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Herbal Medicines in the Treatment of Type 2 Diabetes Mellitus.

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ABSTRACT:

Various reports have shown that chronic low-grade inflammation is associated with the risk of developing type 2 diabetes mellitus and that sub-clinical inflammation contributes to insulin resistance and is linked to the characteristics of metabolic syndrome which primarily include chronic hyperglycemia. Oxidative stress stimulates the generation of inflammatory mediators and inflammation which in turn enhances the production of reactive oxygen species. The interaction between chronic hyperglycemia, oxidative stress, systemic inflammation and the factors promoting prevalence of diabetes mellitus, with particular focus on type 2 diabetes and its secondary complications are the main motivation for the compilation of this article. Phytochemicals, the secondary metabolites produced by the plants, are reported to have both significant beneficial and pharmacological properties in alleviating most of the human ailments especially diabetes mellitus. Herbal medicines are often preferred for the treatment of human ailments because of their availability, accessibility, affordability and non-toxicity. Based on our previous studies on the pharmacological and beneficial properties of various medicinal plants, phytochemicals and the mineral contents, the present article adjudicates the essential role of herbal medicines in the treatment of diabetes and its secondary complications.

INTRODUCTION

Diabetes mellitus (DM) has been recognized as one of the four major non-communicable diseases, namely cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes, that insists on imperative awareness from all key shareholders worldwide in an effort to tackle its increasing prevalence and its associated secondary complications **[1, 2].** Additionally, it is included as one of the top 10 causes of premature mortality worldwide. Further, DM is established as the third-highest risk factor for worldwide early mortality due to chronic hyperglycemia or severe hypoglycemia **[3, 4].** According to the International Diabetes Federation (IDF) report for the year 2022, currently 537 million people are living with DM, and it is projected that by 2045, about 783 million people will be living with DM **[5, 6].** This number is lower because, for each diagnosed case, there will be one undiagnosed case in first-world and eight in third-world countries **[7, 8]**. Factors driving this striking rise in the incidence of diabetes, especially in developing countries, are flaring urbanization and lifestyle changes, including increasing sedentary lifestyles, less physical activity, and the global nutrition transition from nutrient-rich to energy-directed foods **[9, 10]**. Diabetes mellitus is a multifactorial, multisystemic and heterogeneous group of disorders essentially characterized by variable degrees of impaired secretion (T1DM) and/or action of insulin (T2DM), leading to persistent elevation in blood glucose levels **[11, 12].**

ETIOLOGY, CLASSIFICATION AND DIAGNOSIS OF DIABETES MELLITUS

Type 1 diabetes (T1DM) arises due to selective, progressive, and irreversible autoimmune destruction of a critical mass of pancreatic beta cells, varying from rapid to slow decline of insulin synthesis and secretion **[13, 14].** Previously, T1DM was termed juvenile diabetes or insulin-dependent diabetes mellitus (IDDM) as it developed principally in adolescence **[15-17].** However, the view has changed over the past decade, as T1DM may occur at any age and T2DM patients also require insulin treatment when all the oral hypoglycemic drugs are unsuccessful to control the persistent hyperglycemia **[18].** T1DM can develop quickly over weeks or even days. Weight loss is common in people with type 1 diabetes when it first develops and before it is treated,

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but it is less common in people with T2DM. The characteristic features of T1DM include.

1. T1DM accounts for nearly 90% of childhood-onset diabetes and 10% of adult-onset diabetes mellitus **[19].**
2. There is an absolute deficiency of insulin secretion, increased glucagon secretion, and/or failure to respond to oral therapy **[20, 21].**
3. More prone to diabetic ketoacidosis, a grave pathological condition due to excessive breakdown of muscle proteins and fats **[22].**
4. The chief contributors to T1DM include autoimmunity, genetics, and environmental factors **[23, 24].**
5. Nearly 90% of T1DM patients have one or more islet cell auto antibodies such as cytoplasmic islet cell antibodies (ICA), anti-insulin antibodies, glutamate decarboxylase (GADA), and zinc transporter 8 (ZnT8). The presence of two or more auto antibodies is an almost certain predictor of clinical hyperglycemia and T1DM. T1DM patients who are negative for auto antibodies are termed "idiopathic" (Type 1b) **[25-28].**
6. Occasionally, it occurs in association with other autoimmune disorders.
7. Equal frequency in males and females; obesity is rare; and more than 50% concordance in identical twins **[29, 30].**
8. The most robust association with viruses and T1DM involves enterovirus species such as Coxsackievirus, Rubella virus, and Hepatitis C virus **[31].**
9. Increased incidence and prevalence rates of severe hypoglycemic episodes (blood glucose levels below 54 mg/dl) may occur in T1DM patients at least once in two years due to therapeutic hyperinsulinemia, which in turn may arise due to a high dose of insulin administration, incorrect timing related to meals, an increase in glucose utilization during or after physical exercise, an increase in insulin sensitivity due to weight loss, a fall in insulin excretion under pathological conditions such as renal dysfunction or hepatic malfunction, etc **[32, 33].**

Type 2 diabetes mellitus is the most prevalent form due to numerous causes, with a frequency of 90–95% of all known cases in the population **[34-36].** It characterizes a whole spectrum of clinical syndromes, ranging from insulin secretion defects to impaired action on vital tissues. Age, obesity, and mental stress are also known to play a vital role in the development of T2DM. In the initial stages, the pancreas secretes more insulin (hyperinsulinemia) in order to maintain the blood glucose levels within the physiological range **[37].** However, subsequent to the onset of T2DM, the secretion of insulin gradually decreased. The incidence of T2DM at earlier stages recurrently goes undiagnosed because the classic symptoms such as polyuria, polydipsia, and polyphagia develop gradually as hyperglycemia develops, and the insulin levels in such patients are often within the physiological range or elevated **[38].**

According to the American Diabetes Association (ADA), diabetes mellitus can be diagnosed clinically in three ways, and each, in the absence of unequal hyperglycemia, must be confirmed on a subsequent day, by any of the three methods, namely the levels of fasting plasma glucose (FPG) less than 120 mg/dl, two-hour postprandial glucose less than 140 mg/dl, and random glucose less than 180 mg/dl **[39-42].** Nowadays, the levels of glycosylated haemoglobin (HbA1c), a measure of the percentage of haemoglobin that has been bound to glucose for the last three months, are used as a reliable and reproducible index of both diagnostic and prognostic value in the field of diagnosis and treatment of diabetes **[43].** HbA1c is defined as specific glycosylated haemoglobin formed by non-enzymatic ketamine reaction between the carbonyl group of glucose and the N-terminal of the amino acid, valine in one or both beta chains of haemoglobin **[44].**

Recently, HbA1c percentages of less than 7 are regarded as good glycaemic control in diabetic individuals **[45-47].**The classical signs (experienced only by the individual) of DM include polyuria, polydipsia, polyphagia, headache, body pain, whole body itching, discomfort, inactivity, and shortness of breath. The conventional symptoms (detected by someone) include unusual weight loss, psoriasis, frequent infections, foot ulcers, and delays in wound healing. The chronic complications of DM include retinopathy, neuropathy, nephropathy, cardiovascular complications, gastrointestinal disorders, skin infections, genital disorders, impotency and bone deformities. There is a

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strong link between T2DM, chronic hyperglycemia-induced oxidative stress, and inflammation **[48].**

ROLE OF OXIDATIVE STREES IN DIABETES MELLITUS

Free radicals may be defined as an atom or a diatomic or polyatomic molecule that possesses one or more unpaired electron in its outer shell valency orbit but is neither positive nor negatively charged **[49, 50].** Due to their electronic instability, free radicals are inherently highly unstable and extremely active. They always tend to acquire or lose an electron from the adjoining molecule through bonding to gain electronic stability and form a stable compound, acting as an oxidizing or reducing agent **[51].** However, during this process of accepting or donating an electron, the neighboring contributor or beneficiary molecule becomes a free radical **[52, 53].** Thus, the generation of free radicals is a cascade of reactions. Free radicals have acquired growing importance in the fields of biology and medicine, with particular reference to their role in the etiology of several dreadful diseases **[54].**

Most of the free radicals are derived from oxygen, and hence they are frequently termed as "Reactive Oxygen Species" (ROS). The gift of using oxygen has enabled humans and animals to metabolize carbohydrates, fats, and proteins to generate energy in the form of ATP. However, there are negative aspects, since breathing pure oxygen (100%) instead of 20% air is harmful to aerobic organisms **[55, 56].** Free radicals are the products of the partial reduction of oxygen. When an oxygen molecule splits into single atoms, they have an unpaired electron and become free radicals. It has been estimated that more than 5% of consumed oxygen forms free radicals in our human body **[57].**Four-electron reduction of molecular oxygen leads to the generation of water without the generation of ROS, whereas one-electron reduction results in the creation of ROS. The nitrogen-derived free radicals are known as "reactive nitrogen species" **[58, 59].**

Reactive oxygen and nitrogen species may be radical or non-radical compounds. The non-radical species are not free radicals, but they are voluntarily activating free radical reactions in living organisms **[60].** The primary oxygen-free radicals include superoxide and hydroxyl radicals, whereas the non-radical species mainly include hydrogen peroxide, hypochlorous acid, ozone, organic peroxides, aldehydes, peroxynitrile, and singlet oxygen. RNS mainly include radical species such as nitric oxide, peroxynitrite, and nitrogen dioxide, as well as non-radical species such as nitrous acid and dinitrogen tetroxide **[61, 62].**

Free radicals are generated during several endogenous and exogenous processes. Free radical formation occurs continuously in the cells as a consequence of both enzymatic and non-enzymatic reactions **[63, 64].** Enzymatic reactions, which serve as sources of free radicals, include those involved in the respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P-450 system **[65, 66].** Free radicals can also be formed in non-enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions. The mitochondrial electron transport chain (ETC) in the course of oxidative phosphorylation, which generates energy in the form of ATP, is considered to be the primary source of free radicals in the system **[67].** Mitochondria combine oxygen and glucose to produce carbon dioxide, water, and ATP. Free radicals are formed in the body either from normal essential metabolic processes in the human body or from external sources such as X-rays, ozone, cigarette smoking, air pollution, and industrial chemicals **[68].** Free radical-generating substances can be found in the food we eat, the medicines we take, the air we breathe, and the water we drink. The other sources of free radical formation include alcohol, tobacco smoke, pesticides, and pollutants **[69].**

In addition to their harmful effects on health, ROS and RNS can have beneficial effects depending on their function, location, and level. For illustration, superoxide ($O2^{-}$•) and nitric oxide (•NO) radicals at low or optimal concentrations are involved in cellular responses and contribute to signaling pathways **[70, 71].** Free radicals play an indispensable role in numerous biological processes that are essential for life, such as the intracellular destruction of bacteria by phagocytes, especially by granulocytes and macrophages. Free radicals are also implicated in some cellular signaling processes, known as redox signaling **[72].** At low to moderate levels, ROS are beneficial both in regulating processes involving the maintenance of homeostasis as well as a wide variety of cellular functions **[73, 74].**

Nitric oxide (NO), one of the principal oxides of nitrogen, mediates physiological processes in essentially every organ and tissue. Nitric oxide is an endothelium-

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derived relaxing factor (EDRF) biosynthesized endogenously from L-arginine, oxygen, and NADPH by three known NO synthase isoforms: constitutively expressed endothelial NO synthase (eNOS or type 3 NOS) **[51],** neuronal NO synthase (type 1 NOS), and inducible NO synthase (iNOS or type 2 NOS). Reduction of inorganic nitrate may also yield nitric oxide. Nasal breathing produces nitric oxide within the body. NO acts as a signaling molecule in many physiological and pathological processes **[75].** It was proclaimed as the "Molecule of the Year" in 1992. The 1998 Nobel Prize in Physiology or Medicine was awarded for discovering the role of nitric acid as a cardiovascular signaling molecule **[76, 77].** Nitric oxide is highly reactive (having a lifetime of a few seconds), yet it diffuses profusely across the cell membranes. These characteristics make nitric oxide ideal for a transient paracrine and autocrine signaling molecule. It exhibits an extremely broad spectrum of functions, including prevention of blood clotting, regulation of blood pressure, roles in neurotransmission and memory formation, and mediation of the antibacterial and anti-tumour activity of macrophages **[78, 79].**

The inner lining, or endothelium, of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, resulting in vasodilation, which is essential for the prevention of cardiovascular diseases **[80, 81]**. It is also involved in the regulation of blood flow to skeletal muscles, helping to deliver oxygen and other nutrients to the muscles during exercise. Nitric oxide is an important component of the immune response and a powerful neurotransmitter in the central nervous system in the prevention of neurodegenerative diseases **[82, 83]**. In fact, Slldenafil (Viagra) is a drug that exercises the nitric oxide pathway by enhancing the signals that are downstream of the nitric oxide pathway **[84, 85].**

On the other hand, excessive production of free radicals provokes structural modification of vital cellular proteins and the alteration of their functions, leading to cellular dysfunction and distraction of vital cellular processes **[86].** Elevated levels of free radicals cause lipid, protein, and DNA damage. In particular, free radicals can break the lipid membrane, which contains polyunsaturated fatty acids, and increase membrane fluidity and permeability. Protein damage involves site-specific amino acid modification, peptide chain fragmentation, cross-linked reaction product aggregation, electric charge alteration, enzymatic inactivation, and proteolysis susceptibility **[87].** Additionally, ROS can damage DNA through oxidizing deoxyribose, breaking strands, removing nucleotides, modifying bases, and cross-linking DNA- proteins **[88-91]**. Disproportionate amounts of free radical generation often lead to cell damage and apoptosis, contributing to many diseases such as cancer, stroke **[92],** myocardial infarction, diabetes, and other significant conditions **[51].** Many cancers are thought to be the result of interactions between free radicals and DNA that lead to mutations that affect the cell cycle, which then lead to neoplasia **[93].** Because free radicals are necessary for life, the body has several enzymatic mechanisms to minimize radically induced damage and protect against excessive production of free radicals.

The free radicals vary widely in their reactivity; for example, the reactivity of ROS in decreasing order is: OH>O2>H202>NO. Hydroxyl radicals are much more reactive than all other known free radicals, with a half-life period of about 10–10 seconds, and it is estimated that a cell produces around 50 hydroxyl radicals per second **[94,95].**It has been reported that the hydroxyl radicals attack any molecule less than a few nanometers from where they are generated **[96]**.The hydroxyl radical reacts strongly with most organic and inorganic molecules, such as DNA, proteins, lipids, amino acids, sugars, vitamins, and metals, faster than its speed of generation. All mitochondrial enzyme proteins are susceptible to inactivation by hydroxyl radicals, while all amino acid residues of proteins can be oxidized by hydroxyl radicals. It has been estimated that hydroxyl radicals are responsible for more than 60–70% of tissue damage caused by ionizing radiation. Atherosclerosis and cancer, two major causes of death, are salient “free radical” diseases. In atherosclerosis, radical reactions involving diet-derived lipids in the arterial wall and serum to yield peroxides and other substances were reported **[97].**

Superoxide is a highly reactive free radical generated by the immune system to kill invading microorganisms; phagocytes, such as neutrophils, monocytes, macrophages, mast cells, and dendritic cells, are mobilised by chemotaxis to the site of bacterial infection and mediate damage through their surface receptors. It is involved in extensive damage to DNA, oxidation of cholesterol, proteins with electron density amino acid residues, such as cysteine, methionine,

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trptophan, tyrosine, and histidine **[98],** and lipids. Even though the human brain weighs a mere ~1400 g, it consumes 20% of the total basal oxygen (O_2) resources to sustain ATP-intensive neuronal activity to power its ~86 billion neurones and their unfathomably complex networks across trillions of synapses supported by ~250–300 billion glia. Depriving the brain of O_2 for just 30 minutes in an ischaemic stroke elicits a devastating toll: every minute, ~1.9 million neurones and ~14 million synapses expire because, without sufficient O_2, mitochondria are unable to reduce O_2 to H_2O to support ATP synthesis, such that even transitory ischaemia is neurodegenerative. The brain is susceptible to oxidative stress because it harnesses chemically diverse reactive species to perform heterogeneous signaling functions. The human brain consumes ~25% of circulating glucose to support neuronal activity **[99],** corresponding to ~5.6 mg of glucose per 100 g of brain tissue per minute. The fate of glucose in the brain is complex and involves neuronal-glial metabolic coupling. The brain is more susceptible to oxidative stress due to chronic hyperglycemia coupled with low levels of antioxidants.

The liver and brain are the most vulnerable organs next to brain to free radical attack **[100].** Improper metabolism of ROS results in the expression of hypoxia-inducible factor-1 alpha, which increases TNF secretion, leading to an immune response that intensifies liver injury and liver dysfunction. Free radicals can damage cellular macromolecules and, therefore, may participate in hepatocellular injury when produced in excess. The chemical reactivity of nitric oxide (NO) is relatively low, and consequently, its direct toxicity is lower than that of ROS. However, it readily reacts with oxygen, producing the peroxynitrite anion, a very damaging species for DNA, proteins, and lipids **[101,102].** Though nitric oxide is a crucial compound involved in many aspects of health, including blood pressure regulation, athletic performance, and brain function, it is toxic at high exposures. The National Institute for Occupational Safety and Health (NIOSH) has set a permissible exposure limit of 25 ppm (30 mg/m3) over an 8-hour work day and at levels of 100 ppm, nitric oxide causes immediate death. However, nitric oxide is readily converted to nitrates and nitrites by oxygen and water, and its cell signaling is deactivated.

ANTIOXIDANTS AND DIABETES

In order to counteract the deleterious effects of free radicals, nature has gifted us with an array of pharmacologically active molecules collectively termed "antioxidants" **[103-105].** These antioxidants can be generally classified in many different ways: (i) endogenous and exogenous; (ii) natural and synthetic; (iii) enzymatic and non-enzymatic; (iv) polar and non-polar; and (v) by the mechanisms in which they are involved. Endogenous antioxidants mainly constitute enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx). Dietary non-enzymatic antioxidants such as vitamin C, vitamin E, carotenoids, polyphenols, flavonoids, and bioflavonoids are exogenous antioxidants that possess *in vivo* activity and are products of the body's metabolism **[106, 107].**

The first-line defense antioxidants (enzymatic) convert reactive superoxide and hydrogen peroxide into water and oxygen. Non-enzymatic antioxidants can act as a second-line defense against ROS by rapidly inactivating excessive radicals and oxidants. The enzymatic antioxidants further act as the third-line defense involved in detoxification and removal. Antioxidants principally display activities based on three mechanisms: hydrogen atom transfer, single electron transfer, and metal chelation. The antioxidants exert their pharmacological activity through three different pathways: (i) preventive: prevention of free radical formation and its derivatives (ii) interruption: interrupt radical oxidation reaction; and (iii) inactivation: inactivate free radical or radical derivative reaction products **[108].**

The natural biological processes in our system, such as breathing, digestion of food, detoxification, and utilizing fats for energy generation, produce destructive compounds called free radicals. Oxidative stress is a pathophysiological condition wherein the generation of ROS and RNS devastates the cell's inherent antioxidant defenses, leading to impairment of cellular architecture and metabolic functions **[109, 110].** Oxidative stress has been implicated in the initiation, progression, and onset of almost all metabolic, chronic, or cancer disorders, wherein excessive free radicals destroy the cell membrane, inactivate the activity of major enzymes, prevent normal cell division, interfere with energy generation, and cause genetic mutation **[111].** Most of the established drugs prescribed for the treatment of

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dreadful diseases possess antioxidant properties in addition to their pharmacological efficacy **[112].**

ROLE OF HERBAL MEDICINES IN THE TREATMENT OF DIABETES

Throughout the world, several medicinal plants have been found successful for the treatment of numerous primary and secondary health complications, and their demand is increasing exponentially due to the growing recognition of natural products as being non-toxic, more efficacious, and easily available at an affordable price. Phytochemicals produced by plants serve as a priceless chemical library for drug discovery in the pharmaceutical industry. In fact, more than 60% of the marketed medicines are distillations, combinations, reproductions, or variations of substances that exist in nature **[113].** Our ancestors recommended some of the natural products, which are profusely found in nature, long before their medicinal values were established and attested to by scientific validation.

Herbal medicines are often preferred because of their availability, accessibility, and affordability. Phytochemicals are ecologically derived secondary metabolites synthesized by plants to protect themselves against damage due to environmental stress and microbial attacks **[114,115].** However, these phytochemicals are reported to have both beneficial and pharmacological properties in alleviating most human ailments **[116,117].** Compared to humans, plants have highly developed protective systems due to their sessile (stationary) nature, and hence, plants serve as a rich source of novel substances for therapeutic applications **[118, 119].** However, to ensure the safety and efficacy of herbal medicines, standardization and the development of processing aspects for "herbal medicine" are extremely essential.

We have been actively engaged in the identification of medicinal plants with antidiabetic properties for the past two decades and reported the antidiabetic **[120],** antilipidemic **[121,122]** antiulcerogenic **[123],** and antioxidant **[124]** properties of *Aloe vera* leaf gel extract in streptozotocin-induced experimental type 2 diabetes in rats. The seeds of *Eugenia jambolana* **[125,126]** *Momordica Charantia* **[127,128]** *Terminalia chebula* **[129,130],** *Nelumbo nucifera* **[131,132],** *Areca catechu* **[133],** *Cassia auriculata* **[134],** *Artocarpus heterophyllus* **[135],** and *Strychnos Potatorum* **[136]** are reported to possess significant antidiabetic and antilipidemic properties. The leaves of *Murraya Koenigii* **[137,138]** *Pisidium guajava* **[139],** and *Annona Squamosa* **[140, 141]** *Euphorbia hirta* **[142],** *Lippia nodiflora* **[143],** and *Piper betel* **[144-146].** *Sesbania grandiflora* **[147]** is reported to possess significant beneficial and pharmacological properties in the treatment of diabetes. The fruits such as *Morinda citrifolia* **[148],** *Ficus benegalensis***[149],**and *Pithecellobium dulce* **[150,151]** *P raecitrullus fistulosus* **[152],** *Physalis peruviana* **[153],** *Immature palm fruits* **[154,155]** exhibit prominent antidiabetic properties. Similarly, biologically active phytochemicals such as *Resveratrol* **[156-158] and** *fisetin* **[159, 160]** *gossypin* **[161,162]** Rosmarinic acid **[163,164]***Tang eretin* **[165, 166]** *Gymnemic acid, Trigonelline, Ferulic a cid* **[167, 170]** *Silibinin* **[171],** *Morin* **[172, 173]** *Sinapic acid* **[174,175],** *D-Pinitol* **[176],** *Lupeol* **[177],** *syringin* **[178]** *Diosmin* **[179, 180]** 3- Hydroxyflavone **[181],** zinc mixed ligand complex **[182]** and *Swertiamarin* **[183,184],** *Avicularin* **[185, 186]** are reported to have significant properties in controlling chronic hyperglycemica induced hyperlipidemia and oxidative stress in experimental type 2 diabetes in rats. The results of the above earlier reports indicate that the observed pharmacological properties of the medicinal plants indicate the synergetic effect of all phytochemicals present in them. Likewise, the observed antidiabetic and antilipidemic properties of the individual phytochemicals may be due to their significant anti-oxidant properties. In traditional medicine system, the medicinal plants used are very often powder or paste forms of the crude herbs, which often contain both the organic and in-organic constituents. However, experimental studies performed so far on pharmacological properties were mostly with the organic active principals. Some of the in-organic elements such as zinc, vanadium, manganese, chromium and potassium can reduce the blood sugar level and their indirect role in the management of diabetes mellitus is being increasingly recognized. These in-organic trace elements are nutritionally essential for healthy life. Hence, we have studied the role of role of vanadium **[187-190]** in ameliorating chronic hypoglycemia and its secondary complications. Further detailed studies are in progress to elucidate the possible mechanisms by which these phyto-incredients regulate metabolic processes to alleviate chronic hyperglycemia and its secondary complications.

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CONCLUSIONS

In conclusion, the results of the present study provide substantial scientific evidence for the rationale that the phytochemicals and trace elements present in the medicinal plants elicit significant antidiabetic, antilipidemic and antioxidant properties. Isolation and identification of biologically active ingredients from the traditionally important medicinal plants will a pave a new pathway in the treatment of diabetes mellitus and its secondary complications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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