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Oxidative stress and antioxidant effects of herbs and spices in diabetes

C.U. Rajeshwari, R.I. Shobha and B. Andallu

Sri Sathya Sai Institute of Higher Learning, Anantapur Campus, Anantapur-515001, Andhra Pradesh, India

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Abstract

Reactive oxygen and nitrogen species are produced during metabolism and immune activity, and are triggered by several environmental factors such as pollution, chemicals, smoke, and sunlight. Harmful effects of these reactive species include cellular damage to nucleic acids, proteins and lipids leading to several diseases. The quality of life and the lifespan of the patients with these diseases depend on their complications. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications. This has accelerated the global effort to harness and harvest those herbs and spices that bear substantial amount of potential phytochemicals, showing multiple beneficial effects in combating diabetes and diabetes-related complications. Herbal products or plant products rich in phenolic compounds, flavonoids, terpenoids, coumarins, and other constituents show reduction in blood glucose levels. Therefore, to combat the ever-increasing oxidative stress-induced diseases, increased consumption of diet derived antioxidants may be particularly helpful as antioxidants, in diminishing cumulative oxidative damage.

Key words : Reactive oxygen and nitrogen species, oxidative stress, diabetes mellitus, antioxidants, phytochemicals

List of abbreviations

2, 3-DPG	:	2, 3-diphosphoglycerate
ADA	:	American diabetes association
ADP	:	Adenosine diphosphate
AGEs	:	Advanced glycation end products
AI	:	Atherogenic index
ATP	:	Adenosine triphosphate
CAT	:	Catalase
CD	:	Conjugated dienes
CVD	:	Cardiovascular disease
dhBBR	:	Dihydroberberine
DM	:	Diabetes mellitus
DNA	:	Deoxy ribonucleic acid
DNSG	:	Diabetes and nutrition study group
GOT	:	Glutamate oxaloacetate transaminase
GPT	:	Glutamate pyruvate transaminase
GSH	:	Reduced glutathione
GSH-px	:	Glutathione peroxidase
GSSG	:	Oxidized glutathione
GST	:	Glutathione-s-transferase
HDL-c	:	High density lipoprotein cholesterol
HFD	:	High-fat diet
LDL-c	:	Low density lipoprotein cholesterol
LOOH	:	Lipid hydroperoxides
NAD^+	:	Nicotinamide adenine dinucleotide
NADH	:	Reduced nicotinamide adenine dinucleotide
NADPH	:	Reduced nicotinamide adenine dinucleotide phosphate
NO	:	Nitric oxide
NOS	:	Nitric oxide synthase

Author for correspondence: Mrs. C.U. Rajeshwari
Food Science and Nutrition Division, Sri Sathya Sai Institute of Higher Learning, Anantapur Campus, Anantapur-515001, A.P., India
E-mail: rajeswarichandrashekaru@sssihl.edu.in; sairajic@gmail.com
Tel.: +91-9701754790

PPAR-g	:	Peroxisome proliferator activated receptor gamma
PPARs	:	Peroxisome proliferator activated receptors
S-GLUT-1	:	Sodium glucose cotransporter-1
SOD	:	Superoxide dismutase
STZ	:	Streptozotocin
TBARS	:	Thiobarbituric acid reactive substances
TC	:	Total cholesterol
TG	:	Triglyceride
TNFα	:	Tumor necrosis factor α
TXA_2	:	Thromboxane A_2
VLDL	:	Very low density lipoprotein
WHO	:	World health organization

Introduction

Oxidative stress lies at the root cause of a number of chronic diseases such as diabetes, cancer, atherosclerosis, rheumatic arthritis, hematological and neurodegenerative disorders. Diabetes mellitus is one of the primary threats to human health due to rising prevalence, chronic course and alarming complications (Rang *et al*., 2003).

India stands first in the whole world, having the highest number of diabetes patients, mainly of non-insulin dependent diabetes mellitus (NIDDM). The global incidence for all age groups was likely to be 2.8% in 2000 AD and the estimate would reach to 4.4% in 2030 AD (Sarah *et al*., 2004). Within few decades, it will become one of the world's commonest diseases, world's main disablers and killers within the next 25 years. The human population worldwide appears to be in the midst of an epidemic of diabetes. This disease requires medical diagnosis, treatment and changes in life style. Despite the great strides that have been made in the understanding and management of diabetes, the disease and disease-related complications are increasing unabated (Diamond, 2003).

Oxidative stress and diabetes mellitus

Oxidative stress is defined as a disturbance in regular cellular and molecular function, caused by an imbalance between production of reactive species and the natural antioxidant ability of our cells. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) often act mutually to create a state of oxidative stress. ROS are arguably important of the free radicals in biological systems. Many of the defects either at the site of origin or elsewhere are mediated by reactive species from different sources. The production of ROS is usually in balance with the availability and cellular localization of antioxidant enzymes and thiols, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (Gpx) and glutathione (GSH) (Boaz et al., 2000) Figure 1.

Accumulating evidences point to many interesting mechanisms that increased production of reactive oxygen/ nitrogen species and decrease antioxidant protection in diabetic patients (Atalay *et al.*, 2002). The increased oxidative stress as measured by indices of lipid peroxidation and protein oxidation has been shown to be increased in both insulin dependent diabetes mellitus (IDDM), and non-insulin dependent diabetes mellitus (NIDDM) (Cederberg *et al.*,2001a) even in patients without complications. Oxidative stress may be augmented and propagated by tissue damage and cell death, leading to a simultaneous increase in free radical production and compromised inhibitory and scavenger mechanisms, which further worsen the oxidative stress. Experimental evidences indicate that oxidative stress may determine the onset and progression of late diabetes complications (Santini *et al.*,1997).

Complications due to oxidative stress

Diabetes is characterized by chronic high blood glucose that causes glycation of body proteins which leads to severe complications. These complications are classified into acute metabolic and late systemic complications.

Acute metabolic complications

These include diabetic ketoacidosis, hyperosmolar nonketonic coma and hypoglycemia; sub acute complications are thirst, polyuria, lack of energy, visual blurriness and weight loss.

Late systemic complications

These are atherosclerosis, diabetic microangiopathy, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and infections. Diabetes is also accompanied by a substantial increase in atherosclerotic disease of large vessels, including cardiac, cerebral, and peripheral vascular disease, cardiovascular diseases (CVDs) (Notkins, 2002).

Mechanisms underlying oxidative stress

Diabetic micro and macroangiopathy are considered to be polyaetiological multifactorial diseases where persistent hyperglycaemia plays the leading part. A well established correlation exists between development of macro and microvascular diseases in diabetes mellitus. Vascular endothelial cells are an important target of hyperglycemic damage, but the mechanisms underlying this damage are not fully understood. Early marker of such damage is the development of an endothelial dysfunction. On the other hand, it contributes to the origin of oxidative stress. Hence, the patients are exposed to continuously increasing oxidative stress caused by the prolonged hyperglycaemia and conditioned by different pathophysiological processes (Goycheva *et al.*, 2006).

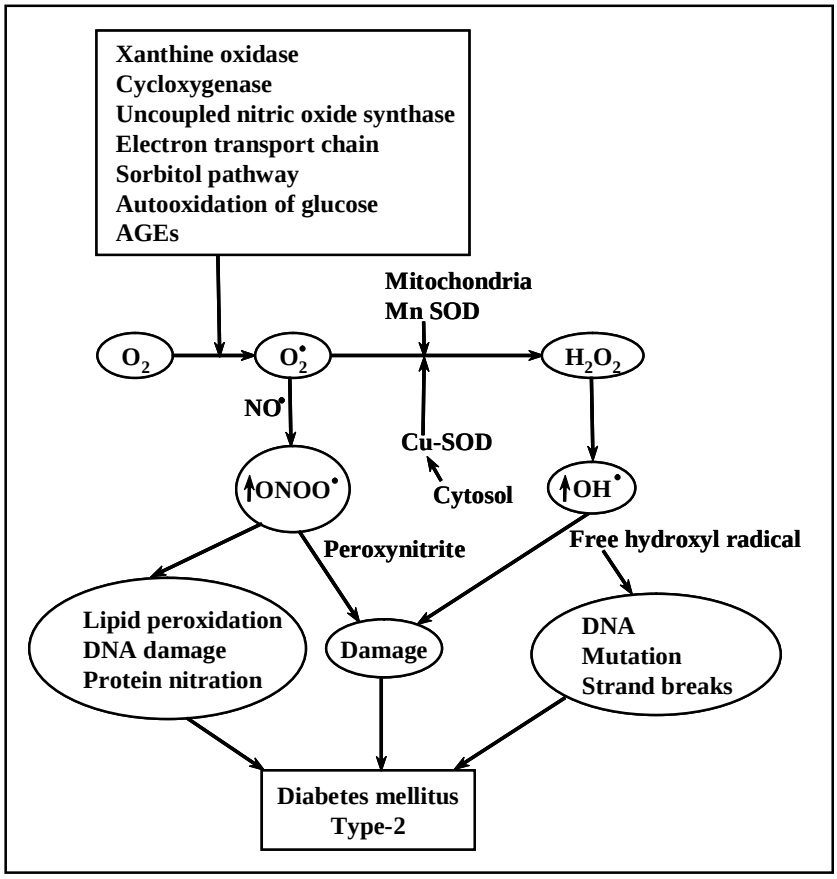

Figure 1: Composite diagram showing different sources leading to enhanced generation of ROS in diabetes (Boaz *et al*., 2000)

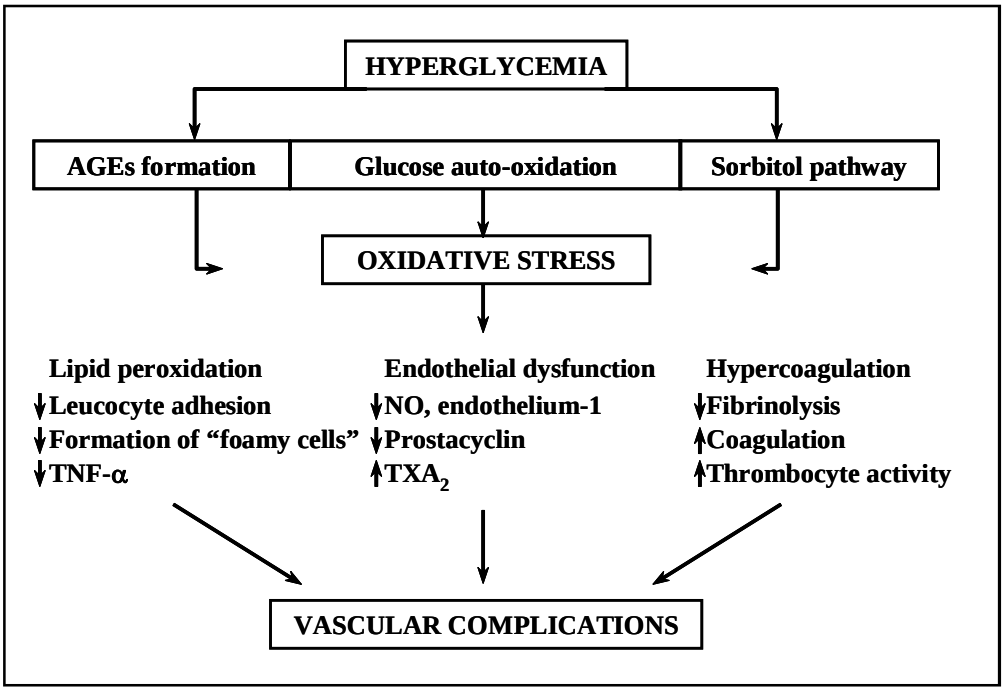

Figure 2: Schematic representation-hyperglycemia and biochemical processes leading to oxidative stress and vascular complications AGEs-Advanced Glycation end products; TXA_2-Thromboxane A_2; TNFα-Tumour Necrosis Factor - α; NO - Nitric Oxide (Goycheva *et al*., 2006)

Hyperglycemia

Hyperglycemia generates ROS, which, in turn causes lipid peroxidation and membrane damage (Bavarva and Narasimhacharya, 2010). Hyperglycemia is also known to bring about an increased production of superoxides and lower the antioxidant enzyme activities, compromising with the body's antioxidant defense systems, leading to development of 'oxidative stress' (Kamalakannan and Prince, 2003). In diabetes, an altered oxidative metabolism is a result either of the chronic exposure to hyperglycaemia or of the absolute or relative insulin deficit because insulin regulates several reactions involved in oxido-reductive metabolism. In the state of chronic hyperglycaemia, non-enzymatic glycosylation of proteins sets in (Goldstein *et al.,* 2005; Goycheva *et al.,*2006) Figure 2.

Glucose auto-oxidation products can attach to specific receptors from the surface of endothelial cells and change their properties. For instance, their combining with nuclear factor kappa-B (NF-kB) stimulates the synthesis of atherogenic circulating adhesive molecules and inflammatory cytokines (Tumor necrosis factor- TNFα). For their part, they regulate cellular growth, proliferation and migration and they have a very important role for early formation of atherosclerotic lesions. Hyperglycaemia in non-insulin dependent diabetic cells activate aldose reductase enzyme, which leads to intensive metabolization of glucose into sorbitol and fructose (Figure 2). It reduces the proportion of NAD^+/NADH and increases the proportion of NADH/NAD^+. The trouble in the oxidation of NADH in the respiratory chain is indicated as"hyperglycaemic pseudo hypoxia" that leads to increased quantity of ROS in the cells (Ho and Bray, 1999).

The increased formation of ROS is reinforced also by the real hypoxia related to vessel complications in diabetes mellitus. Reinforced formation of ROS in the conditions of pseudo and real hypoxia could be connected with activation of protein kinase C, a key enzyme in transmission of signals (the inclusion of sorbitol way increases *de novo* diacylglycerols synthesis which is a cause for activating protein kinase C in endothelial cells). Protein kinase C phosphorylates and thus, activates phospholipase A that releases arachidonic acid from membrane phospholipids as at the same time, the quantity of superoxide radicals and prostanoides is increased (Koya and King, 1998).

Lipid peroxidation

Peroxidation of membrane lipids and circulating lipoproteins including cholesterol and oxidative damage of cellular proteins and DNA, and less protein in retina are all considered to be the mechanisms by which the oxygen-free radicals and peroxides cause diseases. Lipid peroxidation in individuals with clinical manifestations of atherosclerosis may be dependent on underlying abnormalities in glucose metabolism. Excess lipid peroxidation as measured by formation of thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides (LOOH) and / or conjugated dienes (CD) has been found in most studies (Nordman *et al.,*1992).

The increased peroxidation can result in changes in cellular metabolism of the hepatic and extra-hepatic tissues. Products of lipid peroxidation formed in the primary site, reaching other organs and tissues *via* the blood stream provoke lipid peroxidation there and consequently causes cellular and tissue damage. Increased accumulation of lipid peroxidation products in cells can result in cellular dehydration, whole cell deformity and cell death. Lipid oxidation is in most instances, a free radical chain reaction that can be described in terms of initiation, propagation, branching and termination process (Winrow *et al.,*1993) Figure 3.

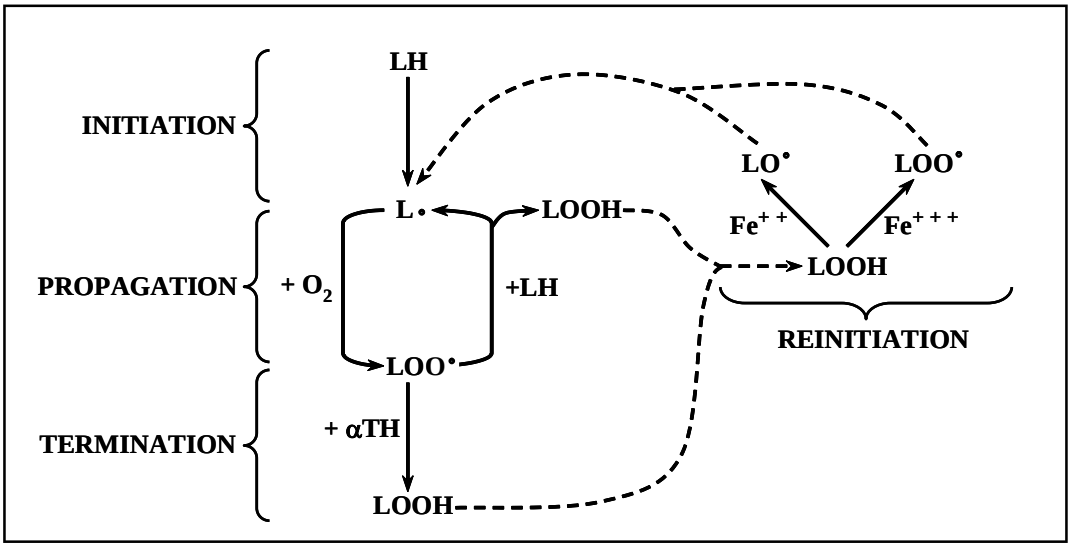

Figure 3: Lipid peroxidation process (Winrow *et al.,* 1993)

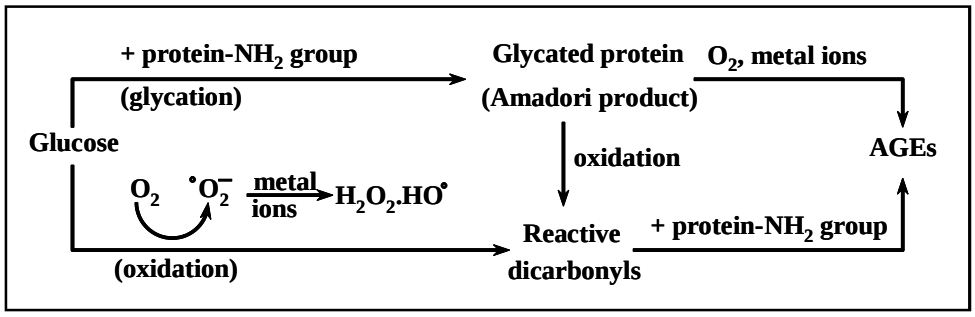

Figure 4: Formation of advanced glycation end products (AGEs) by combination of glycation and oxidation (Radoi *et al.*,2012)

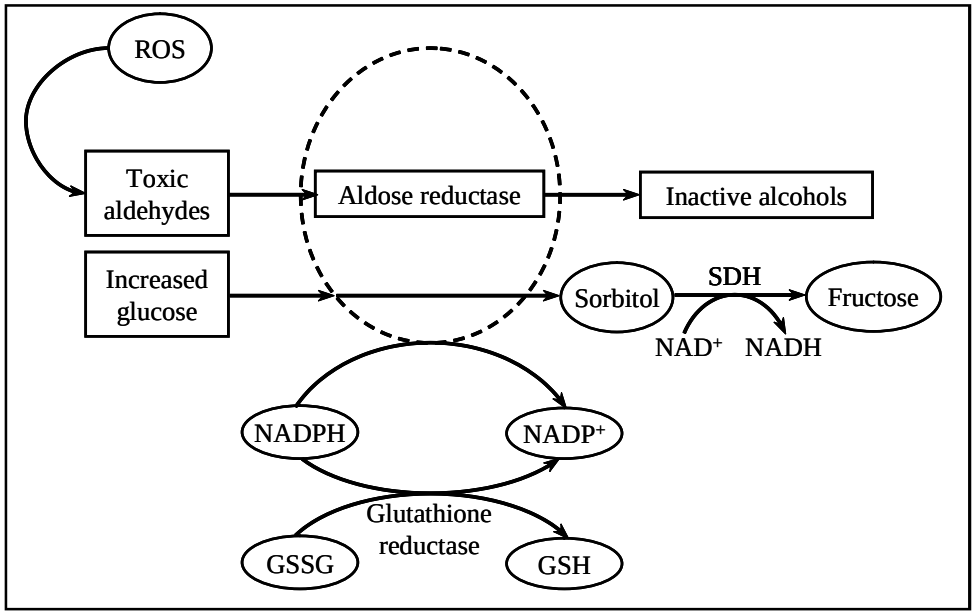

Figure 5: The polyol pathway (Morrison *et al.*, 1970)

Protein oxidation

Proteins are major biological targets for oxidative damage within cells, owing to their high abundance and rapid rate of reaction with radicals and excited-state species, including singlet oxygen. ROS modify amino acid side chains of arginine, lysine, threonine and proline residues to form protein carbonyls. They can be readily measured by the reaction with 2,4-dinitro phenyl hydrazine, using spectrophotometric, immunohistochemical and radioactive counting methods. Protein carbonyl content is the most widely used marker of oxidative modification of proteins and suggested to be reliable marker of oxidative stress. Elevated carbonyl levels were detected both in type 1 and type 2 diabetes (Cederberg *et al.*,2001a) and also in experimental diabetes (Rajeshwari *et al.*,2011). Furthermore, protein carbonyl content is well correlated with the complications of diabetes. Protein oxidation mechanisms result in a wide array of modifications, from backbone cleavage or protein cross linking to more subtle modifications such as side chain oxidations. Protein oxidation occurs as part of normal regulatory processes, as a defense mechanism against oxidative stress, or as a deleterious process (Cederberg *et al.*, 2001a).

Advanced glycation end products

Advanced glycation end products (AGEs) are proteins that have undergone irreversible, non-enzymatic glycation (Radoi *et al.*,2012) Figure 4. A physiological process in chronic hyperglycaemia and AGEs interact with specific receptors on target cells, leading to the activation of pathological signaling pathways that increase oxidative stress and promote inflammation and pro-coagulant activity. The non-enzymic glycation reaction proceeds slowly through different stages, leading to alterations of protein structure and molecular surface topology that profoundly change the biochemical properties of affected molecules. The major biological effects of excessive glycation include: inhibition of regulatory molecule binding, cross linking of glycated proteins, trapping of soluble proteins by glycated extracellular matrix, decreased susceptibility to proteolysis, inactivation of enzymes and transcription factors, abnormalities of nucleic acid function,

and increased immunogenicity in relation to immune complex formation (Ahmed, 2005). Glycation *in vivo* is slow and reversible at physiological glucose levels, tending mostly to affect proteins with a very slow turnover, for example collagen in some connective tissues, and crystalline lens. Glycation is faster at elevated glucose, occurring in diabetic patients. Some tissues, such as liver, kidneys, and erythrocytes are more susceptible to AGE formation than the others (Bohlender *et al.*, 2005).

The polyol pathway

Under normoglycemia, most of the cellular glucose is phosphorylated into glucose 6-phosphate by hexokinase. A minor part of nonphosphorylated glucose (approximately3%) enters the so-called polyol pathway, the alternate route of glucose metabolism, implicating the enzyme aldose reductase which normally has the function of reducing toxic aldehydes in the cell to inactive alcohols, but when the glucose concentration in the cell becomes too high, aldose reductase is induced which reduces glucose to sorbitol, in the presence of NADPH, which is later oxidized to fructose by the sorbitol dehydrogenase at the cost of NAD^+. Under hyperglycemia, there is an increase in the use of glucose through the pentose phosphate pathway together with increased conversion of glucose *via* the polyol pathway (more than 30%of glucose) as hyperglycemia induces aldose reductase enzyme in polyol pathway (Morrison *et al*., 1970) Figure 5.

Sorbitol accumulation

The process that leads to diabetes-related organ damage is the accumulation of sorbitol in certain tissues and organs. When glucose levels are elevated (hyperglycemia), sorbitol is produced inside the cells faster than it can be broken down. Since sorbitol cannot cross cell membranes, it builds up inside the cells and draws water in by the process of osmosis. This sorbitol-induced osmotic swelling is believed to be one of the main causes of tissue damage in diabetics and leads to the development of cataract in the eyes (Anderson and Ward, 1979).

Dyslipidaemia

Early small cross-sectional studies found the associations between atherosclerotic vascular disease and serum triglyceride, and with low density lipoprotein cholesterol (LDL-c), and an inverse association with high density lipoprotein cholesterol (HDL-c). In another small cross-sectional study, males with macrovascular disease had higher total and LDL-c concentrations than those without, while in females those with macrovascular disease had higher triglyceride, total cholesterol and LDL-c concentrations, and lower HDL2-c, HDL3-c and apolipoprotein A1 concentrations than those without (Seviour *et al*., 1988).

Role of herbs and spices in diabetes prevention

The management of diabetes is a global problem until now as successful treatment is not yet discovered. The introduction of insulin and later oral hypoglycemic agents revolutionized the management of diabetes mellitus. Inspite of advances in drug management of diabetes, there are still complications and adverse drug reactions. None of them were unequivocally successful in maintaining normal blood glucose levels and in avoiding complications (Goycheva *et al*., 2006). There are many synthetic medicines developed for patients, but it is the fact that it has never been reported that someone had recovered totally from diabetes. Many diverse therapeutic strategies for the treatment of type 2 diabetes are in use. The conventional available therapies for diabetes include stimulation of endogenous insulin secretion, enhancement of the action of insulin at the target tissues by oral hypoglycemic agents such as biguanides and sulfonylureas and the inhibition of degradation of dietary starch by glycosidases (Eichler 7*et al*., 1984). Although, oral hypoglycemic agents/insulin are the mainstay of treatment of diabetes and are effective in controlling hyperglycemia. They have prominent side effects and fail to significantly alter the course of diabetic complications. Majority of the available drugs act with a range of action to fight hyperglycemia, the efficacy of these drugs is compromised in several ways for individual agents act only on a part of the pathogenic process and only to a partial extent but not wholly and, hence, the disease is still progressing (Tiwari and Rao, 2002).

Most of the drugs from plant sources are secondary metabolites which have no role in plant metabolisms but are postulated to play a significant role in the plant defense mechanism. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possible use in the treatment of NIDDM patients (Bailey and Day, 1989). The products obtained range from marine algae and fungi to phytogenetically advanced classes of compounds. Plants that demonstrate hypoglycemic activities within the body, play a major role in folk medicine, and various studies on folklore have identified approximately 50 plants that affect glucose level in blood (Singh, 2011). There are about 200 pure compounds from plant sources reported to show blood glucose lowering effect. The compounds may be alkaloids, carbohydrates, glycosides, flavonoids, steroids, terpenoids, peptides and amino acids, lipids, phenolics, glycopeptides and iridoids. Main symptoms targeted were thirst, polyuria and glycosuria (Marles and Farnsworth, 1995).

Because, diabetes is associated with a disturbed equilibrium between pro-oxidants and antioxidants, the potential effects of antioxidant nutrients in the herbal therapeutics are currently a topic of intense research. Increased consumption of traditional herbs and spices helps in neutralizing the normal

level of oxidative damage, caused by the free radicals by enhancing the level of antioxidants in blood, cells and tissue fluids. Therefore, to combat the ever-increasing oxidative stress, diet derived antioxidants may be particularly helpful in diminishing cumulative oxidative damage (Sen *et al.,* 2010).

In particular, **diet control** is the main treatment for type 2 diabetes and for a large proportion of patients, dietary change alone may be efficient to control the major abnormalities [Diabetes and Nutrition Study Group (DNSG)] (DNSG,1988). The American Diabetes Association (ADA) also advises against routine supplements of synthetic antioxidants and the persons with diabetes should be educated about the importance of consuming adequate amounts of vitamins and minerals from natural food sources (ADA, 2002), *viz.*, herbs and spices. Antioxidants are also widely used as ingredients in dietary supplements in the hope of maintaining health and preventing diseases (Bjelakovic *et al.,* 2007). Dietary agents from herbs and spices consist of a wide variety to biologically active compounds that are ubiquitous in plants, and have been used in traditional medicines for thousands of years (Sporn and Liby, 2005).

The interest in natural products for use as medicine has acted as a catalyst for exploring methodologies involved in obtaining the required plant materials for pharmacological screening and drug development. Hence, ethnobotanical studies are recognized as the most viable method of identifying herbs and spices or refocusing on those earlier reported for bioactive constituents (Igoli *et al.,* 2005).

Antidiabetic plants in traditional medicines

The ethnobotanical information reports about 800 plants that may possess antidiabetic potential. A wide array of plant derived active principles, representing numerous chemical compounds, has demonstrated activity consistent with their possible use in the treatment of diabetes mellitus Tiwari *et al*., 2013. Marles and Farnsworth (1995) estimated that more than 1000 plant species are being used as folk medicine for diabetes. Biological actions of the plant products used as alternative medicines to treat diabetes are related to their chemical composition. Ayurvedic antidiabetic herbs improve digestive power, increase one of the Rasas (gastric secretions); being Laghu, get easily digested in the body and being Ruksha, decrease output of overall body fluids, *e.g.* urine, sweat *etc*. Food items which are 'madhumehaghna' (antidote), form an important underlying principle of therapy for prameha (diabetes) patient. Several species of herbal drugs have been described in the scientific and popular literature as having antidiabetic activity (Valiathan, 1998).

The demand for plant-based medicines, health products, pharmaceuticals, food supplement and cosmetics are increasing in both developing and developed countries, due to the growing recognition that the natural products are non-toxic, have lesser side effects and are easily available at affordable prices (Ripa *et al.,* 2010). Among the various medicinal and culinary herbs, some endemic species are of particular interest because they may be used for the production of raw materials or preparations containing phytochemicals with significant antioxidant capacities and health benefits. The World Health Organization (WHO) recommended the search for beneficial use of medicinal plants for the treatment of diabetes mellitus (WHO, 1985). Several investigations have been conducted and many herbs and spices have shown positive activities (Shinwaikar *et al*., 2004).

Scientific validation of several Indian plant species has proved the efficacy of the botanicals in reducing the sugar level. However, there are numerous other plants still await scientific inquiry, which have been mentioned in the indigenous systems of health care all over the world. A large number of plants, screened for their antidiabetic effect, have yielded certain interesting leads, but till todate no plant-based drug has reached such an advanced stage of investigation or development as to substitute or reduce the need for the currently-available oral synthetic drugs. However, the interest in herbal drug research continues with an expectation that some day or the other, a safer and more effective compound with all the desired parameters of a drug that could replace the synthetic medicines will be available (Fansworth, 1996).

Proposed mechanisms of botanical actions

Despite the historical use of botanicals to treat diabetes and its related symptoms, one of the major concerns for this area of study is the paucity of definitive and consistent data on efficacy, and more importantly, a lack of knowledge about precise mechanism(s) of action. However, there is growing evidence in this area, and if a botanical is demonstrated to have a favorable effect on a given mechanism, that will provide the rationale for further and more definitive studies on a particular botanical. The physiological parameters that regulate glucose metabolism and the pathophysiological changes that occur and that give rise to diabetes have been studied for years. These involve the interplay and function of multiple peripheral tissues, such as liver, muscle, and adipose tissue. In order to exert an effect, botanicals may theoretically modulate glucose at several different levels in multiple tissues (Cefalu and Ribnicky, 2009). Thus, based on reported abnormalities for type 2 diabetes, botanicals could be proposed to affect the whole-body metabolism by modulating adipocyte function and thus, regulating endocrine secretions that play a role to enhance the skeletal muscle insulin action. In addition, based on the known abnormalities, botanicals may regulate hepatic processes, that is, hepatic

gluconeogenesis, and may affect the whole-body glucose levels. In this regard, a specific agent termed as "biguanide" (metformin) and derived from botanical sources appears to improve hyperglycemia by regulating hepatic processes. Type 2 diabetes is clearly a disorder that involves insulin secretory defects, and enhancing pancreatic β-cell function is another proposed pathway by which botanicals may theoretically work. Enhancing insulin secretory function, may not be solely an acute effect. But as intensively pursued in preclinical and clinical trials, if a particular agent is shown to enhance proliferation and/or modulate apoptosis of islet tissue, this may markedly impact the natural progression of diabetes. In this regard, there is evidence to support the botanical modulation of these processes (Cefalu and Ribnicky, 2009).

Role of phytochemicals in diabetic therapy

The antidiabetic compounds known are of diverse chemical nature and their solubility differs. Based on the mechanism of action, the efficacy of any herbal drug will differ in type 1 and type 2 models. For developing herbal medicine to treat diabetes, one should know other pharmacological activities including toxicity, if any. There are numerous plants used to treat diabetes in Indian traditional medicine which include tribal and folk medicine practiced by various ethnic groups in remote villages and tribal pockets. Varying levels of scientific studies have been done on many of these plants. Out of the plants studied pharmacologically, most of them are shown to have antidiabetic and /or hypoglycemic activities. However, these studies are scattered and incomplete and not available in one place for reference. Further, most of the antidiabetic plants used in ethnomedicine are also used for various other ailments in traditional medicine. Scientific studies have also detected several other pharmacological properties in most of these herbal drugs (Subramoniam, 2003). Although several drugs / therapeutic agents have been designed and targeted for the disease and disease complications, many of these drugs exert various side/toxic effects such as hepatotoxicity or cardiac failure *etc*. Various phytochemicals /drugs /diet therapies were reported to control blood glucose levels of diabetic subjects /animal models when judiciously used in selective cases. However, these failed to control the complications of diabetes. Even the antihyperglycemic effect exerted by those appeared to be transient. Hence, search for natural dietary therapeutic methods for controlling diabetes are much active since diet plays a key role in the treatment of diabetes (Hagura, 2000).

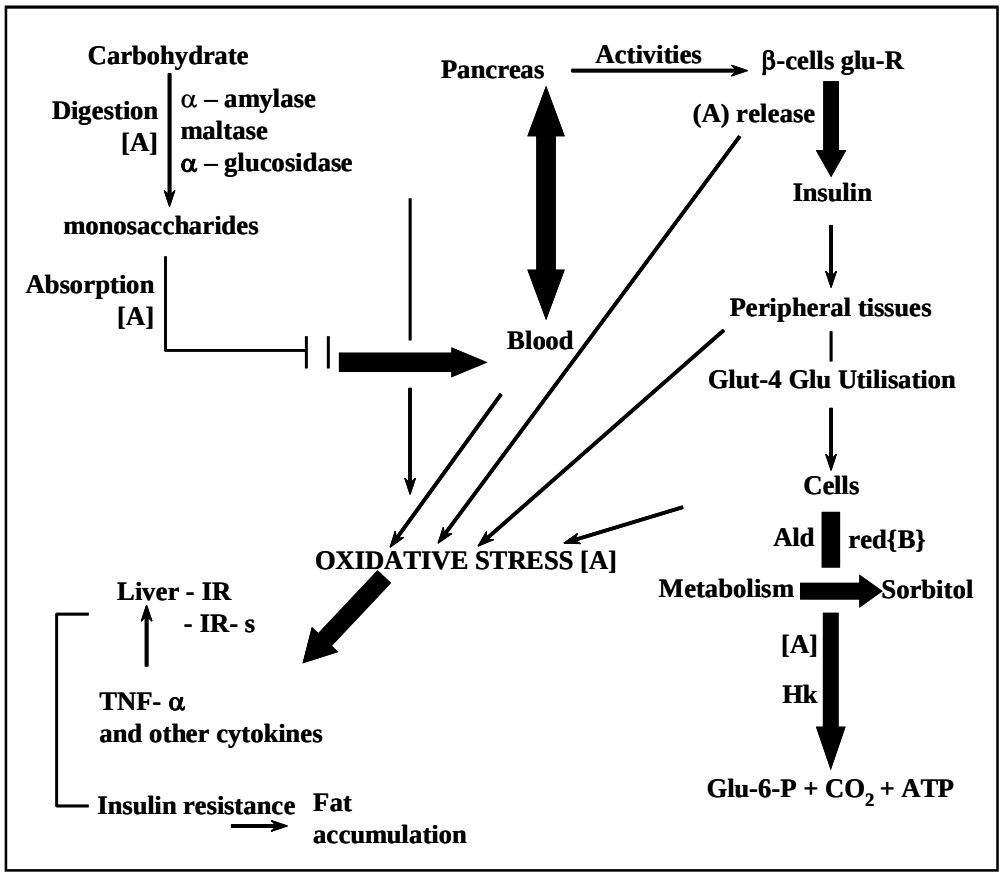

Figure 6: Sites of action of phytochemicals [A], phytochemical [B] and Aldose reductase inhibitor (Tiwari and Rao, 2002)

Though hyperglycemia is a classical risk factor for the development of diabetic complications. There is no consensus regarding the pathogenic links between hyperglycemia and the complications (The Diabetes Control and Complications Trial Research Group) (1993). There are a number of equally tenable hypotheses on the origin of complications beyond hyperglycemic consideration. The multifactorial pathogenicity of diabetes, hence, demands a multimodal therapeutic approach (Tiwari and Rao, 2002). They described the pathways of metabolism and targets where imbalance/ insufficiencies in function lead to hyperglycemia and resultant diabetic syndrome. They also pointed out that phytochemicals isolated from different traditional/medicinal plants of various or similar nature exhibit multiple activities as are known to act on a variety of targets by various modes and mechanisms to fight against diabetes and the related complications (Figure 6).

Inhibition of carbohydrate hydrolyzing enzymes

Polyphenols, phytates, tannins, sugar shaped alkaloids and N-containing sugars (Asano, 2000) inhibit the activity of various digestive enzymes (α amylase, sucrase and a glycosidase *etc*.) and are identified to be principle substances for suppressing postprandial hyperglycemia (Watanabe *et al.*,1997). However, these do not cause any net nutritional calorific loss as they act mostly by slowing down the digestion of carbohydrates (Kim *et al.*, 2000).

Manipulation of glucose transporters

Catechin, epicatechin, epigallocatechin, isoflavones, phenolic compounds, tannic acid, chlorgenic acid, crude saponin fractions and saponins from different plant extracts inhibit Na^+ dependent D-glucose uptake in intestinal brush border membrane vesicles as these compounds are potent inhibitors of sodium glucose cotransporter-1 (S-GLUT-1) (Welch *et al.*,1989).

Delaying gastric emptying rate

Gastric emptying is a highly regulated process and is perturbed by edible gums, which delay the transfer of glucose from the stomach to small intestine, and also delay glucose transport at the site of intestinal brush border membrane. Viscous polysaccharide gums and soluble fibers (Wolever, 1990) increase viscosity of gastrointestinal content and delay digestion and absorption of carbohydrates.

Pancreoprotective and / or β cells regenerative and / or insulinogenic effect

Some plant extracts exhibit pancreoprotective and restorative effect in experimental diabetic rats. *Agrimony eupatrori* and *Coriandrum sativum* exhibited insulin like activity and *Zizypus jujube* showed insulin release like glibenclamide, *Ficus bengalensis*, swerchirin from *Swertia chirayta*, D-400, a herbomineral preparation, *Aegle marmelose* (Sharma *et al.*,1997) possess insulinogenic activity (Tiwari and Rao, 2002).

Inhibition of aldose reductase activity

The inhibitors of aldose reductase activity have been proved to improve the diabetic complications in experimental animals. Flavonoids derived from various plants (*Myrcia multiflora*) and curcumin present in *Curcuma longa* (Arun and Nalini, 2002) inhibit aldose reductase activity and impart beneficial action in diabetic complications (Tiwari and Rao, 2002).

Regulation of key enzymes of metabolic pathways

A number of hypoglycemic agents were reported to influence the key enzymes of different metabolic pathways (glycolysis, glycogenolysis, gluconeogenesis, glycogenesis *etc*.), thereby controlling hyperglycemia in diabetic humans and experimentally induced diabetic animals. Some decrease the production of glucose *via* glycogenolysis and gluconeogenesis and increase hepatic glycogenesis (*Murayya koenigii* and *Brassica juncea*), some increase transport and oxidation of glucose *via* glycolysis (*Argimony eupatoria)*, some increase hepatic glycolysis (*Blighta sapida*), some increase utilization of glucose by peripheral tissues (*Trigonella foenum graceum)*, some improve glucose tolerance (*Momordica charantia*) and some control gluconeogenesis (*Coccinia indica, Allium sativum*) (Sheela and Augusti, 1992), *Latheranthum madegaskar perivinkle* (*Anderson* and *Ward* 1979).

Scavenging free radicals and /or influencing antioxidant enzymes

'Trasina' a herbal formulation exhibited antihyperglycemic activity by scavenging free radicals and *Bordetella pertusiss, Capparis decidua, Coriandrum sativum, Curcuma longa and Trigonella foenum graceum* were reported to possess antioxidant property (Tiwari and Rao, 2002).

Many antidiabetic products of herbal origin are now available in the market. Inolter is one of them; each capsule of Inoltar contains *Momordica charantia* (fruits, seeds and leaves, 100 mg), *Trigonella foenum graceum* (seeds, pods and leaves, 100 mg), Asphalt (100 mg), *Gymnema sylvestre* (root and leaves, 100 mg) and *Eugenia jambolena* (seeds, fruits and bark). Inoltar is claimed to have property of releasing insulin from islets of Langerhans and acts as an insulin sensitizer (Shanmugasunderam *et al.*, 1990). A scientific clinical trial has been conducted to study the role of Inoltar (herbal product) in the management of type 2 diabetes (Kothari *et al.*, 2002).

The efficacy of hypoglycemic herbs has been mediated by increasing insulin secretion (ginseng, bitter melon, aloes, *Biophytum sensitivum*), enhancing glucose uptake by adipose and muscle tissues (ginseng, bitter melon and cinnamon), inhibiting glucose absorption from intestine (myrcia and sanzhi) and inhibiting glucose production from hepatocytes (berberine, fenugreek leaves) (Hui *et al.*,2009).

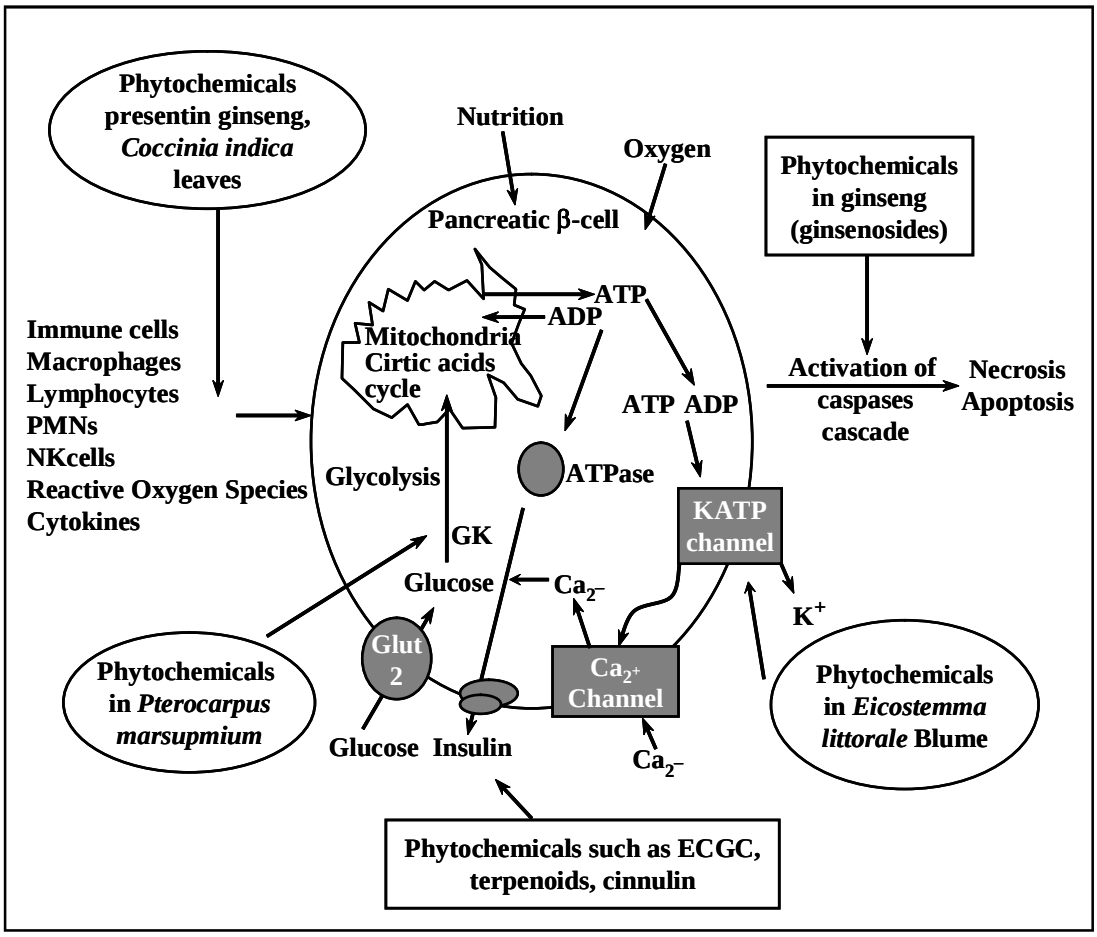

Figure 7: Insulin secretion and pancreatic β-cell apoptosis (The action sites of the hypoglycemic herbs are indicated with arrows) (Hui *et al.*, 2009)

Glucose is taken up into α-cells *via* glucose transporters. It is metabolized in glycolysis and Krebs cycle, resulting in an increased ratio of ATP to ADP in the cytoplasm. This closes ATP-sensitive potassium channels (KATP channels), leading to cell membrane depolarization and subsequently opening voltage-gated Ca^{2+} channels. These changes increase free Ca^{2+} concentration ($[Ca^{2+}]i$) in cytoplasm and eventually triggers insulin secretion. In apoptosis, stimuli promotes the release of caspase activators from mitochondria and result in the activation of caspases procedure, by cleaving the effector caspases, which interacts with a variety of cellular proteins, resulting in directly or indirectly the morphological and biochemical characteristics of cell apoptosis. The action sites of hypoglycemia herbs are indicated with arrows (Hui *et al.*, 2009) Figure 7.

The antidiabetic effects of ginseng have been investigated with aqueous or ethanol ginseng extracts. *Radix ginseng alba* improved hyperglycemia in KKAy mice, possibly by blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase, while *Radix ginseng palva* has a similar effect through the up-regulation of adipocytic peroxisome proliferator activated receptor gamma (PPAR-g), protein expression and inhibition of intestinal glucose absorption (Chung *et al.*,2001). Clinical efficacy of ginseng is thought to be mediated by multiple factors (Ng and Yeung, 1985): the component panaxans (panaxans A to E) elicits hypoglycemia in both normal and diabetic mice; the component adenosine inhibits catecholamine-induced lipolysis; both components of carboxylic acid and peptide 1400 inhibit catecholamine-induced lipolysis in rat epididymal fat pads; and the component 2, 3-diphosphoglycerate (2,3-DPG) provokes insulin secretion in diabetic and glucose-loaded normal mice. Not only does ginseng benefit serum glucose control in diabetic patients, but also aids central nervous system complications in them. Alternation expression of nitric oxide synthase (NOS) gene is implicated in the pathogenesis of numerous secondary complications in diabetes patients which could be suppressed by the administration of ginseng root. Pharmacological studies confirmed that ginseng possesses multiple actions (neuroprotective, immunomodulation and anticancer effects) (Wu *et al.*, 2007).

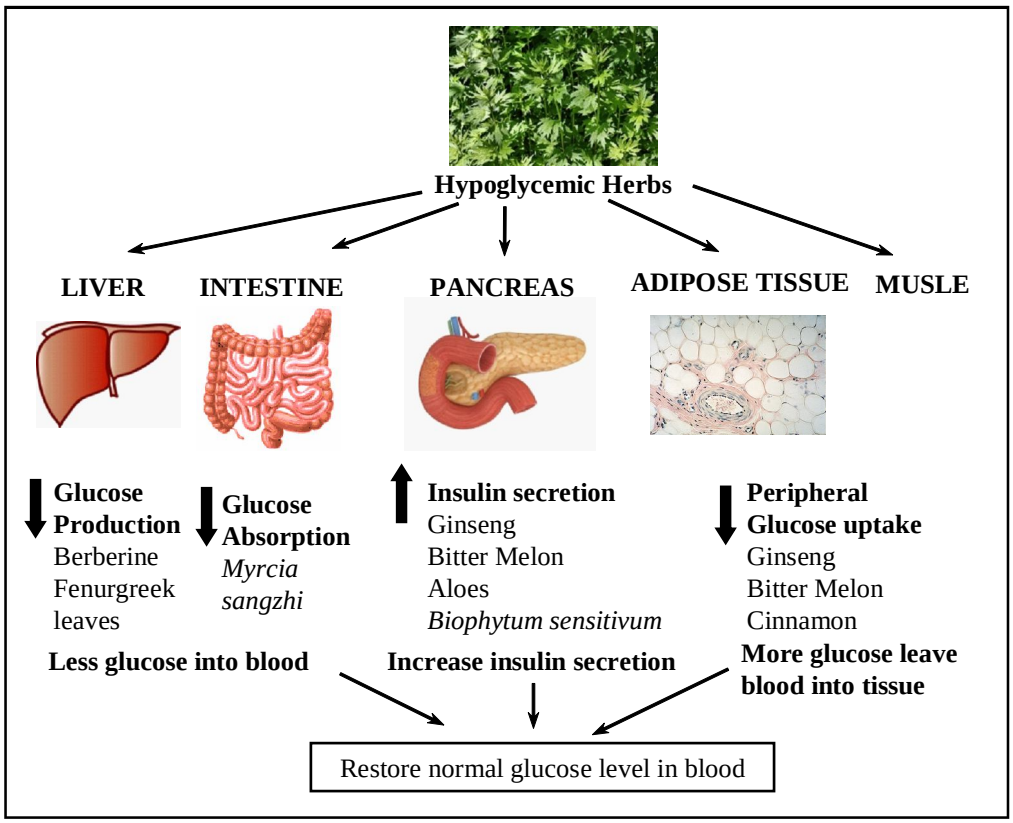

Figure 8: Action sites of herbs in diabetes treatment (Hui *et al.*, 2009)

Dietary cumin (*Cuminum cyminum*) showed marked hypoglycemic and hypolipidemic responses in type 2 diabetes patients. The coriander (*Coriandrum sativum* L.) seeds showed significant hypoglycemic activity by enhanced glycogenesis, glycolysis and decreased glycogenolysis and gluconeogenesis in experimental diabetic rats, which may be due to increased utilization of glucose in liver for glycogen synthesis and decreased degradation of glycogen to give blood glucose (Chitra and Leelamma,1997).

In vivo experiments revealed antioxidant role of coriander seeds as evidenced by elevated serum non-enzymatic and erythrocyte enzymatic antioxidants and very effectively decreased lipid peroxidation in erythrocytes and plasma in type 2 diabetes patients (Andallu and Ramya, 2004; Rajeshwari and Andallu, 2011). Administration of aniseeds (*Pimpinella anisum*) (Rajeshwari *et al.*, 2011) (5g/day) and mint leaves (*Mentha spicata*) to two different groups of NIDDM patients for 60 days, encountered oxidative stress by significantly decreasing lipid peroxidation, protein oxidation and decreasing the activity of erythrocyte catalase (CAT), increasing serum α carotene, vitamin A, E and C in both the groups of diabetics. Besides, the treatments increased the activity of erythrocyte antioxidant enzyme, *i.e.* glutathione-S-transferase (GST) and reduced glutathione (GSH) content (Rajeshwari *et al.*,2012).

Bitter melon (*Momordica charantia*) can be used as a dietary supplement in herbal medicine for the management of diabetes and/or metabolic syndromes (Cefalu *et al.*,2008). Bitter melon regulated cell signalling pathways in pancreatic β-cell, adipocytes and muscles. Ethyl acetate (EA) extract of bitter melon activated peroxisome proliferator receptors (PPARs) α and γ (Chuang *et al.*,2006), modulated the phosphorylation of IR and its downstream signaling pathway, thereby lowered plasma apoB-100 and apoB-48 in mice fed with high-fat diet (HFD). The momordicosides (Q, R, S and T) stimulate GLUT4 translocation of the cell membrane and increase the activity of AMP-activated protein kinase (AMPK) in both L6 myotubes and 3T3-L1 adipocytes, thereby enhancing fatty acid oxidation and glucose disposal during glucose tolerance tests in both insulin-sensitive and insulin-insensitive mice (Tan *et al.*,2008).

Coptis chinensis, commonly used to treat diabetes in China possesses berberine, an isoquinoline alkaloid as the active ingredient of *Coptis chinensis* in roots, rhizomes, stems and barks. Intragastric administration of berberine (100 and 200 mg/kg) in diabetic rats decreased fasting blood glucose levels and serum content of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-c), increased high density lipoprotein cholesterol (HDL-c) and nitric oxide (NO) level, and blocked the increase of superoxide dismutase (SOD)

and glutathione peroxidase (GSH-px) levels (Tang *et al.*,2006). Furthermore, berberine significantly decreased the activity of intestinal disaccharidases and β-glucuronidase in STZ-induced diabetic rats. Recently, dihydroberberine (dhBBR), an identified berberine derivative, demonstrated *in vivo* beneficial effects in rodents fed with high-fat diet (Turner *et al.*, 2008).

Thus, the major goal in treating diabetes is to minimize elevation of blood glucose without causing abnormally low levels of blood glucose. The action mechanisms for hypoglycemic herbs are multiple (Figure 8), such as increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from heptocytes (Hui *et al.*,2009).

Studies have unequivocally demonstrated the anti-diabetic potential of fenugreek in both type 1 and type 2 diabetes. Addition of fenugreek seeds to the diets of diabetic patients or animals resulted in a fall in blood glucose and improvement in glucose tolerance (Sharma *et al.*,1996). The spice probably delays gastric emptying by direct interference with glucose absorption and the gel forming dietary fiber reduces the release of insulinotropic hormones and gastric inhibitory polypeptide (Srinivasan, 2005). Sauvaire *et al*. (1998) reported that 4-hydroxy isoleucine has insulinotropic activity and partly accounts for the antidiabetic property of fenugreek seeds. The hypoglycemic potency of garlic and onion has been attributed to the sulfur compounds, namely 2-propenyl disulfide and 2-propenylpropyl disulfide, respectively (Augusti and Sheela, 1996).

Turmeric (*Curcuma longa*) is another spice possessing beneficial hypoglycemic effect and to improve glucose tolerance in a limited number of studies (Tank *et al.*, 1990). High blood cholesterol is an added risk factor that determines the rate of decline of kidney function in diabetics. Dietary curcumin and onion have been found to have a promising ameliorating influence on the severity of renal lesions in streptozotocin diabetic rats (Babu and Srinivasan, 1999).

Relative effectiveness of cinnamon (*Cinnamomum zeylanicum*), cardamom (*Elettaria cardamomum*) and ginger (*Zingiber officinalis*) and their mixture as fed to diabetic rats was investigated (at 7% level), using alloxan-injected Sprague Dawley male rats. Spice diets showed maximum improvement in diabetic rats, in particular that of the ginger and combined spices formulation. Cinnamon and cardamom diets lowered the internal organs weight, previously raised by diabetes. All spices and the combined formulation diets showed 12.07 to 23.42% reduction of blood glucose. In this connection, cardamom diet revealed 12.68% reduction in glucose, indicating its value for diabetics. Maximum improvement of the renal function occurred in cinnamon-fed diabetic rats. Cardamom diet showed pronounced decrease in serum creatinine, urea and uric acid levels. Spice treatments with cardamom lowered the liver enzyme activities, *i.e*., maximum reduction of glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) recorded for the liver function. Cardamom was active in reducing lipid profile of diabetic rats i.e. maximum decrease of total cholesterol (TC), triglycerides (TG), total lipids (TL), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and Atherogenic Index (AI) in serum of diabetic rats was observed (El-yamani, 2011).

Present status and future prospects

Diabetes is becoming something of a pandemic and despite the recent surge in new drugs to treat and prevent the condition; its prevalence continues to soar. Perhaps the most worrying aspect of all is that, the rise is even reflected in children (Ludwig and Ebbeling, 2001). Although several drugs targeted for carbohydrate hydrolyzing enzymes (pseudosaccharides), release of insulin from pancreatic β-cells (sulphonyl urea), glucose utilization (biguanides), insulin sensitizers, the glitazones are meant to target the problem of insulin resistance and enhance insulin action at the cellular level; however, some of these drugs are linked to liver toxicity (triglitazone), including a number of deaths from hepatic failure and raising the symptoms and risk factors of heart disease leading to heart failure (rosiglitazone). Therefore, as the longterm risk and effect on the complications of diabetes related with these drugs are not yet clear, UK Drug and Therapeutic Bulletin warrants that patients taking glitazones be monitored for signs of heart failure (Tiwari and Rao, 2002).

The beneficial multiple activities like manipulating carbohydrate metabolism by various mechanisms, preventing and restoring integrity and function of β-cells, insulin-releasing activity, improving glucose uptake and utilization and the antioxidant properties present in medicinal plants offer exciting opportunity to develop them into novel therapeutics. Thus, there are many such potential medicinal plants with real impact on the improvement of these detrimental parameters in diabetes patients which need to be screened further for their bioactive compounds. The major hindrance in the amalgamation of herbal medicine into modern medical practices is the lack of scientific and clinical data and better understanding of the efficacy and safety of herbal products in experimental screening methods is important to establish the active component and appropriate extract of the plant (Ali, 2009). A reverse pharmacological approach, inspired by traditional medicine and Ayurveda, can offer a smart strategy for new drug candidates to facilitate the discovery process and also for the development of rational synergistic botanical formulations (Patwardhan and Mashelkar, 2009).

To achieve a blockbuster status, clear evidence of the advantage over the existing therapy is the most important need of the day. The ability of modern medicine and healthcare systems to adequately manage symptoms of chronic and terminal disease is a central theme. The systematic reviews and meta analysis of clinical trials are the foundation of their success. Unfortunately, despite the apparent supremacy in terms of multiple therapeutic approaches of herbal medicines, well-organized, rigorous clinical trail evidences are not adequately available in order to advocate their scientific merit and supremacy over the existing drugs. Though the markets for herbal medicines are booming (Brevoort, 1998) and evidence for effectiveness is growing, it is also being simultaneously counterbalanced by inadequate regulations (Ernst, 2000).

Therefore, the product standardization, efficacy, safety and therapeutic risk/benefit associated with the use of herbal medicines need proper evaluation. A sound basic and rigorous clinical investigation to confirm and advocate the excellence over the existing therapies of traditional medicinal plants, preparation (s) mechanism(s) of action and therapeutic effects is absolutely warranted.

Summary

- Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications. Medicinal and herbal plant products prevent chronic diseases and favorably influence health. Herbs and spices are traditionally used from times immemorial in many countries for the treatment of diabetes mellitus.
- Protective effects of exogenously administered antioxidants have been extensively studied in animal models and human subjects within recent years, thus throwing light on the relationship between free radicals, diabetes and its complications.
- *In vitro* and clinical studies on such plants provide additional useful ways to probe the interconnections of oxidant stress and diabetes, and there is a need to continue to explore bioactive compounds and their mechanisms by which they decrease oxidative stress and thereby prevent the development of complications in diabetes mellitus.

Conflict of interest

We declare that we have no conflict of interest.

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