Diabetes mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospects

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According to recent estimates, the human population worldwide appears to be in the midst of an epidemic of diabetes. Despite the great strides that have been made in the understanding and management of diabetes, the disease and disease-related complications are increasing unabated. Parallel to this, recent developments in understanding the pathophysiology of the disease process have opened up several new avenues to identify and develop novel therapies to combat the diabetic plague. Concurrently, phytochemicals identified from traditional medicinal plants are presenting an exciting opportunity for the development of new types of therapeutics. This has accelerated the global effort to harness and harvest those medicinal plants that bear substantial amount of potential phytochemicals showing multiple beneficial effects in combating diabetes and diabetes-related complications. Therefore, as the disease is progressing unabated, there is an urgent need of identifying indigenous natural resources in order to procure them, and study in detail, their potential on different newly identified targets in order to develop them as new therapeutics. This article presents an overview of multiple aspects of the pathobiology of diabetes mellitus and multimodal therapeutic effect of medicinal plants/phytochemicals and discusses the present status and future prospects of these medicines.

THERE are an estimated 143 million people worldwide suffering from diabetes[1], almost five times more than the estimates ten years ago. This number may probably double by the year 2030 (ref. 2). Therefore, the human population worldwide appears to be in the midst of an epidemic of diabetes. Reports from the World Health Organization (WHO) indicate that diabetes mellitus is one of the major killers of our time, with people in Southeast Asia and Western Pacific being most at risk[3].

Diabetes is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. This results primarily in elevated fasting and postprandial blood glucose levels. If this imbalanced homeostasis does not return to normalcy and continues for a protracted period of time, it leads to hyperglycemia that in due course turns into a syndrome called diabetes mellitus. There are two main categories of this disease. Type 1 diabetes mellitus also called insulin-dependent diabetes mellitus (IDDM) and Type 2, the noninsulin-dependent diabetes mellitus (NIDDM). IDDM represents a heterogenous and polygenic disorder, with a number of non-HLA loci (about 20) contributing to the disease susceptibility[4]. Though this form of diabetes accounts for 5 to 10% of all cases, the incidence is rapidly increasing in specific regions. It is estimated that incidence of Type 1 diabetes will be about 40% higher in the year 2010 than in 1997 (ref. 5), and yet there is no identified agent substantially capable of preventing this type of disease[6–8]. NIDDM is far more common and results from a combination of defects in insulin secretion and action. This type of disease accounts for 90 to 95% of all diabetic patients. Treatment of Type 2 diabetes is complicated by several factors inherent to the disease process, typically, insulin resistance, hyperinsulinemia, impaired insulin secretion, reduced insulin-mediated glucose uptake and utilization[9–11].

Despite the great strides that have been made in understanding and management in this disease, serious problems like diabetic retinopathy[12], diabetic nephropathy[13] and lower extremity amputation[14] continue to confront patients and physicians. The graph of diabetes-related mortality is rising unabated[15]. Certain population subgroups have prevalence rates of disease approaching 50% and this is strongly related to the epidemic of obesity and socio-economic inequalities that plague our society[16].

Defects in carbohydrate metabolizing machinery and consistent efforts of the physiological systems to correct the imbalance in carbohydrate metabolism place an overexertion on the endocrine system, which leads to the deterioration of endocrine control. Continuing deterioration of endocrine control exacerbates the metabolic disturbances and leads primarily to hyperglycemia. This presents a moving therapeutic target that requires a range of different agents to address the different features of the disease at different stages of its natural history[17]. Although biomedical science has unravelled substantially

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the pathobiological processes involved in causing/fostering diabetes, and has designed therapeutic agents with a range of action to fight hyperglycemia, the efficacy of these therapeutic agents is compromised in several ways. For individual agents act only on part of the pathogenic process and only to a partial extent[18–21]. This may be the reason that even after so much advancement in understanding the disease process and availability of a wide range of therapeutic agents, the disease is still progressing.

Multiple defects in the pathophysiology of diabetes are mostly imprecisely understood, and therefore warrant not isolating a single drug target to the reversal of all or majority of aspects of the disease[17], as biological systems are too complex to be fully understood through conventional experimentation and also because they are nonlinear. They also may have properties that are not obvious from biological considerations alone. For example, though hyperglycemia is a classical risk factor for the development of diabetic complications, there is no consensus regarding the pathogenic links between hyperglycemia and diabetic complications[22]. There are a number of equally tenable hypotheses on the origin of complications beyond hyperglycemic consideration. Therefore, the unidirectional therapeutic approach in the management of diabetes does not appear to be the way to address this problem.

On the other hand, the therapeutic approach of several traditional medicinal systems is more holistic. The fundamental mechanisms of these medicinal systems are still unexplainable using modern tools. The medicinal preparations in traditional medicines contain a variety of herbal and non-herbal ingredients that are thought to act on a variety of targets by various modes and mechanisms.

This article presents an overview of diabetic pathogenesis, particularly impaired carbohydrate metabolism leading to hyperglycemia, diabetes and oxidative stress. It analyses how herbal medicines and their ingredients correct/manipulate the vitiated homeostasis of carbohydrate metabolism providing multiple therapeutic benefits in diabetes mellitus, and also discusses the present status and future prospects of these medicines.

Impaired carbohydrate metabolism and hyperglycemia

Carbohydrates from various dietary sources are the primary exogenous source of glucose. Glucose is the main fuel for energy requirement of the body. Therefore, a continuous supply of glucose is necessary to ensure proper function and survival of all organs. Hence, mammals have evolved sophisticated systems to maintain glucose levels in the blood within tight limits, despite large fluctuations in food intake. Homeostatic mechanisms are in place to maintain blood glucose levels within a very narrow range (of around 5 mM), protecting the body against hypoglycemia during periods of fasting and against excessively high levels following the ingestion of a high carbohydrate diet. These goals are met chiefly through the hormonal modulation of the production of glucose by the liver and the peripheral uptake of glucose by skeletal muscle, heart muscle and fat. When mammals fast, glucose homeostasis is achieved by triggering expression of gluconeogenic genes in response to glucagon, and when they take a carbohydrate-rich diet, the function is taken over by insulin for its uptake and utilization peripherally. The impairment in glucose metabolism, therefore, may lead to physiological imbalance and warrants proper management.

Starting from the carbohydrate ingestion, breakdown into the monosaccharides, their building blocks glucose, sucrose and fructose to the downhill utilization of glucose for generation of energy, Figure 1 presents in brief a systematic sketch of the pathways involved in carbohydrate metabolism. Any vitiation, therefore, in normal glucose metabolic pathway may lead to the impaired glucose metabolism, the onset of hyperglycemia and subsequently, diabetes mellitus. This flow chart also presents points where modern therapeutics targets and traditional medicines have shown their therapeutic potential.

After the breakdown of carbohydrates by digestive enzymes, the released glucose becomes the primary stimulus for the β-cells of the pancreatic islets. Prolonged exposure of pancreatic islets to elevated glucose concentration has been shown both *in vitro* and *in vivo* to impair glucose-stimulated insulin release[23,24]. Glucose stimulation of pancreatic islet β-cells initiates a cascade of events resulting in insulin secretion and is dependent on an increase in intracellular Ca^{2+} (refs 25 and 26). This increases the phosphoinositide hydrolysis, inositol 1,4,5-triphosphate (IP-3) production and mobilizes Ca^{2+} from intracellular IP-3-sensitive Ca^{2+} stores in the pancreatic β-cells[27]. Regulation of glucose metabolism is a key aspect of metabolic homeostasis and insulin is the dominant hormone influencing this regulatory system. One of the major effects of insulin is to enhance overall glucose disposal, and this is achieved by stimulation of glucose uptake into the target tissues. This task is facilitated by insulin-sensitive glucose transporter (GLUT-4), which is uniquely expressed in skeletal muscles, cardiac muscles and adipose tissues[28]. This action of insulin in the regulation of glucose homeostasis in post-absorptive state is a very important function in maintaining euglycemia and preventing hyperglycemia[29]. The molecular and cellular biology of GLUT-4 is a complicated science. Further, understanding of GLUT-4 biology may provide novel therapeutics in insulin resistance in Type 2 diabetes, for GLUT-4 is the key facilitator responsible for the maintenance of euglycemia in the body[30]. Glucose-stimulated release of insulin and insulin-guided metabolism of glucose are therefore, the primary balancing factor in maintaining euglycemic state in the blood (Figure 1). How-

ever, this homeostatic relationship is disturbed when glucose remains at supraphysiological level for a protracted period of time, a consequence referred to as glucose toxicity[31,32].

The establishment of association between toxic effects of elevated concentration of glucose on β-cells' function, changes in key constituents of insulin gene expression and insulin synthesis reveals that among several operating mechanisms, the potential mechanism is chronic oxidative stress accelerating overt generation of reactive oxygen species (ROS)[33–35] that adversely affects the islets' functions[36,37]. ROS can also be formed by chronic exposure to hyperglycemia that involves non-enzymatic glycation proteins and the formation of products that in turn lead to the generation of ROS[33,34].

Chronic oxidative stress due to hyperglycemia may therefore play an important role in progressive β-cell dysfunction. Studies have demonstrated that this can be ameliorated by antioxidants of varied nature[38,39]. Furthermore, it is important to note that pancreatic islets themselves have low expression of antioxidant enzymes[36,37] and might be susceptible to ROS. Radical scavengers/antioxidants, therefore, may find varied application at this juncture.

Hyperglycemia-induced oxidative stress and diabetic complications

Hyperglycemia alone does not cause diabetic complications. It is rather the detrimental effect of glucose toxicity due to chronic hyperglycemia, which is mediated and complicated through oxidative stress. Diabetic hyperglycemia causes a variety of pathological changes in small vessels, arteries and peripheral nerves. Vascular endothelial cells become primary vulnerable targets of hyperglycemic damage as glucose continuously flows through them. Hyperglycemia increases the production of ROS inside

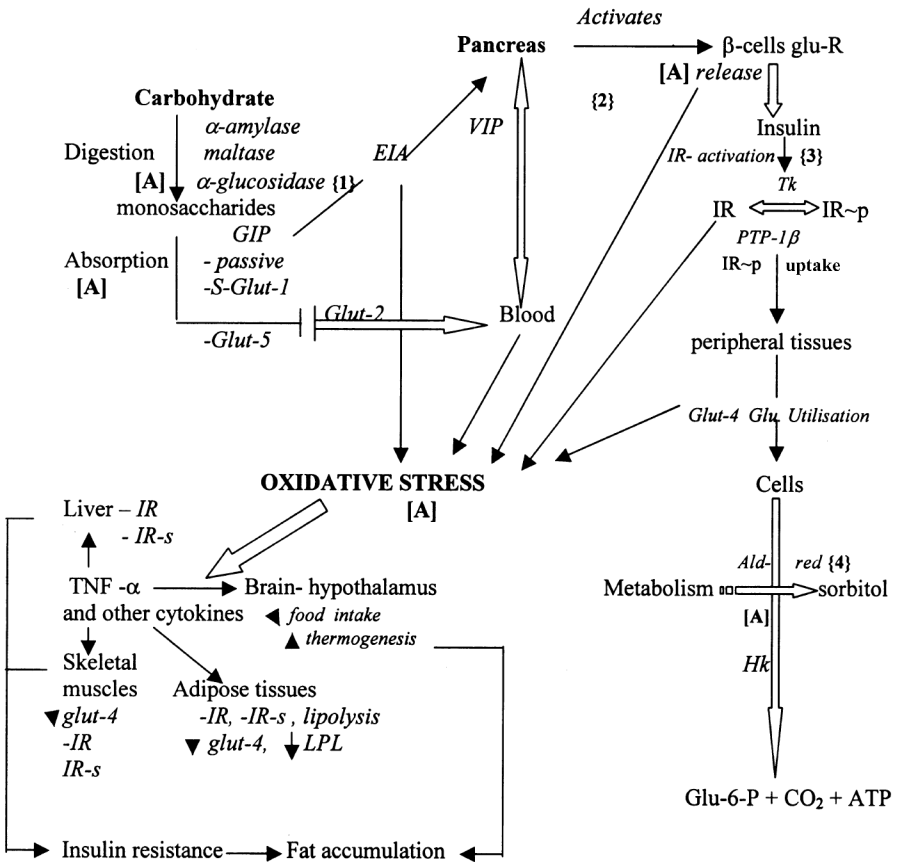

Figure 1. Sketch of pathways of carbohydrate metabolism and targets where imbalance/insufficiencies in function lead to hyperglycemia and resultant diabetic syndrome. S-Glut-1, Sodium glucose co-transporter-1; GIP, gastrointestinal peptide; VIP, Vasoactive intestinal peptide; EIA, Entero-insular axis; glu-R, Glucose receptor; IR, Insulin receptor; IR-s, Insulin receptor substrate; Tk, Tyrosine kinase enzyme; PTP, Protein phosphotyrosin phosphatase; TNF, Tumour necrosis factor; Ald-Red, Aldose reductase; Hk, Hexokinase; LPL, Lipoprotein lipase, ⊣ ⊢, Brush border – basolateral membrane of the intestinal epithelium; {1}α-Glucosidase inhibitors; {2}, Sulphonyl ureas; {3}, Biguanides, and {4}, Aldose reductase inhibitors are the available therapies at the particular points and synthetic medicines available. [A] denotes points where phytochemicals of various or similar nature have been shown to demonstrate multiple activities.

the aortic endothelial cells[40]. Hyperglycemia-induced activation of protein kinase-C (PK-C) isoforms[41], increased formation of glucose-derived advanced glycation end-products[42], and increased glucose flux through aldose reductase pathways are some of the known biochemical mechanisms of hyperglycemia-induced tissue/organ damage.

However, the belief that these metabolic pathways have their independent origin has undergone some changes recently. Nishikawa *et al.*[43] have proposed a single unifying hypothesis (Figure 2) linking these mechanisms by which elevated concentrations of glucose perturb cellular properties in a fundamental way. Hyperglycemia aggravates endothelial ROS generation by a variety of mechanisms. Suppression of intracellular mitochondrial, ROS over-production by use of low-molecular weight inhibitors and antioxidants prevents glucose-induced activation of PK-C, formation of advanced glycation end-products, sorbitol accumulation and activation of cytokines. This study has opened a new avenue to make a radical approach for the treatment of diabetic complications[43,44].

ROS increases the generation of TNF-α expression and aggravates oxidative stress[45]. Increased liberation of cytokines like TNF-α and interluekines has been implicated in the pathogenesis of insulin resistance (Figure 1). TNF-α is a putative inhibitor of tyrosine phosphorylation on insulin receptor and post-receptor signalling intermediates[46]. TNF-α is a pleiotropic cytokine involved in many metabolic responses in both normal and pathophysiological states. It has a central role in obesity, modulating energy expenditure, fat deposition and insulin resistance[47]. TNF-α may produce insulin resistance by a decrease in autophosphorylation of insulin receptor[48], conversion of insulin receptor substrate-1 into an inhibitor of insulin receptor tyrosine kinase activity[49], decrease in GLUT-4 transporter in muscle cells[48], increase in circulating fatty acids, altering β-cell function[50,51] and also increase in triglycerides and decrease in high density lipoprotein[52]. TNF injection to healthy individuals reduces insulin sensitivity by inducing hyperglycemia without lowering plasma insulin levels. Adipocytes exposed to TNF become insulin-resistant, since insulin is not able to stimulate hexose transport. This appears to be the consequence of down-regulation in expression of GLUT-4, the insulin stimulable glucose transporter[47]. Antioxidants and polyphenolic compounds have been shown to scavenge free radicals, reduce oxidative stress and decrease the expression of TNF-α[53–56]. Therefore, phytochemicals appear to manipulate by various indirect mechanisms, the complications of diabetes mediated through oxidative stress, ROS or TNF-α.

The nuclear targets/transcription factors that regulate glucose homeostasis represent a potentially large class of therapeutic targets. However, they represent rather more complex targets for therapeutic intervention than metabolic targets as they are usually expressed in multiple tissues and potentially regulate large number of genes. Furthermore, the precise mechanisms of these targets and behaviours of transcription factors in regulating biological functions are poorly understood. The long-term safety aspects of therapies developed on these targets await time-testing.

Multiple approaches of phytomedicines in combating diabetic disorders

Progress in understanding the metabolic staging of diabetes over the past few years has led to significant advances in regimen for treatment of this devastating disease. The most challenging goal in the management of patients of diabetes mellitus is to achieve blood glucose level as close to normal as possible[57]. In addition, postprandial hyperglycemia (PPHG) or hyperinsulinemia are independent risk factors for the development of macrovascular complications of diabetes mellitus[58]. This section presents a composite view of the multiple target beneficial effects of the plant medicines/phytochemicals.

Glucose absorption

Starting from the very beginning of carbohydrate metabolism, release of glucose and transport across the intestinal brush border membrane down to the blood stream, has attracted much attention recently as potential targets to control PPHG. In this category, majority of recent studies report the potential of antidiabetic medi-

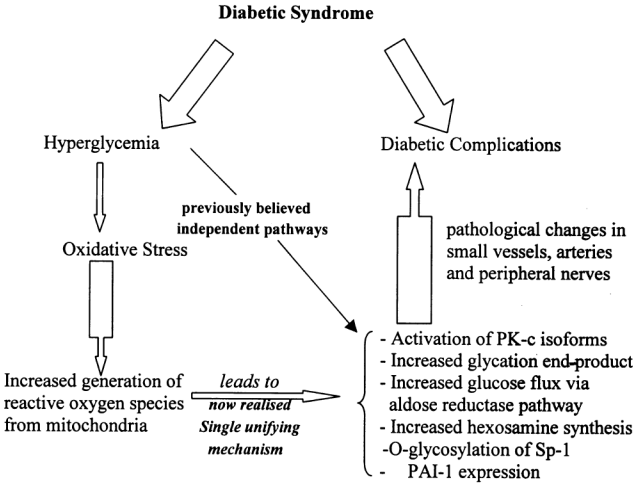

Figure 2. Single unifying mechanism of oxidative stress due to persistent hyperglycemia, which leads to overt generation of ROS in mitochondria. This results in a variety of harmful oxidative products previously believed to be originated independently. These oxidative products are known to complicate the diabetic pathology. The relevance of each of the pathways is supported by animal studies in which pathway-specific inhibitors prevent various hyperglycemia-induced abnormalities. Normalizing levels of mitochondrial, ROS have been shown to prevent formation of the above products[42,43].

cinal plants on inhibition of carbohydrate hydrolysing enzymes, α-amylase and α-glucosidase and manipulation of glucose transporters. A wealth of literature has emerged now, showing the potential effect of phytochemicals in inhibiting α-amylase[58] and α-glucosidase[59]. Kobayashi *et al.*[60] reported screening of various plants for α-amylase inhibitory activity and the resultant *in vivo* PPHG activity.

Tea polyphenolics, apart from their much-cited antioxidant activities, also have been reported to inhibit α-amylase and sucrase, and have been shown to be the principle substance for suppressing PPHG[61–63]. Furthermore, these polyphenolics also inhibit glucose transport across the intestine by inhibiting sodium glucose co-transporter-1 (S-GLUT-1)[64]. (+) catechin, (-) epicatechin, (-) epigallocatechin and epicatechin gallate[64], isoflavones from soybeans[65], polyphenolic compounds, tannic acid, chlorgenic acid[66], crude saponin fractions from *Gymnema sylvestre*[67,68] and other saponins from several plant extracts[69,70] have been shown to possess potent S-GLUT-1-mediated inhibition of glucose and antihyperglycemic activity. The manipulation of S-GLUT-1-mediated transport along with α-amylase and α-glucosidase inhibitory activity by plant phenolics make them hence, very exciting candidates in the control and management of hyperglycemia.

Recently, Matsuda *et al.*[71] studied in detail the structure activity relationship among saponins isolated from various sources and their hypoglycemic activity. The 3-*O*-glucuronic acid moiety of oleanolic acid possesses strong hypoglycemic activity. The 28-ester glucoside moiety however, reduces the activity. The 3-*O*-glucuronic acid glycosides are more potent than 3-*O*-glucopyranosyl analogues. The 6′-methyl esters of glucuronic acid moiety strongly reduce hypoglycemic activity. Regarding mechanism of action, the authors propose that these compounds act as hypoglycemic by delaying the transfer of glucose from the stomach to the small intestine, the main site of glucose absorption and by inhibiting the glucose transport at the site of intestinal brush border membranes. Drugs that reduce PPHG by suppressing the absorption of carbohydrate are effective in NIDDM prevention and treatment.

It is envisaged therefore, that there are several approaches to retard glucose uptake in the small intestine: (a) by inhibiting digestive enzymes, (b) by inhibiting active transport of glucose across intestinal brush border membrane, and (c) by delaying the gastric emptying rate of gastrointestinal content. The water-soluble dietary fibres, guar gum, pectin[72,73], polysaccharides contained in plants[74,75] have been reported to increase the viscosity of gastrointestinal content, thereby decreasing the gastric emptying rate and suppressing/delaying the digestion and absorption of carbohydrates.

The α-glucosidase inhibitors are currently the most commonly used oral agents for ameliorating PPHG because of the lack of hypoglycemic threat, and more importantly because of the prospect of blood glucose control without hyperinsulinemia and body weight gain[57]. At present three glucosidase inhibitors – acarbose[76], miglitol and voglibose[77] – are available for the treatment of patients with Type 2 diabetes mellitus. Inhibition of glucosidase and amylase should result in delayed carbohydrate digestion and glucose absorption, with attenuation of PPHG excursion. It has been reported that α-glucosidase inhibitors usually do not alter the total amount of carbohydrate absorbed and therefore, do not cause any net nutritional calorific loss, and they act mostly by slowing down the carbohydrate digestion[58,77].

KK-A^y mice have genetically determined obesity, and diabetic complications like hyperglycemia, hyperinsulinemia, glucosuria and severe insulin resistance. These symptoms increase with age at least up to 16 weeks. This model therefore has become a very close model to mimic NIDDM. Takki *et al.*[78] have reported using this model that apart from many activities reported for glycerrhizin, the main substance from licorice root, it also inhibits S-GLUT-1-mediated glucose transport, suppresses rise in fasting blood glucose and insulin level and improves glucose tolerance.

β-*cell regeneration and insulin releasing activity*

Alloxan and streptozotocin (STZ) are the chemicals used conventionally to produce diabetes and hyperglycemia in experimental animals by selectively destroying β-cells. These chemicals induce necrosis to islet β-cells through free radical-mediated damage. It has been a difficult task to regenerate β-cells once they are destroyed. However, a crude extract of *Pterocarpus marsupium*, [an Ayurvedic medicinal plant (vijayasar in Hindi) advocated for diabetes mellitus], in the form of water decoction has been reported to have protective and restorative effect in alloxan-induced diabetic rats by Chakravarty *et al.*[79]. The same authors later isolated the active principle as (-) epicatechin from *P. marsupium* which was shown to possess preventive as well as restorative properties of β-cells against alloxan-induced damage. These results were substantiated by histological observations. The regeneration of β-cells' normal function was evidenced by blood sugar values in these animals[80]. Jahromi *et al.*[81] identified some more flavonoids from *P. marsupium* as liquiritigenin and pterosupin, and reported hypolipidemic properties of these phytochemicals in experimental animals.

Gymnema sylvestre, an Indian medicinal plant, has long been known to possess antidiabetic activities. It is popularly known in Hindi as 'gurmar' meaning sugar destroyer. This name is attributed to the plant owing to its sweet-taste suppressing property. Extracts of this plant have been reported to possess a variety of actions related to the antidiabetic properties like reduction in insulin requirement possibly by enhancing endogenous insulin

availability, improving vitiated blood glucose homeostasis, better control of hyperlipidemia associated with diabetes, reduction in amylase activity in serum, increase in β-cell function as shown by higher levels of serum C-peptide[82,83]. The water-soluble alcoholic extracts of *G. sylvestre* leaves were found to regenerate β-cells in pancreatic islets of STZ-induced diabetic rats[83]. Water-soluble alcoholic extracts of *G. sylvestre* leaves have also been reported to potentiate insulin release from pancreatic β-cells in different animal models representing hyperglycemia and diabetes[84]. The dried powder of *G. sylvestre* was found not only to regulate the blood sugar homeostasis in alloxan-induced diabetic rats but it also increased the activity of enzymes responsible for utilization of glucose by insulin-dependent pathway[85]. The chemistry and pharmacology of *G. sylvestre* have been reviewed recently by Siddiqui *et al.*[82]. The authors conclude that though various components from crude mixtures of *G. sylvestre* have been separated and tested for hypoglycemic activity and extracts from leaves have been found effective in controlling the absorption of sugar, the exact components responsible for activity are yet to be confirmed. Baskaran *et al.*[86] studied the effect of extracts of *G. sylvestre* leaves in controlling hyperglycemia in Type 2 diabetic patients. The authors observed that the extract produced a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins, with a decrease in conventional drug dosages. Some patients were able to discontinue conventional drugs and even maintain their blood glucose homeostasis with extracts alone. In insulin-dependent patients, prolonged administration of a water-soluble extract of leaves of *G. sylvestre* produced a reduction in insulin requirement, improved blood glucose homeostasis, better controlled hyperlipidemia, reduced serum amylase activity and increased β-cell functions[83].

Hypoglycemic activity of *Zizyphus jujuba* was first reported on normoglycemic rats by Aydin *et al.*[87]. Recently, Ignacimuthu and Amalraj[88] reported the antidiabetic and antihyperlipidemic effect of *Z. jujuba* in alloxan-induced diabetic rats, which was fairly comparable to that of glibenclamide. The authors propose that alkaloid barberine present in the leaves of the plant may be responsible for its hypoglycemic activity and suggest that chemical constituents in *Z. jujuba* may have the ability to release insulin from pancreatic β-cells and also have the potential to protect it from alloxan-induced damage in experimental animals.

Trigonella foenum-graceum L. fenugreek seeds (methi in Hindi) have been reported to possess hypoglycemic and hypolipidemic properties in animal experiments[89] as well as in human and clinical cases[90–95]. Recently, Ravikumar and Anuradha[96] reported the antioxidant property of fenugreek seeds in diabetic rats.

The holy basil (tulasi in Hindi), *Ocimum sanctum* and *O. album* have been observed to decrease the fasting and postprandial blood and urinary glucose levels in Type 2 diabetic patients. The dried powder of leaves also mildly reduced cholesterol level[97].

There are several reports where medicinal plants have been found to possess hypoglycemic, antidiabetic, hypolipidemic and antioxidant activities. Similarly, there may be several unexplored plants that may contain more yields of active principles known to possess multiple activities in this regard[98] compared to the plant materials reported in the classical literature of traditional medicines.

Aldose reductase pathway inhibitors

Aldose reductase, the key enzyme of the polyol pathway, has been demonstrated to play an important role in etiopathology of diabetic complications such as neuropathy, cataract, nephropathy and retinopathy. Aldose reductase catalyses the reduction of glucose into sorbitol. Sorbitol does not readily diffuse across the cell membrane and intracellular accumulation of sorbitol is responsible for cataract in diabetic complications. The inhibitors of aldose reductase (sorbinil, tolrestate) have been proved to improve the diabetic complications in experimental animals[99] and clinical trials[100]. Several plant-derived flavonoids, apart from possessing their common antioxidant activity, have been reported to inhibit aldose reductase activity and impart beneficial action in diabetic complications[101–104]. Similarly, these phytochemicals may also contribute beneficially in mitigating glucose autoxidation[105], glycation, and act against the major contributors for increased free radicals generation in diabetic lens[106,107]. Recently, Lim *et al.*[108] have identified butein as the most promising antioxidant and aldose reductase inhibitor for prevention and treatment of diabetic complications. Similarly, flavanone and flavonol glucosides isolated from a plant popularly known as 'plant insulin' (*Myrcia multiflora* – a Brazalian medicinal plant) have been reported to possess aldose reductase inhibition, α-glucosidase inhibition and potential for hypoglycemic activity in alloxan-induced diabetic animals[109].

Antioxidant defence

The antioxidant defence system represents a complex network with interactions, synergy and specific tasks for a given antioxidant[110]. Recent studies[111–113] show that majority of the plasma antioxidants are depleted in Type 2 diabetes patients. The depletion of antioxidants in the diabetic patients was independent of body mass index and dietary intake and this depletion is a major cause of diabetes-related complications and onset of other disease conditions like atherosclerosis and coronary heart disease[110–112]. Antioxidant activities of the majority of compounds mentioned in the text have been reviewed recently[114–116] and their benefits in oxidative stress and related disease conditions have been widely described. It appears therefore, that apart from acting on carbohydrate

metabolic targets compounds present in medicinal plants alone or in combination, possess a variety of beneficial activities and have the potential to impart therapeutic effect holistically in complicated disorders like diabetes and its complications.

The oxidative stress and resultant tissue damage are hallmark of chronic diseases and cell death, and diabetes is not the exception. Baynes and Thorpe[117] have recently discussed some of the paradigms of oxidative stress in diabetes. Whether oxidative stress occurs at an early stage in diabetes, preceding the appearance of complications, or whether it is merely a common consequence of the tissue damage reflecting the presence of complication, is a matter of scientific debate. But, it is true that oxidative stress plays an important role in diabetic complications. Baynes and Thorpe[117] argue that treatment of diabetes with antioxidant therapy is like applying water to a burning house and is certainly helpful in limiting the conflagration. Obviously, if antioxidant therapy is helpful in relieving symptoms and complications in a diabetic patient based on the present evidences, the physician will consider this aspect first to relieve and improve his patient[3]. Finding out the real cause and understanding becomes the secondary consideration to be explained and addressed later. Present therapeutic strategies mostly try to relieve the clinical manifestation of diabetes and its complications. The major challenge in diabetes research is to define not only the cause–effect relationship between various risk factors and complications, but also to comprehend the effects of pharmaceutical agents that are beneficial in the management of diabetic complications. Nonetheless, the rationale for the therapeutic use of antioxidants in cases of diabetes[118–120] and other critical disease conditions is emerging fast[121].

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[122,123]. Although several drugs targeted for carbohydrate hydrolysing enzymes (pseudosaccharides), release of insulin from pancreatic β-cells (sulphonyl urea), glucose utilization (biguanides), insulin sensitizers, PPARγ agonists (glitazones) are in clinical practice, the growing diabetes market observes a number of changes. 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 (troglitazone), including a number of deaths from hepatic failure[124–126] and raising the symptoms and risk factors of heart disease leading to heart failure (rosiglitazone)[125]. Therefore, as the long term of 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[127].

On the other hand, traditional medicinal plants with various active principles and properties as discussed in this article have been used since ancient times by physicians and laymen to treat a great variety of human diseases such as diabetes, coronary heart disease and cancer[116,128]. 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.

The *multifactorial pathogenicity* of diabetes demands *multi-modal* therapeutic approach. Thus, future therapeutic strategies require the combination of various types of multiple agents. Gale[125] laments that '. . . the rise of modern medicine has largely been based on new drugs, and most of us can expect to hobble to our graves on the crutch of polypharmacy'. However, *medicatrix naturae* – the power of self-preservation or adjustment has been the *motto* of traditional medicinal practice, which prescribes polyherbal formulations. The theories of polyherbal formulation have the synergistic, potentiative, agonistic/antagonistic pharmacological agents within themselves due to incorporation of plant medicines with diverse pharmacological actions. These pharmacological principles work together in a dynamic way to produce maximum therapeutic efficacy with minimum side effects. Traditional medicinal preparations therefore, should not be considered just as a collection of therapeutic recipes. They are formulated and prepared keeping in mind the conditions of sickness and the healing properties of individual ingredients. It is important therefore, that herbal medicines and preparations should be taken with the consideration of their holistic therapeutic approach. The multiple activities of plant-based medicinal preparations meant for diabetes offer enormous scope for combating the threat of the diabetic epidemic.

To achieve a blockbuster status, clear evidence of the advantage over the existing therapy is the most important requirement of the day. The ability of modern medicine and health care 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[129] and evidence for effectiveness is growing, it is also being simultaneously counterbalanced

by inadequate regulation[130]. 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 required.

Note added in the proof: J. Marks in *Science* (2002, **296**, 686–689) observes: 'The World Health Organization predicts that the number of cases world wide for diabetes now is 150 million – will double by the year 2005.'

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