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Plants as Antidiabetic Agents: Traditional Knowledge to Pharmacological Validation

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Abstract
Diabetes is the most devastating and serious of all metabolic diseases. The available natural remedies are considered as a valuable source of therapeutic agents. A scientific validation of the reported antidiabetic plants on the basis of their traditional use may pave the way for the development of novel and effective antidiabetic drugs. Such approaches are the necessity of the day because the available medicines are insufficient to manage all the consequences of diabetes, and the economic problems and a shortage of current therapies in most developing countries. This review comprises information about antidiabetic medicinal plants of Pakistan with respect to traditional knowledge. The article also includes the *in-vitro* or *in-vivo* potential, toxicity, mode of action, and perspective for future research. This effort may serve as a leading point for the formulation of novel herbal mixtures, development of antidiabetic drugs or their precursors.
Keywords: Antidiabetic medicinal plants; traditional knowledge; pharmacological validation.

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INTRODUCTION

Diabetes describes a group of chronic metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (Ogurtsova *et al.,* 2017; Ortiz-Andrade *et al.,* 2005). It also leads to hyperlipidemia, atherosclerosis, and hypertension (Luo *et al.,* 2004) dysfunction and failure of various organs (Brunton, 2009) blindness, kidney failure, lower limb amputation, dementia and some forms of cancer (Federation, 2013; Organization, 2016). A World Health Organization (WHO) report indicates that diabetes will be the seventh leading cause of death in 2030 (Mathers and Loncar, 2006; Wild *et al.,* 2004). The International Diabetes Federation (IDF) estimated that in 2013, 382 million people had diabetes worldwide and that this figure would rise to 592 million by 2035 (Federation, 2013). Out of this, a huge number, 80%, live in low and middle-income countries, with more than 60% living in Asia and nearly one-third in China. A study reported the prevalence of diabetes to be 34.80%, prevalence in women was calculated to be 31.20% and in males 40.40% (Muhammad *et al.,* 2013). The incidence of diabetes is higher in developing countries due to quick and ongoing socioeconomic transition; this factor will likely lead to further rises in the disease (Guariguata *et al.,* 2014). The IDF estimates that the number of people with diabetes in South Asia will increase to 120.9 million, 10.2% of the adult population, by 2030 (Whiting *et al.,* 2011). India with more than 65.1 million diabetic people is the second country next to China in the IDF global list of top 10 countries for people with diabetes. According to an IDF report of (2014), Pakistan and Bangladesh also have large numbers of people with diabetes and occupy 12th and 13th positions, respectively (Nanditha *et al.,* 2016). However, in developed countries as in China (20.8%) and USA (17.7%), the occurrence and consequences associated with diabetes are also high, and that that may rise up to 42.3% and 30.3% by 2030, respectively (Wild *et al.,* 2004).

Diabetes is of three types: type 1 or insulin-dependent, type 2 or non–insulin dependent and gestational diabetes. In Type 1 diabetes, the body produces inadequate insulin to regulate the level of glucose in the blood. This leads to excessive urination, constant hunger, thirst, vision changes, weight loss, and fatigue. In such cases, insulin is provided to the patient for survival. Its cause is still not identified and is therefore not preventable. In Type 2 diabetes the body is unable to use efficiently insulin released from the pancreas. The majority of diabetic people are affected by type 2 - that accounts for 90%–95% of all diabetic cases. This shows similar symptoms to type 1 but is less noticeable and may go undiagnosed for several years until complications have already arisen. Gestational diabetes is characterized by high blood glucose levels that occur due to hormonal changes during pregnancy in genetically predisposed individuals. It is more common among obese women and women with a family history of diabetes. It usually is resolved once the baby is born. However, after pregnancy, 5% - 10% of women with gestational diabetes are found to have type 2 diabetes.

Currently, large amounts of antidiabetic medicines are available in the pharmaceutical market used for the treatment of diabetes and its related complications. These antidiabetic medicines are; biguanides e.g., metformin, which increases cellular responses to insulin and reduces the amount of glucose released by the liver into the blood. Sulphonylureas increase pancreatic insulin secretion e. g, chlorpropamide, glimepiride, glipizide, and glyburide. Glitazones, or thiazolidinediones, e. g., pioglitazone and rosiglitazone enhance the effect of insulin in the muscle and fat and reduce glucose production by the liver. Alpha-glucosidase inhibitors e. g., acarbose and miglitol inhibit the activity of intestinal enzymes responsible for the breakdown of polysaccharides into glucose, hence, reducing the amount of glucose absorbed in the gut. Dipeptidyl peptidase-4 (DPP4) inhibitors have multiple effects, including increases in pancreatic insulin secretion, examples of such drugs are, alogliptin, linagliptin, and saxagliptin. Sodium-glucose co-transporter 2 (SGLT2) inhibitors include canagliflozin and dapagliflozin inhibiting the re-absorption of glucose in the kidneys. Meglitinides e. g., repaglinide and nateglinide, also stimulate insulin secretion. In spite of the use of these antidiabetic medicines, there is no effective therapy available to completely cure the disease. The available antidiabetic medicines are effective in some way but managing diabetes through the use of the available antidiabetic medicines without any side effects is still a challenge (Lo and Wasser, 2011). Thus, alternative therapy from the herbal origin is required in this shift towards the indigenous plants and herbal formulations.

Traditional use of plants is gaining reputation as an alternative to provide a sound base for evaluation of antidiabetic crude extracts, isolation of active constituents and herbal formulation. Around the world, over 1200 plants species have been reported to be used for the treatment of diabetes (Grover *et al.,* 2002; Marles and Farnsworth, 1995). In developing countries, such practices are common where people used medicinal plants for a long time, these plants had a hypoglycemic potential to alleviate the symptoms of diabetes (Ernst, 1997). The remedies and antidiabetic agents obtained from these plants on account of their pharmacological effects reverse diabetic consequences. They may enhance release of insulin from β-cell (Eddouks *et al.,* 2005) or restore the number of β-cells. Some plants show their antidiabetic effect by lowering absorption or transport of carbohydrates in order to maintain blood glucose levels. Some other plants slow down the synthesis of glucose by inhibiting enzymes like glucose-6-phosphatase, fructose 1, 6-bisphosphatase, etc.

Besides these, the antioxidant potential of plants can treat the symptoms of diabetes. Therefore, it is now essential to explore the potentials offered by the traditional medicinal plants through integrated approaches toward the management and prevention of diabetes. This review was initiated with the aim of compiling traditional antidiabetic plants, associated traditional knowledge, their efficacy, limitations, and, with a view to further investigation. Thus, the information provided may be helpful to health practitioners, pharmacologists and researchers.

Methodology

A literature search was made to collect information on the plants from electronic databases, Google Scholar, Scopus, Pub Med and Science Direct with key terms; ethnomedicinal plants, antidiabetic, hypoglycemic and hyperglycemic potential published until May 2017. Scientific names and family names of the reported plants were confirmed from taxonomic literature.

Ethnobotanical studies, indigenous knowledge, and diversity of antidiabetic plants in Pakistan

Indigenous use of medicinal plants has been documented in ethno botanical surveys from various parts of Pakistan. These surveys show that people residing in rural areas usually depend on the available medicinal plants for diseases treatment due to limited or inaccessible health facilities. The greater use of medicinal plants can also be linked to poor economic conditions, cultural preference and easy accessibility to natural resources. Out of 5700 available medicinal plants in Pakistan (Ahmad and Husain, 2008), several plants have been reportedly used for the treatment of serious disorders like cancer, diabetes, hepatitis, and malaria. Among these, several reports lack supporting information like part used formulation methods, time and duration of use of remedies, dose, and gender. According to (Albuquerque *et al.,* 2014) a huge amount of data have been collected through ethnopharmacological surveys performed worldwide, much of the collected data found being not adequately sound for bio-prospecting purposes both from a pharmacological point of view and in the data collection of ethnopharmacological surveys. As, improper remedies, dosage, harmful side-effects and ambiguous products create a potential risk if not administered appropriately (Robinson and Zhang, 2011). Unfortunately, such information was also not collected for some traditional antidiabetic plants in Pakistan. Furthermore, the literature search indicates that there is a single ethnobotanical study from the district of Attock in Pakistan (Ahmad, 2009), that focuses only on medicinal plants used against diabetes.

Ethnomedicinal plants used in the treatment of diabetes in Pakistan include 185 plants species belonging to 70 families. Among these 70 families are; Asteraceae with (16 species) was prominent, followed by Fabaceae (15 species), Lamiaceae (8 species), Solanaceae (7 species), Cucurbitaceous (7 species), Moraceae (7 species), Rhamnaceae (6 species), Zygophyllaceae (6 species), Myrtaceae (5 species), Euphorbiaceous (5 species) and Rosaceae (5 species). Three families with four species each were; Asclepiadaceae, Meliaceae, and Polygonaceae and 10 families with three species each was; Apiaceae, Apocynaceae, Berberidaceae, Gentianaceae, Liliaceae, Malvaceae, Mimosaceae, Oleaceae, Poaceae, and Rutaceae. Among the other families, 9 families each contributed two species were; Adiantaceae, Alliaceae, Bignoniaceae, Brassicaceae, Cactaceae, Capparidaceae, Elaeagnaceae, Pinaceae, and Scrophulariaceae. The remaining (37) families each contributed single species. On the basis of life form habit herbs (105 species) (57. 06%) were found frequently used followed by trees (57 species) (31.67%) and shrubs (22 species) (12.22%). A few plant species were found to be used traditionally in other countries for the same purpose. This indicates that their traditional knowledge has either originated through ethnic links or acquired independently over time.

A few of the plants have been reported in many research articles that indicate the familiarity of these plants among various societies in Pakistan for treatment of diabetes. These also include important antidiabetic plants which have been confirmed and employed in isolated bioactive constituents. The mostly reported plants include six plants; *Hedera nepalensis*, *Caralluma tuberculata*, *Berberis lycium*, *Melia azedarach*, *Syzygium cumini*, *Momordica charantia* reported in (14), (12), (10), (9), (9) and (6) publications, respectively. Four plants reported in (6) publications each include; *Citrullus colocynthis*, *Fagonia cretica*, *Fumaria indica* and *Taraxacum officinale* and two plants reported in (5) publications each is; *Kickxia ramosissima* and *Ziziphus jujuba*. In the other plants,(9) species *Allium cepa*, *Catharanthus roseus*, *Cuscuta reflexa*, *Morus alba*, *Rhazya stricta*, *Solanum nigrum*, *Withania coagulans*, *Zizyphus oxyphyla* and *Justicia adhatoda* each has been reported in (4) publications. Nineteen plants; *Acacia nilotica*, *Ajuga bracteosa*, *Allium sativum*, *Aloe barbadensis*, *Artemisia parvifolia*, *Azadirachta indica*, *Bergenia ciliata*, *Caralluma edulis*, *Euphorbia thymifolia*, *Juniperusexcelsa*, *Olea ferruginea*, *Punica granatum*, *Solanum surattense,* *Teucrium stocksianum*, *Trigonella foenum-graecum*, *Withania somnifera*, *Ziziphus mauritiana*, *Ziziphus nummularia* and *Zizyphus sativa* each one has three citations. Such higher use of plants among various societies may be linked to their wide distribution and medicinal value. Various plants were evaluated for the antibacterial activity (Shahzad *et al.,* 2017). However, some plant species, due to their limited distribution in some parts of Pakistan, have been documented in the ethnobotanical studies conducted in these areas.

It is essential to confirm which plant parts are used in the preparation of remedies because the active chemical ingredients vary within plant parts (George, 2000). Among the plant parts, leaves (75 species) have been reported as mostly used in the formulation of remedies followed by whole plants (61species), fruit (43 species), seeds (34 species), root (22 species), stem (13species), bark (13species),flower (10species) shoot (7species), aerial parts (6species), gum (5species), latex (3species), wood (3species), bulb (2species) and rhizome (1species). However, in traditional therapies, the whole plant is rarely used for medicine, as one part of those plants may be quite toxic or useless, and another may be quite harmless and useful (Karunamoorthi, 2013). Therefore, a systematic survey of the traditional plants is essential to document valuable information for pharmacological and clinical investigations in order to discover their antidiabetic potential.

Scientific validation of the traditional antidiabetic plants of Pakistan

Among the reported antidiabetic plants from Pakistan, several plants have been investigated pharmacologically across the globe for their antidiabetic properties. Among these pharmacological studies, (36) research studies have been conducted on the basis of the traditional use of plants. In all these studies, researchers have confirmed their traditional antidiabetic use, with 63% studies (Saltan *et al.,* 2017; Upadhya *et al.,* 2004) that gave positive results and have shown significant antidiabetic properties. This shows that traditional remedies may provide a better opportunity for the discovery of new and effective antidiabetic agents. Among the other pharmacological studies with random selection, several plants species have shown significant antidiabetic properties. No negative result has been reported for any of the randomly selected plants. The greatest variety of the plants has provided the prospect to find new active constituents and mechanisms on a chemotaxonomic basis. Alongside this, the quantity and effectiveness of plant constituents vary according to geographic regions and are influenced by various factors including seasons, environment, plant part, intra-species variation, and plant age (Weenen *et al.,* 1990). Therefore, further evaluation is necessary to assess their antidiabetic potential, bioactive constituents and to establish their efficacy for better health opportunities.

Currently used approaches to bioassay-guided antidiabetic drug discovery can be divided into two main classes: in vivo and in vitro techniques. The pharmacological studies conducted for the reported plants include (155) in vivo studies and (25) in vitro studies. Only five clinical studies have been conducted by researchers. In the in vivo studies, diabetes is mostly induced in animal models, which is considered as suitable methods for the evaluation of physiological and biochemical parameters in diabetic conditions. In most of these studies, the hyperglycemic condition is created with significant changes in insulin levels, lipids metabolism, and oxidative enzymes. The liver and kidneys are severely affected, as these organs synthesize lipids and proteins and regulate glucose levels in the blood. Later, such alterations lead to hyperlipidemia and vascular problems. Therefore, rodents, including mice, rats, and rabbits are a suitable and commonly used model for investigation of in vivo antidiabetic properties of plants. In the current review of the antidiabetic potential of the reported ethnomedicinal plants, researchers have used rats in (130), mice in (24) and rabbits in (8) studies. Most researchers experimented on the rats, which are the preferred models. In the in vivo investigation, researchers have used two main diabetes inducing agents; alloxan in (54) studies and streptozotocin in (73) studies of the reported plants. In four research studies, nicotinamide had been used with streptozotocin. In some experiments, the antidiabetic potential of plants had been determined in normal (7), glucose-loaded (18), genetically (4) and insulin resistant animal models (1).

Fortunately, in most of the pharmacological studies, researchers have used aqueous extract in (57) and ethanolic extract in (30) studies. Both these solvents are acceptable and commonly used in traditional medicinal preparations. In some studies, researchers have used raw plant materials in the form of juice, latex or powder (Akinmoladun and Akinloye, 2007; Waheed *et al.,* 2007). However, a literature search on the pharmacology of antidiabetic plants indicates that researchers have used other solvents such as benzene, chloroform, dichloromethane, ethyl acetate, methanol, methylene chloride and petroleum ether. Therefore, the use of such solvents in preparation of extract for pharmacological investigation is not according to the indigenous methods of preparation of plant extracts. Such investigation of plants may affect the results obtained. However, a complication has been observed in case of *Gentiana olivieri,* being traditionally used as the antidiabetic agent. No effect was observed for aqueous extract of aerial parts, while its methanolic extract has shown significant activity in glucose-hyperglycemic rats within 2h (Sezik *et al.,* 2005). In a single in vivo study on antihyperglycemic activity of *Foeniculum vulgare,* essential oil blood glucose levels had decreased from 162.5 ± 3.19 mg/dl to 81.97 ± 1.97 mg/dl; it also improved the pathological changes noticed in kidney and pancreas of STZ induced diabetic rats.

Few studies suggested higher doses that may not be of practical use, e. g., the aqueous extract of *Withania coagulans* had shown a maximum fall of 33.2% in FBG after 4h at a dose 1000mg/kg, and a dose of 1000 mg/kg reduced the FBG levels by 52.9% on 30th day comparable to glipizide at 49.2%. Similarly, a higher dose of 1000 mg/kg of *Vernonia cinerea* barks and leaves methanolic extract has significantly ($p < 0.05$) decreased BGL after 3hrs in alloxan induce rats. Alongside this, few studies report the administration of extract by intra-peritoneal route (Bhowmik *et al.,* 2009). A recent study on the hypoglycemic activity of *Cissampelos pareira* (Piero *et al.,* 2015) also confirmed that the extract administration with the intraperitoneal route is more effective than the oral route. (Eddouks and Maghrani, 2004) found that *Fraxinus excelsior* seeds aqueous extract 10 mg/kg/h administered intravenously, produce a significant decrease in blood glucose levels in normal rats ($P < 0.001$) - even more than standard Vanadate (0.8/kg/h) in diabetic rats ($P < 0.001$). Such routes of administration of extract are not employed in the traditional therapy of herbal medicines but they may be helpful to determine the effectiveness of plant extract in reversing diabetic consequences because, in oral administration, the extract passes through the gut before being absorbed into the blood. A report on the antidiabetic potential of *Justicia adhatoda* L. has been published in a banned journal, African Journal of Biotechnology (Gulfraz *et al.,* 2011).

The antidiabetic potential of the reported plants in the pharmacological study was recognized by their potentials as; hypoglycemic or antihyperglycemic agent which enhanced insulin production and restored pancreatic β-cell mass (Sebbagh *et al.,* 2009), decreasing HbA1c (Huseini *et al.,* 2009), creatinine, urea, cholesterol, triglycerides, low-density lipoprotein cholesterol, very low-density lipoprotein-cholesterol and increasing in high-density lipoprotein, decreasing effects on LPO, SOD and GSH activity (Omara *et al.,* 2012). Besides these, there was a reduction of β-thromboglobulin and platelet aggregation (Asad et al., 2011), decreases in MDA levels (Upadhya *et al.,* 2004), and free radicals and bilirubin in plasma *(El-Demerdash et al.,* 2005), properties of serum enzymes like alkaline phosphatase, acid phosphatase and lactate dehydrogenase and liver glucose-6-phosphatase (Sheela and Augusti, 1992), TBARs level, HOMA_IR, ASAT, ALAT,GGT, serum oxaloacetate transaminases, pyruvate transaminases, (SGPT) content (Wani *et al.,* 2011) and inhibition of protein tyrosine phosphatase1B (Oh *et al.,* 2005). These plants also improve body weight, total proteins, albumin, globulin (Helal *et al.,* 2014), muscle and liver glycogen contents. In the in vitro investigation, the inhibition of dipeptidyl peptidase IV activity (Yogisha and Raveesha, 2010), glucose uptake by hemi-diaphragm,α-amylase and α-glucosidase and enhancement of glucose transport into L6 myotubes (Ahmed *et al.,* 2004) had been noticed. Several researchers have observed that plant extracts also decrease the oxidative stress of diabetes-inducing agents in rodent models. Alongside this, diabetes-induced sexual disability can be corrected through the extract of *Orchislatifolia*. This indicates that traditional antidiabetic plants in various ways restore metabolic and structural changes that usually arise in diabetes.

Some plant extracts enhance secretion of insulin from pancreas e.g., *Albizzia lebbeck, Ailanthus altissima, Allium sativum, Arctium lappa*, *Argyrolobium roseum, Artemisia annua, Azadirachta indica, Butea monosperma, Caralluma tuberculata, Catharanthus roseus, Citrullus colocynthis, Cucurbita maxima, Dalbergia sissoo, Eriobotrya japonica, Ficus bengalensis, Fraxinus excelsior, Luffa acutangula, Moringa oleifera, Morus alba, Nerium oleander, Olea europaea and Ricinus communis* have been confirmed as insulin tropic agents. In the other studies, a few plant fractions or constituents have been confirmed as increasing insulin secretion or insulin tolerance. The polyphenol-rich gel extract of *Aloe vera* containing aloin (181.7 mg/g) and aloe-emodin (3.6 mg/g) has improved insulin tolerance in insulin-resistant mice (Pérez *et al.,* 2007). The butanolic fraction of *Argyrolobium roseum* has stimulated insulin secretion in the in vitro (RINm5F cells) and in vivo model (Ahmed *et al.,* 2008). Similarly, benzyl derivatives isolated from the methanol extract of the *Moringa oleifera* fruit has stimulated insulin secretion from the pancreatic β-cell line INS-1. The polysaccharide-Ia isolated from *Opuntia dillenii* protects the liver from peroxidation and improves the sensitivity of target cells in diabetic mice to insulin (Zhao *et al.,* 2011).

Only two studies (Ebong *et al.,* 2008) have reported the synergistic effect of the two important antidiabetic plant extracts, i.e., *Azadirachta indica,* and *Vernonia amygdalina*. These two studies are not enough as large numbers of antidiabetic plants have been documented in the literature. The synergistic effect is the combined effect of the constituents of two or more extracts, the effects being higher than if employed independently. Such a combination of extracts is in accordance with the formulation of herbal mixture where two or more plant extracts are combined. In such cases, some constituent may support the bioactive agent by enhancing its availability, decreasing metabolite formation and preventing its secretion (Rasoanaivo *et al.,* 2011). This idea has gained popularity among pharmacologists in the way of the formulation of herbal remedies containing various plant extracts. Therefore, assessment of the synergistic effect of these traditional antidiabetic plants may pave the way for combating the consequences of this metabolic disorder.

Several researchers have validated the antidiabetic potential of the reported plants through investigation of extracts and their bioactive constituents. These constituents include flavonoids and tannins isolated from *Adiantum capillus veneris*, Vitexin from *Argyrolobium roseum*, 3-O-galloylepicatechin and 3-O-galloylcatechin from *Bergenia ciliata*, vanillic acid and 4-hydroxybenzoic acid from *Elaeagnus angustifolia*, quinovic acid, quinovic acid-3β-O-β-D-glycopyranoside, quinovic acid-3β-O-β-D-glucopyranosyl-(28→1)-β-D-glucopyranosyl ester and stigmasterol from *Fagonia cretica*, bergenin from *Ficus racemosa*, Isoorientin from *Gentiana olivieri*, flavonoids pectolinarigenin, pectolinarin from *Kickxia ramosissima*, stearoyl glucoside of ursolic acid, urs-12-en-3β-ol-28-oic acid 3β-D-glucopyranosyl-4′- Octadecanoate from *Lantana camera*, Mangiferin, from *Mangifera indica*, Charantin from *Momordica charantia*, Oleanolic acid from *Olea europaea*, *polysaccharide* from *Opuntia dillenii*, fructans and fructo-oligosaccharides from *Orchis latifolia*, quercetin-3-O-α-D-galactopyranoside from *Rhododendron arboreum*, Lupeol, 12-oleanen-3-ol-3ß-acetate, stigmasterol and ß-sitosterol from *Syzygium cumini* and saponin from *Tribulus terrestris*.

Some plants have been subjected to clinical trials. The gel added a diet of *Aloe vera* which was fed to 5,000 angina pectoris patients for five years and which decreased triglycerides, total cholesterol, fasting and post-prandial BGL in diabetic patients, total lipid and increased HDL (Perez *et al.,* 2007). In another clinical study, the juice of the same plant reduced BGL in 50 men and 22 women from 257.14±7.78 to 141.92±4.12 and showed significant decreases in triglyceride levels on day 42 (Yongchaiyudha *et al.,* 1996). The fruit capsule of *Citrullus colocynthis* significantly decreased HbA1c and fasting BGL in 50 type II diabetic patients (Huseini *et al.,* 2009). The aqueous extract of *Momordica charantia* and *Eugenia jambolana* for 15 days substantially prevented hyperglycemia and hyperinsulinemia induced by a diet high in fructose in 10 Type 2 diabetic patients (Waheed *et al.,* 2007). Administration of two capsules (500 mg) of the aqueous extract of *Fraxinus excelsior* with 7 days break in 16 (50 g) glucose-induced postprandial hyperglycemic persons, showed a decrease in postprandial glucose levels and a significant increase in insulin secretion (Visen *et al.,* 2009). This indicates that further clinical investigation of the traditionally used antidiabetic plants is imperative in order to provide a sound base for the development of antidiabetic agents.

Toxicology

Medicinal plants are considered safe due to their long historical use, but many serious side effects have been reported in the literature (Izzo, 2004; Whitton *et al.,* 2003). These effects may be direct, allergic and due to the contamination or interactions with other drugs or herbs (Seth and Sharma, 2004). Information on the toxicity of medicinal plants is rarely documented in the ethnopharmacological surveys as is the case in Pakistan where nearly all such studies lack information on the toxic effects of medicinal plants. The correct use of traditional medicines can reduce the risks of toxicity. According to (Calixto, 2000) the idea that traditional medicinal products which come from natural sources are completely safe, is dangerously false. This current medicinal plants utilization is largely based on long-term clinical practices with little or no information on their effectiveness and safety (Zhu *et al.,* 2002). Several plants have been tested in the pharmacological studies for their toxicity. Among these three plants, *Artemisia herba-alba*, *Bombax ceiba* were confirmed as toxic agents with obvious effects on behavior(Sathish Sekar et al., 2005). Therefore, the development of safe and effective products needs to be carefully observed in terms of their on-going development. It has become essential, therefore, to furnish the general public, including healthcare professionals, with adequate information to facilitate a better understanding of the risks associated with the use of these products and to ensure that all medicines are safe and of suitable quality.

FUTURE PROSPECTS

The pharmacological and clinical studies conducted around the globe have validated many of the reported plants for their potential use against the consequences of diabetes. This provides a prospect for further research in order to find novel antidiabetic agents, their potentials, mechanisms of action and synergistic effects for the eventual formulation of herbal mixtures and their combination with synthetic medicines. Such efforts will be more lucrative if their side effects are confirmed by careful clinical studies. Alongside these, new techniques must be employed to get excellent plant products in high amounts and to determine their potentials more accurately.

CONCLUSION

The current review comprises 185 plants traditionally used in the therapy of diabetes in various parts of Pakistan. The pharmacological studies indicate that nearly all of the investigated plants have shown antidiabetic activity and may serve as novel antidiabetic agents. Studies into the therapeutic efficacy and safety of these plants are also necessary because several plants have shown toxic effects. The increasing incidences of diabetes have turned the attention of researchers towards ways of discovering alternative therapies for diabetes. This research work may provide novel approaches for the development of plant-based herbal mixtures and antidiabetic agents from indigenous plant resources.

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CONFLICT OF INTEREST

All the authors have declared that no conflict of interest exists.

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