid treatment ameliorates metabolic parameters, blood pressure, vascular reavtivity and morphology of vessels already damaged by streptozotocin-diabetes. Nutrition and Metabolism. 2000;13:308-318.

[49] Obrosova I, Fathallah L, and Greene D. Early changes in lipid peroxidation and antioxidative defense in rat retina. European Journal of Pharmacology. 2000;398:139-146.

[50] Cinar M, Ulker S, Alper G, and Evinc A. Effect of dietary vitamin E supplementation on vascular reactivity of thoracic aorta in streptozotocin-diabetic rats. Pharmacology. 2001;62(1):56-64.

[51] Maritim A, Sanders R, Watkins J.I. Effects of alpha-lipoic acid on biomarkers of oxidative stress in streptozotic-induced diabetic rats. Journal of Nutrition and Biochemistry. 2003;14(5):288-294.

[52] Rauscher F, Sanders R, and Watkins J.I. Effects of coenzyme Q10 treatment on antioxidant pathways in normal and streptozotocin- induced diabetic rats. Journal of Biochemistry and Molecular Toxicology. 2001;15:41-46.

[53] Kedziora-kornatowska K, Szram S, Kornatowski T, Szadujkis-Szadurski L, Kedziora J, and Bartosz G. Effect of vitamin E and vitamin C supplementation of antioxidative

state and renal glomerular basement membrane thickness in diabetic kidney. Experimental Nephrology. 2003;95:134-143.

[54] Ziegler D, Hanefeld M, Ruhnau K..J, Meissner H.P, Lobisch M, Schutte K, and Gries F.A Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). Diabetologia. 1995;38(12):1425-1433.

[55] Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Moller W, Tritschler H.J, and Mehnert H. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy. Free Radical Research. 1999;31(3):171-179.

[56] Ziegler D, Hanefeld M, Ruhnau K, Hasche H, Lobisch M, Schutte K, Kerum G, and Malessa R. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7- month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetes Care. 1999;22(8):1296-1301.

[57] Skyrme-Jones R.A, O'Brien R.C, Berry K.L, and Meredith I.T. Vitamin E supplementation improves endothelial function in type I diabetes mellitus: a randomized, placebo-controlled study. Journal of the American College of Cardiology. 2000;36(1): 94-102.

[58] Gaede P, Poulsen H.E, Parving H.H, and Pedersen O. Double-blind, randomized study of the effect of combined treatment with vitamin C and E on albuminuria in Type 2 diabetic patients. Diabetes and Medicine. 2001;18(9):756-760.

[59] Lonn E.M, Yusuf S, Dzavik V, Doris C.I, Yi Q, Smith S, Moore-Cox A, Bosch J, Riley W.A, Teo K.K. Effects of ramipril and vitamin E on atherosclerosis : The study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). Circulation. 2001;103(7):919-925.

[60] Beckman J.A, Goldfine A.B, Gordon M.B, Garrett L.A, Keaney J.F Jr, and Creager M.A. Oral antioxidant therapy improves endothelial function in Type 1 but not Type 2 diabetes mellitus. American Journal of Physiology. 2003;285(6):2392-2398.

[61] Mariod A.A., Matthaus B., and Hussein I. H. "Antioxidant properties of methanolic extracts from different parts of Sclerocarya birrea," International Journal of Food Science and Technology. 2008;43:921–926,

[62] Adaramoye O.A. and Adeyemi E.O. Hypoglycaemic and hypolipidaemic effects of fractions from Kolaviron, a biflavonoid complex from Garcinia kola in streptozotocin- induced diabetes mellitus rats. Journal of Pharmacy and Pharmacology. 2006;58:121-128.

[63] Rauter A.P., Martins A., Borges C., Mota-Filipe H., Pinto R., Sepodes B. and Justino J. Antihyperglycaemic and protective effects of flavonoids on streptozotocin-induced diabetic rats. Phytotherapy Research. 2010;24(2): S133-S138.

[64] Nakamura T, Kaneda Y and Ogihara T. Hepatocyte growth factor prevents endothelial cell death through inhibition of bax translocation from cytosol to mitochondrial membrane. Diabetes. 2002;51: 2604–2611.

[65] Hakkinen S.H., Karenlampi S.O., Heinonen I.M., and Mykkanen H. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. Journal of Agriculture and Food Chemistry. 1999;47:2274-2279.

[66] Larocca L.M., Teofili, L., Sica, S., Pierelli L., and Menichella G. Quercetin inhibits the growth of leukemic progenitors and induces the expression of transforming growth factor-B1 in these cells. Blood. 1995;85:3654-3661

[67] Cox D., Whichelow M.J, and Prevost T.A. Antioxidant effects of flavonoids. Public Health Nutrition. 2000;3:19-29.

[68] Chang W.S, Lee, Y.J, Lu, F.J. and Chiang, H.C. Inhibitory effects of flavonoids on xanthine oxidase. Anticancer Research. 1993;13:2165-2170.

[69] Chen Y.T, Zheng R.L., Jia Z.J. and Ju Y. Flavonoids as superoxide scavengers and antioxidants. Free Radical Biology and Medicine. 1990;9:19-20.

[70] Fiorani M., Guidarelli A., Blasa M., Azzolini C., Candiracci M., Piatti E., and Cantoni O. Mitochondria accumulate large amounts of quercetin: prevention of mitochondrial damage and release upon oxidation of the extra-mitochondrial fraction of the flavonoid. Journal of Nutrition and Biochemistry. 2010;21:397-404.

[71] Meyers K.J., Rudolf J.L. and Mitchell A.E. Influence of dietary quercetin on glutathione redox status in mice. Journal of Agriculture and Food Chemistry. 2008;56:830-836.

[72] Abd El-Baky A.E. Quercetin protective action on oxidative stress, sorbitol, insulin resistance and beta cells function in experimental diabetic rats. International Journal of Pharmaceutical Studies and Research 2011;2(2)11-18.

[73] Kwon O, Eck P, Chen S, Corpe C.P, Lee J.H, Kruhlak M, and Levine M. Inhibition of the intestinal glucose transporter GLUT2 by flavonoids. Federation of American Societies for Experimental Biology Journal. 21: 2007;366-77.

[74] Manzano S and Williamson G. Polyphenols and phenolic acids from strawberry and apple decrease glucose uptake and transport by human intestinal Caco-2 cells. Molecular Nutrition and Food Research. 2010;54:1773-80.

[75] Vessal M, Hemmati M, and Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comparative Biochemistry and Physiology Part C: Toxicology. 2003;135:357-64.

[76] Coskun O, Kanter M, Korkmaz A, and Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat páncreas. Pharmacology Research. 2005;51: 117-23.

[77] Kobori M, Masumoto S, Akimoto Y, and Takahashi Y. Dietary quercetin alleviates diabetic symptoms and reduces streptozotocininduced disturbance of hepatic gene expression in mice. Molecular Nutrition and Food Research. 2009;53: 859-68.

[78] Elberg G, Jinping L, Leibovitch A, and Shechter Y. Non-receptor cytosolic protein tyrosine kinases from various rat tissues. Biochimica et Biophysica Acta. 1995;1269:299-306.

[79] Portillo M.P., Aguirre L, Arias N, Macarulla M. T, and Gracia A. Beneficial Effects of Quercetin on Obesity and Diabetes. The Open Nutraceuticals Journal. 2011;4: 189-198.

[80] Youl E, Bardy G, Magous R, Cros G, Sejalon F, Virsolvy A, Richard S, Quignard J.F, Gross R, Petit P, Bataille D, and Oiry C. Quercetin potentiates insulin secretion and protects INS-1 pancreatic b-cells against oxidative damage via the ERK1/2 pathway. British Journal of Pharmacology. 2010;161(4):799-814.

[81] Longuet C, Broca C, Costes S, Hani E.H, Bataille D, and Dalle S. Extracellularly regulated kinases (p44/42 mitogen-activated protein kinases) phosphorylate synapsin I and regulate insulin secretion in the MIN6 beta-cell line and islets of Langerhans. Endocrinology. 2005;146: 643-54.

[82] Rivera L, Morón R, Sánchez M, Zarzuelo A, and Galisteo M. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese zucker rats. Obesity. 2008;16:2081-7.

[83] Hussain S.A, Ahmed Z.A., Mahwi T.O., and Aziz T.A. Quercetin Dampens Postprandial Hyperglycemia in Type 2 Diabetic Patients Challenged with Carbohydrates Load International Journal of Diabetes Research. 2012;1(3): 32-35.

[84] Steward L.K, Wang Z, Ribnicky D, Soileau J.L, Cefalu W.T, and Gettys T.W. Failure of dietary quercetin to alter the temporal progression of insulin resistance among tissues of C57BL/6J mice during the development of diet-induced obesity. Diabetologia. 2009;52: 514-23.

[85] Wein S, Behm N, Petersen R.K, Kristiansen K, Wolffram S. Quercetin enhances adiponectin secretion by a PPARא independent mechanism. European Journal of Pharmaceutical Sciences. 2010;41:16-22.

[86] Hertog M.G., Hollman P.C., Katan M. B. and Kromhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in The Netherlands. Nutrition and Cancer. 1993;20:21–29.

[87] Janbaz K.H., Saeed S.A. and Gilani A.H Protective effect of rutin on paracetamol- and CCl4-induced hepatotoxicity in rodents. Fitoterapia. 2002;73: 557–563.

[88] Navarro-Núñez L., Lozano M.L, Palomo M, Martínez C, Vicente V, and Castillo J, "Inhibits Platelet Adhesion and Thrombus Formation and Synergizes with Aspirin in the Suppression of the Arachidonic Acid Pathway", Journal of Agriculture and Food Chemistry. 2008;56(9): 2970–6.

[89] Kamalakkannan N and Prince P.S.M. Antihyperglycaemic and Antioxidant Effect of Rutin, a Polyphenolic Flavonoid, in Streptozotocin-Induced Diabetic Wistar Rats. Basic, Clinical Pharmacology and Toxicology. 2006;98: 97–103.

[90] Kozlov A.V., Ostrachovitch E.A. and Afanas'ev I.B. Mechanism of inhibitory effects of chelating drugs on lipid peroxidation in rat brain homogenates. Biochemical Pharmacology. 1994;47:795–799.

[91] Fernandes H., Angélica A., Lourenzi E., Novelli B., Okoshi K., Okoshi M.P, Di Muzio B.P., Guimarães J.F.C, Fernandes A Jnr. Influence of rutin treatment on biochemical alterations in experimental diabetes. Biomedicine and pharmacotherapy. 2010;64(3): 214-219.

[92] Alsaif M.A. Beneficial Effects of Rutin and Vitamin C Coadministration in a Streptozotocin-Induced Diabetes Rat Model of Kidney Nephrotoxicity. Pakistan Journal of Nutrition. 2009;8 (6):745-754.

[93] Sattanathan K., Dhanapal C.K.,and Manavalan R. LDL lowering properties of rutin in diabetic patients. International Journal of Pharma and Bio sciences. 2010;1(4): 0975-6299.

[94] Hunyadi A, Martins A, Hsieh T.J, Seres A, Zupko´ I. Chlorogenic Acid and Rutin Play a Major Role in the In Vivo Anti-Diabetic Activity of Morus alba Leaf Extract on Type II Diabetic Rats. PLoS ONE 2012;7(11): e50619. doi:10.1371/journal.pone. 0050619.

[95] Carmada L., Distefano V., DelBosco S.F., and Schillaci D. Antoproliferative activity of citrus juices and HPLC evaluation of their flavonoid composition. Fitoterapia. 2007;78:426-429.

[96] Galati E.M, Monforte M.T, Kirjavainen S, Forestieri A.M, and Trovato A. Il Farmaco, 1994;49:709.

[97] Crespo M.E, Galvez J, Cruz T, Ocete M.A, and Zarzuelo A. Antiinflammatory activity of diosmin and hesperidin in rat colitis induced by TNBS. Planta Medica. 1999;65:651-653.

[98] Hitzenberger G. Therapeutic effectiveness of flavonoids shown on the example of DafIonC4 500 mg. Wein. Med. Wochenschr. 1997;174:409.

[99] Rezai-Zadeh K, Douglas Shytle R, Bai Y, Tian J, Hou H, Mori T, Zeng J., Obregon D., Town T., and Tan, J. Flavonoid-mediated presenilin-1 phosphorylation reduces Alzheimer's disease beta-amyloid production. Journal of Cellular and Molecular Medicine. 2009;13:574-88.

[100] Lacombe C, Lelievre J.C, Bucherer C, and Grimaldi A. Activity of Daflon 500 mg on the hemorheological disorders in diabetes. International Angiology. 1989;8:45-48.

[101] Valensi P.E, Behar A, De-Champvallins M.M, Attalah M, Boulakia F.C, and Attali J.R. Effects of a purified micronized flavonoid fraction on capillary filtration in diabetic patients. Diabet Med. 1996;13:882-888.

[102] Manuel Y, Keenoy B, Vertommen J, and De Leeuw I. The effect of flavonoid treatment on the glycation and antioxidant status in type 1 diabetic patients. Diabetes Nutrition and Metabolism. 1999;12:256-263.

[103] Tanaka T. Makita H., Kawabata K., Mori H., Kakumoto M and Satoh K. Carcinogenesis. 1997;18: 957.

[104] Tirkey N, Pilkhwal S, Kuhad A, and Chopra K. Hesperidin, a citrus bioflavonoid, decreases the oxidative stress produced by carbon tetrarchloride in rat liver and kidney. BMC Pharmacology. 2005;5:2.

[105] Jung U.J, Lee M.K, Park Y.B, Kang M.A and Choi M.S. Effect of citrus flavonoids on lipid metabolism and glucose-regulating enzyme mRNA levels in type-2 diabetic mice. International Journal of Biochemistry and Cell Biology. 2006;38:1134-1145.

[106] Kaur G, Tirkey N, Chopra K. Beneficial effect of hesperidin on lipopolysaccharide-induced hepatotoxicity. Toxicology. 2006;226: 152-160.

[107] Pari L. and Srinivasan S. Antihyperglycemic effect of diosmin on hepatic key enzymes of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats, Biomedicine and Pharmacotherapy. 2010;64(7):477-481.

[108] Silambarasan T and Raja B. Diosmin, a bioflavonoid reverses alterations in blood pressure, nitric oxide, lipid peroxides and antioxidant status in DOCA-salt induced hypertensive rats. European Journal of Pharmacology. 2012;679(1): 81-89.

[109] Kraft K. Artichoke leaf extract—recent findings reflecting effects on lipid metabolism, liver and gastrointestinal tracts. Phytomedicine. 1997;4(4), 369-378.

[110] Ross J.A and Kasum C.M. Dietary flavonoids: bioavailability, metabolic effects, and safety. Annual Review of Nutrition. 2002;22:19-34.

[111] Choi J.S, Choi Y.J, Park S.H, Kang J.S, and Kang Y.H. Flavones mitigate tumor necrosis factor-alpha-induced adhesion molecule upregulation in cultured human endothelial cells: role of nuclear factor-kappa B. Journal of Nutrition. 2004;134:1013–9.

[112] Loizzo M.R, Said A, Tundis R, Rashed K, Statti G.A, Hufner.A., and Menichini.F. Inhibition of angiotensin converting enzyme (ACE) by flavonoids isolated from Ailanthus excelsa (Roxb) (Simaroubaceae). Phytotherapy Research. 2007;21:32–6.

[113] Ma X, Li Y.F, Gao Q, Ye Z.G, Lu X.J, Wang H.P, Jiang, H.D., Bruce, I.C. and Xia, Q. Inhibition of superoxide anionmediated impairment of endothelium by treatment with luteolin and apigenin in rat mesenteric artery. Life Sciences. 2008;83:110–7.

[114] Xu K., Liu B., Ma Y., Du J., Li G., Gao H., Zhang Y. and Ning Z. Physicochemical Properties and Antioxidant Activities of Luteolin-Phospholipid Complex. Molecules. 2009;14:3486-93.

[115] Horvathova K., Chalupa I., Sebova L., Tothova D., Vachalkova A. Protective effect of quercetin and luteolin in human melanoma HMB-2 cells. Mutation Research. 2005;565:105-12.

[116] Odontuya G., Hoult J.R., and Houghton P.J. Structure-activity relationship for antiinflammatory effect of luteolin and its derived glycosides. Phytotherapy Research. 2005;19: 782-6.

[117] Cheng I.F. and Breen K. On the ability of four flavonoids, baicilein, luteolin, naringenin, and quercetin, to suppress the Fenton reaction of the iron-ATP complex. Biometals. 2000;13:77-83.

[118] Hu C, and Kitts D.D. Luteolin and luteolin-7-O-glucoside from dandelion flower suppress iNOS and COX-2 in RAW264.7 cells. Molecular and Cellular Biochemistry. 2004;265:107-113.

[119] Wruck C.J., Claussen M., Fuhrmann G., Romer L., Schulz A., Pufe T., Waetzig V., Peipp M., Herdegen T., Gotz M.E. Luteolin protects rat PCl2 and C6 cells against MPP+ induced toxicity via an ERK dependent Keap1-Nrf2-ARE pathway. Journal of Neural Transmission. 2007;72:57-67.

[120] Choi B.M, Lim D.W, Lee J.A, Gao S.S, Kwon D.Y, and Kim B.R. Luteolin suppresses Cisplatin-induced apoptosis in auditory cells: possible mediation through induction of heme oxygenase-1 expression. Journal of Medicinal Food. 2008;11:230-6.

[121] Qiusheng Z., Yuntao Z., Rongliang Z., Dean G., Changling L. Effects of verbascoside and luteolin on oxidative damage in brain of heroin treated mice. Pharmazie. 2005;60:539-43.

[122] Manju V., Balasubramaniyan V., Nalini N. Rat colonic lipid peroxidation and antioxidant status: the effects of dietary luteolin on 1,2-dimethylhydrazine challenge. Cellular and Molecular Biology Letters. 2005;10: 535-51.

[123] Zarzuelo A., Jiménez I., Gámez M.J., Utrilla P., Fernadez I., Torres M.I., and Osuna I. Effects of luteolin 5-O-b-rutinoside in streptozotocin-induced diabetic rats. Life Sciences. 1996;58, 2311–2316.

[124] Kim J. S., Kwon C. S., and Son K. H. Inhibition of alpha-glucosidase and amylase by luteolin, a flavonoid. Bioscience, Biotechnology and Biochemistry. 2000;64(11): 2458-61.

[125] Ding L, Jin D, and Chen X. Luteolin enhances insulin sensitivity via activation of PPARγ transcriptional activity in adipocytes. Journal of Nutrition and Biochemistry; 2010;21(10): 941-7.

[126] Bohm F, Tinkler J.H, and Truscott T.G. Carotenoids protect against cell membrane damage by the nitrogen dioxide radical. Natural Medicine. 1995;1:98-99.

[127] Porrini M and Riso P. Lymphocyte lycopene concentration and DNA protection from oxidative damage is increased in women after a short period of tomato consumption. Journal of Nutrition. 2000;130:189-192.

[128] Arab L. and Steck S. Lycopene and cardiovascular disease. American Journal of Clinical Nutrition. 2000;71: 1691S-5S.

[129] Kuhad A., Sethi R. and Chopra K. Lycopene attenuates diabetes-associated cognitive decline in rats. Life Sciences. 2008;83:128–134.

[130] Agarwal S, and Rao A.V. Tomato Lycopene and Its Role in Human Health and Chronic Diseases. Canadian Medical Association Journal. 2000;163(6) : 739.

[131] Basuny A.M, Mostafat D.M. and Azouz A. Supplementation of polyunsaturated oils with lycopene as natural antioxidant and antipolymerization during heating process. Minia Journal of Agricultural Research and Development. 2006;26: 449-469.

[132] Basuny A.M, Gaafar A.M. and Arafat S.M. Tomato lycopene is a natural antioxidant and can alleviate hypercholesterolemia. African Journal of Biotechnology. 2009;23: 6627-6633.

[133] Hisao G, Fong T.H, Tzu N.H, Lin K.H, Chou D.S, and Sheu J.R. A potent antioxidant, lycopene, affords neuroprotection against microglia activation and focal cerebral ischemia in rats. In Vivo. 2004;18: 351- 356.

[134] Gunasekera R.S, Sewgobind K., Desai S., Dunn L, Black H.S., McKeehan W.L, and Patil B. Lycopene and lutein inhibit proliferation in rat prostate carcinoma cells. Nutrition and Cancer. 2007;58:171–177.

[135] Akbaraly N.T, Faure H., Gourlet V., Favier A. and Berr, C. Plasma carotenoid levels and cognitive performance in an elderly population: Results of the EVA Study. Journals of Gerontology, Series A, 2007;62: 308–316.

[136] Riso P., Visioli F., Grande S., Guarnieri S., Gardana C., Simonetti P., Porrini M. Effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. Journal of Agriculture and Food Chemistry. 2006;54, 2563–2566.

[137] Krinsky N.I. Carotenoids as antioxidants. Nutrition. 2001;17: 815-817.

[138] Mortensen A., Skibsted L.H., Truscott T.G. The interaction of dietary carotenoids with radical species. Archives of Biochemistry and Biophysics. 2001;385, 13–19.

[139] oung A.J. and Lowe G.M. Antioxidant and prooxidant properties of carotenoids. Archives of Biochemistry and Biophysics. 2001;385, 20–27.

[140] El-Agamey A., Lowe, G.M., McGarvey D.J., Mortensen A., Phillip D.M, Truscott T.G., Young A.J. Carotenoid radical chemistry and antioxidant or pro-oxidant properties. Archives of Biochemistry and Biophysics. 2004;430:37–48.

[141] Krinsky N.I and Johnson E.J. Carotenoid actions and their relation to health and disease. Molecular Aspects of Medicine. 2005;26: 459–516.

[142] Polidori M.C., Mecocci P., Stahl W., Parente B., Cecchetti R., Cherubini A., Cao P., Sies H., Senin U. Plasma levels of lipophilic antioxidants in very old patients with Type 2 diabetes. Diabetes/Metabolism Research and Reviews. 2000;16:15–19.

[143] Coyne T, Ibiebele T.I, Baade P.D, Dobson A, McClintock C, Dunn S, Leonard D, Shaw J. Diabetes mellitus and serum carotenoids: Findings of a population-based study in Queensland, Australia. American Journal of Clinical Nutrition. 2005;82: 685–693.

[144] Ford E.S, Will J.C, Bowman B.A, and Narayan K.M. Diabetes mellitus and serum carotenoids findings from the Third National Health and Nutrition Examination Survey. American Journal of Epidemiology. 1999;149:168-176.

[145] Kuhad A., and Chopra K. Lycopene ameliorates thermal hyperagesia and cold allodynia in STZ-induced diabetic rat. Indian Journal of Experimental Biology. 2008;46:108-111.

[146] Krul C, Luiten-Schuite A, Tenfelde A, van Ommen B, Verhagen H, and Havenaar R. dAntimutagenic activity of green tea and black tea extracts studied in a dynamic in vitro gastrointestinal model. Mutation Research. 2001;474:71–85.

[147] Schmidt M, Schmitz H.J, Baumgart A, Guedon D, Netsch M.I, Kreuter M.H, Schmidlin C.B, and Schrenk, D. Toxicity of green tea extracts and their constituents in rat hepatocytes in primary culture. Food Chemistry and Toxicology. 2005;43:307– 14.

[148] Sutherland B.A., Rosanna M.A., Rahman, Appleton I. Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration Journal of Nutritional Biochemistry. 2006;17:291– 306.

[149] Ruch R.J, Cheng S.J, and Klaunig J.E. Prevention of cytotoxicity and inhibition of intercellular communication by antioxidant catechins isolated from Chinese green tea. Carcinogenesis. 1989;10:1003–8.

[150] Guo Q, Zhao B, Li M, Shen S, and Xin W. Studies on protective mechanisms of four components of green tea polyphenols against lipid peroxidation in synaptosomes. Biochim Biophys Acta; 1996;1304:210– 22.

[151] Sawai Y and Sakata K. NMR analytical approach to clarify the antioxidative molecular mechanism of catechins using 1,1- diphenyl-2-picrylhydrazyl. Journal of Agriculture and Food Chemistry. 1998;46:111 –4.

[152] Kashima M. Effects of catechins on superoxide and hydroxyl radical. Chemical and Pharmaceutical Bulletin (Tokyo). 1999;47:279– 83.

[153] Nanjo F, Mori M, Goto K, and Hara Y. Radical scavenging activity of tea catechins and their related compounds. Bioscience Biotechnology Biochemistry.1999;63:1621–3.

[154] Zhao B, Guo Q, and Xin W. Free radical scavenging by green tea polyphenols. Methods in Enzymology. 2001;335:217–31.

[155] Sang S, Tian S, Wang H, Stark R.E, Rosen R.T, Yang C.S, and Ho C.T. Chemical studies of the antioxidant mechanism of tea catechins: radical reaction products of epicatechin with peroxyl radicals. Bioorganic and Medicinal Chemistry. 2003;11:3371– 8.

[156] Grinberg L.N, Newmark H, Kitrossky N, Rahamim E, Chevion M, and Rachmilewitz E.A. Protective effects of tea polyphenols against oxidative damage to red blood cells. Biochemistry and Pharmacology. 1997;54:973– 8.

[157] Seeram N.P and Nair M.G. Inhibition of lipid peroxidation and structure–activity-related studies of the dietary constituents anthocyanins, anthocyanidins, and catechins. Journal of Agriculture and Food Chemistry. 2002;50:5308– 12.

[158] Anderson R.F, Fisher L.J, Hara Y, Harris T, Mak W.B, Melton L.D, and Packer J.E. Green tea catechins partially protect DNA from hydroxyl radical induced strand breaks and base damage through fast chemical repair of DNA radicals. Carcinogenesis; 2001;22:1189– 93.

[159] Skrzydlewska E, Ostrowska J, Farbiszewski R, and Michalak K. Protective effect of green tea against lipid peroxidation in the rat liver, blood serum and the brain. Phytomedicine. 2002;9:232– 8.

[160] Anderson R.A and Polansky M.M. Tea enhance insulin activity. Journal of Agriculture and Food Chemistry. 2002;50: 7182-7186.

[161] Sabu M.C, Smitha K, and Kuttan R. Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. Journal of Ethnopharmacology. 2002;83:109-116.

[162] Tsuneki H, Ishizuka M, Terasawa M, Wu J.B, Sasaoka T, and Kimura I. Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic (db/db) mice and on glucose metabolism in healthy humans. BMC Pharmacology. 2004;4:18-27.

[163] Fukino Y, Shimbo M, Aoki N, Okubo T, and Iso H. Randomized controlled trial for an effect of green tea consumption on insulin resistance and inflammation markers. Journal of Nutritional Science and Vitaminology (Tokyo); 2005;51:335-342.

[164] Rizvi S.I, Abu Zaid M, Anis R, and Mishra N. Protective role of tea catechins against oxidation-induced damage of type 2 diabetic erythrocytes. Clinical and Experimental Pharmacology and Physiology. 2005;32:70–75.

[165] Rizvi S.I, and Abu Zaid M. Impairment of sodium pump and Na/H exchanger in erythrocytes from NIDDM patients. Effect of tea catechins. Clinica Chimica Acta. 2005;354: 59–67

[166] Qin B., Panickar K.S., and Anderson R.A. Cinnamon: Potential role in the prevention of insulin resistance, metabolic syndrome, and type 2 diabetes. Journal of Diabetes Science and Technology. 2010;4: 685–693.

[167] Sirichai A., Weerachat S., Aramsri M., Sathaporn N., and Sirintorn Y. Cinnamic Acid and Its Derivatives Inhibit Fructose-Mediated Protein Glycation. International Journal of Molecular Sciences. 2012;13:1778-1789.

[168] Lee E.J., Kim S.R., Kim J., and Kim Y.C. Hepatoprotective phenylpropanoids from Scrophularia buergeriana roots against CCl4-induced toxicity: Action mechanism and structure-activity relationship. Planta Medica. 2002;68: 407–411.

[169] Natella F., Nardini M., Di, Felice M., and Scaccini C. Benzoic and cinnamic acid derivatives as antioxidants: Structure-activity relation. Journal of Agriculture and Food Chemistry.1999;47:1453–1459.

[170] Liu I.M., Hsu F.L, Chen C.F, and Cheng J.T. Antihyperglycemic action of isoferulic acid in streptozotocin-induced diabetic rats. British Journal of Pharmacology. 2000;129: 631–636.

[171] Shahidi F. and Naczk M. Cereals, legumes and nuts. In " Phenolics in Food and Nutra ceuticals, CRC press, Boca Raton, 2004;17-166.

[172] Nenadis N., Lazaridou O. and Tsimidou M. Use of reference compounds in antioxidant activity. Pancreas. 2007;15(3): 246-50.

[173] Kanchana G., Shyni W.J, Rajadurai M. and Periasamy R. Evaluation of Antihyperglycemic Effect of Sinapic Acid in Normal and Streptozotocin-Induced Diabetes in Albino Rats. Global Journal of Pharmacology. 2011;5(1): 33-39.

[174] Masoko P., Mmushi T. J., Mogashoa M. M., Mokgotho M. P., Mampuru L. J., and Howard R.L. "In vitro evaluation of the antifungal activity of Sclerocarya birrea extracts against pathogenic yeasts," African Journal of Biotechnology. 2008;7: 3521–3526.

[175] Njume C., Afolayan A. J., Green E., and Ndip R. N. "Volatile compounds in the stem bark of Sclerocarya birrea (Anacardiaceae) possess antimicrobial activity against drug-resistant strains of Helicobacter pylori. International Journal of Antimicrobial Agents. 2011;38(4): 319-324

[176] Dieye A.M, Sarr A, Diop S.N, Ndiaye M, Sy G.Y, Diarra M, Rajraji G.I, Ndiaye S.A and Faye B. Medicinal plants and the treatment of diabetes in Senegal: survey with patients. Fundamental and Clinical Pharmacology. 2008;22: 211–216.

[177] Dimo T., Rakotonirina S.V., Tan P.V., Azay J, Dongo E, Kamtchouing P, and Cros G. Effect of Sclerocarya birrea (Anacardiaceae) stem bark methylene chloride/methanol extract on streptozotocin-diabetic rats. Journal of Ethnopharmacology. 2007;110: 434–438.

[178] Kirtikar, K. R. and Basu, B. D. Indian Medicinal Plants, Bishen Singh Mahendra Pal Singh, Dehradun,, 1998;2(7):22462247.

[179] DeFeudis F.V, Papadopoulos V and Drieu K. Gingko biloba extracts and cancer: a research area in its infancy. Fundamentals of Clinical Pharmacology. 2003;17: 405- 17.

[180] Takeoka G.R and Dao L.T. Antioxidant constituent of almond [Prunus dulcis (Mill.) D.A. Webb.] hulls. Journal of Agriculture and Food Chemistry. 2003;51: 496-501.

[181] Van Rensburg W.J, Ferreira D, Malan E and Steenkamp J.A. Tyrosinase catalysed biphenyl construction from flavan-3-ol substrates. Phytochemistry. 2000;53: 285-92.

[182] Kumar R.S, Rajkapoor B, Perumal P, Dhanasekaran T, Josea M.A. and Jothimanivannan C. Antitumor Activity of Prosopis glandulosa Torr. on Ehrlich Ascites Carcinoma (EAC) Tumor Bearing Mice. Iranian Journal of Pharmaceutical Research. 2011;10: 505-510.

[183] Siddhuraju P. Antioxidant activity of polyphenolic compounds extracted from defatted raw and dry heated Tamarindus indica seed coat. LWT Food Science and Technology. 2007;40:982-990.

[184] Maiti R, Das U.K and Ghosh D (). Attenuation of Hyperglycemia and Hyperlipidemia in Streptozotocin- Induced Diabetic Rats by Aqueous Extract of Seed of Tamarindus indica. Biological and Pharmaceutical Bulletin. 2005;28:1172-1176.

[185] Martinello F, Soaresm S.M and Franco J.J. Hypolipidemic and antioxidant activities from Tamarindus indica L. pulp fruit in hypercholestromic hamsters. Food and Chemical Toxicology. 2006;44:810-818.

[186] Sudjaroen Y, Haubner R, Wu°rtele G, Hull W.E, Erben G, Spiegelhalder B, Changbumrung S, Bartsch H and Owen R.W (). Isolation and structure elucidation of phenolic antioxidants fromTamarind (Tamarindus indica L.) seeds and pericarp. Food and Chemical Toxicology. 2005;43:1673-1682.

[187] Mahmoudzades-Sagheb H, Heidari Z, Shahraki M and Moudi B. A stereological study of effects of aqueous extract of Tamarindus indica seeds on pancreatic islets in Streptozotocin-induced diabetic rats. Pakistan Journal of Pharmaceutical Sciences. 2010;23:427-434.

[188] Lebovitz, H.E. Postprandial hyperglycemic state: importance and consequences. Diabetes Research and Clinical Practice. 1998;40: S27–S28.

[189] DeFronzo R.A. Pharmacologic Therapy for Type 2 Diabetes Mellitus. Annals of Internal Medicine. 1999;131:281-303.

[190] Bailey C.J. Potential new treatments for type 2 diabetes. Trends in Pharmacological Sciences. 2000;1(7):259-65

IntechOpen

IntechOpen