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Herbal Drugs Used for the Treatment of Diabetes: A Review

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ABSTRACT

Diabetes mellitus (DM) is the commonest endocrine disorder that affect more than 100 million people worldwide (6% of the population). It is cause by the absence or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. The prevalence of diabetes mellitus is expected to reach up to 4.4% in the world by 2030. Among all type of diabetes, type 2 diabetes is main complication. Many diabetic patients are known to use herbal medicines with antidiabetic properties in addition to their mainstream treatments, which may present both a benefit as well as potential risk to effective management of their disease. In this review we evaluate the clinical and experimental literature on herb–drug interactions in the treatment of diabetes. A list of medicinal plants with proven antidiabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled. These include, *Allium sativum*, *Eugenia jambolana*, *Momordica charantia, Ocimum sanctum, Phyllanthus amarus, Pterocarpus marsupium, Tinospora cordifolia, Trigonellafoenum graecum and Withania somnifera.*

Introduction:

Diabetes mellitus is a disorder that affects the body's ability to make or use insulin. Insulin is a hormone produced in the pancreas that helps transport glucose (blood sugar) from the bloodstream into the cells so they can break it down and use it for fuel. People cannot live without insulin. Diabetes results in abnormal levels of glucose in the bloodstream. This can cause severe short-term and long term consequences ranging from brain damage to amputations and heart disease.

1.2 Types and differences of diabetes:

There are several forms of diabetes. Scientists are still defining and categorizing some of these variations and establishing their prevalence in the population. Types of diabetes include:

1.2.1 Type 1 diabetes: An autoimmune disease in which the immune system mistakenly destroys the insulin-making beta cells of the pancreas. It typically develops more quickly than other forms of diabetes. It is usually diagnosed in children and adolescents, and sometimes in young adults. To survive, patients must administer insulin medication regularly. Type 1diabetes used to be called juvenile diabetes and insulin-dependent diabetes

mellitus (IDDM). However, those terms are not accurate because children can develop other forms of diabetes, adults sometimes develop type 1, and other forms of diabetes can require insulin therapy. A variation of type 1 that develops later in life, usually after age 30, is called latent autoimmune diabetes of adulthood (LADA). Sometimes patients with autoimmune diabetes develop insulin resistance because of weight gain or genetic factors. This condition is known as double diabetes.

1.2.2 Type 2 diabetes:

A disorder of metabolism, usually involving excess weight and insulin resistance. In these patients, the pancreas makes insulin initially, but the body has trouble using this glucose-controlling hormone. Eventually the pancreas cannot produce enough insulin to respond to the body's need for it. Type 2 diabetes is by far the most common form of diabetes, accounting for 85 to 95% of cases in developed nations and an even higher percentage in developing nations, according to the International Diabetes Federation. This disease may take years or decades to develop. It is usually preceded by pre diabetes, in which levels of glucose (blood sugar) are above normal but not high enough yet for a diagnosis of diabetes. People with pre diabetes can often delay or prevent the escalation to type 2 diabetes by losing weight through improvements in exercise and diet, as the Diabetes Prevention Program and other research projects have demonstrated. Type 2 diabetes used to be called adult-onset diabetes and non-insulin-dependent diabetes mellitus (NIDDM). Those terms are not accurate because children can also develop this disease, and some patients require insulin therapy.

3. Herbal–drug interaction and its mechanisms of action

Two (or more) drugs when administered together have the potential to cause chemical or pharmacological interactions. Such interactions may alter the effect of either agent, leading to decreased or increased effectiveness or severity of adverse effects. The outcomes are dependent on many chemical and pharmacological factors, such as the physicochemical nature of the drugs in use and how they affect each other pharmacokinetically and pharmacodynamically. Although, the mechanisms of interactions between herbs and drugs are similar, they are more complex in nature when several compounds are involved. Herb–drug interactions (HDI) may affect clinical safety and efficacy via additive/synergistic or antagonistic interactions among the herbal components and drug molecules. Whilst negative or harmful interactions tend to receive more attention due to safety considerations, additive/synergistic effects induced by HDIs may result in an enhancement of desired pharmacological effects. For example, the blood glucose lowering effect of antidiabetic drugs has been shown to be increased by agrimony. A number of mechanisms may be associated with pharmacokinetic HDIs including quantitative alterations in renal clearance bioavailability ;drug distribution, absorption ;and elimination processes . Hepatic metabolic enzyme systems, particularly the cytochrome P450 (CYP450) isoenzyme family, remain a common pathway for pharmacokinetic HDIs. Many anti-diabetic drugs are substrates of CYP450 isoenzymes, e.g. pioglitazone, repaglinide and rosiglitazone for CYP2C8, glibenclamide, glimepiride, glipizide, nateglinide and rosiglitazone for CYP2C9, proguanil for CYP2C19, and pioglitazone and repaginate for CYP3A4 . A large number of herbs have also been suggested to affect the CYP450 system. For example, St John's wort inhibits CYP2C and CYP3A and ginkgo inhibits CYP3A4, CYP2C9 and CYP2C19. Pharmacodynamic HDIs can modify the drug/herb actions in a qualitative manner through effects on various organs, receptor sites or enzymes. Such interactions can result in antagonistic, additive or synergistic effects. For example, many herbal medicines possess antioxidant properties which could be beneficial for reducing oxidative stress, a key pathogenic factor of diabetes . Several pharmaceutical agents effective in reducing diabetic mortalities (e.g., 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have also been shown to have antioxidant activities . When these herbs and drugs are used together, pharmacodynamic HDI (either additive/synergistic) may occur. Some of the known interactions between selected antidiabetic drug and antidiabetic herbs are discussed in "Common herb–drug interactions in diabetes".

4. Common herbal –drug interactions in diabetes

The co-administration of antidiabetic herbs and pharmaceutical agents may result in HDIs leading to enhanced effects (which may be desirable clinically), decreased pharmacological effects, or adverse drug events, such as hypoglycaemia. The following section provides a brief discussion of common antidiabetic herbs and their potential interactions with antidiabetic agents. Literature searches were conducted with PubMed and Google Scholar up to June 2017. The selection of medicinal plants for inclusion is based on their consistent use over long periods and on the strength of available data on effectiveness or adverse/synergistic effects.

Aloe vera—Aloe barbadensis Aloe vera is native to Africa and is one of the more than 400 species of the genus Aloe. The presumed major active components include carbohydrates (e.g., mannan, galactose-rich polysaccharides), and galacturonic acid . Traditional literature reveals a wide range of clinical uses of this plant from cosmeceuticals through to immunity and organ care. In diabetes, aloe vera has been shown to significantly reduce blood glucose levels . Several studies report potential interactions between aloe vera and antidiabetic drugs. Of note is its interaction with glibenclamide, a sulphonylurea which exerts its antidiabetic potential by inhibiting ATP sensitive potassium channels in pancreatic β cells, resulting in cell membrane depolarization and subsequent insulin release. The combination of aloe vera and antidiabetics has generally been shown to have an additive effect. For instance, aloe has been shown to produce a greater anti-hyperglycaemic effect, when compared to the sole therapy with glibenclamide, pioglitazone or repaglinide .

Ginseng-Panax ginseng and Panax quinquefolium Both Panax ginseng and Panax quinquefolium, two important members of the ginseng family, have been shown to possess antidiabetic properties affecting insulin dependent and insulin independent pathways . The bioactive constituents responsible for ginseng's antidiabetic actions are likely to be attributed to its ginsenosides. Although the precise active components responsible for this anti-diabetic action are unknown, studies with compound K (CK), a final metabolite of protopanaxadiol ginsenosides demonstrate that CK exhibits anti-hyperglycaemic effects through an insulin secreting action similar to metformin. The combined treatment of CK and metformin has been shown to elicit additive effects compared to individual components being used alone. Significant improvements were observed in plasma glucose and insulin levels, homeostasis model assessment-insulin resistance (HOMA-IR) and in haematoxylin and eosin-stained liver tissues.

Table 1. Indian medicinal plants with antidiabetic and related beneficial properties

Plant Name	Ayurvedic/common name/herbal formulation	Antidiabetic and other beneficial effects in traditional medicine
Annona squamosa	Sugar apple	Hypoglycemic and antihyperglycemic activities of ethanolic leaf-extract, Increased plasma insulin level
Areca catechu	supari	hypoglycemic
Boerhavia diffusa	punarnava	Increase in hexokinase activity,decrease in glucose-6-phosphatase and fructose bis-phosphatase activity, increase plasma insulin level, antioxidant
Capparis decidua	Karir or Pinju	Hypoglycemic, antioxidant, hypolipidaemic
Coccinia indica	Hypoglycemic	Hypoglycemic
Emblica officinalis	Amla, Dhatriphala, a constituent of herbal formulation, "Triphala"	Decreases lipid peroxidation, antioxidant, hypoglycemic

Enicostemalittorale	krimihrita	Increase hexokinase activity, Decrease glucose 6-phosphatase and fructose 1,6 bisphosphatase activity. Dose dependent hypoglycemic activity
Ficusbengalenesis	bur	Hypoglycemic and antioxidants
Gymnem asylvestre	Gudmar or Merasingi	Anti-hyperglycemic effect, hypolipidemic
Hemides mus indicus	Anantamul	Anti snake venom activity, anti-inflammator
Hibiscus rosa-sinesis	Gudhal or Jasson Initiates	Initiates insulin release from pancreatic beta cells
Ipomoea batatas	Sakkargand	Reduces insulin resistance
Momordica cymbala	Kadavanchi	Hypoglycemic, hypolipidemic
Murraya koenigii	Curry patta	Hypoglycemic, increases glycogenesis and decreases
Phaseolu s vulgaris	Hulga white kidney bean	Hypoglycemic, hypolipidemic, inhibit alpha amylase activity, antioxidant. Altered level of insulin receptor and GLUT-4 mRNA in skeletal muscle
Punicagr anatum	anar	Antioxidant, anti-hyperglycemic effect
Salacia reticulata	Vairi	inhibitotory activity against sucrase, α-glucosidase inhibitor
Swertia chirayita	Chirata	Stimulates insulin release from islets
Syzygiu malternifolium		Hypoglycemic and antihyperglycemic
Terminalia belerica	Behada, a constituent of “Triphala”	Antibacterial, hypoglycemic
Terminalia chebula	hirda	Antibacterial, hypoglycemic
Tinosp oracrispa		Anti-hyperglycemic, stimulates insulin release from islets
Vincarosea	Sadabahar	Anti-hyperglycemic
Withania somnifera	Ashvagandha, winter cherry	Hypoglycemic, diuretic and hypocholesterolemic

5. Mechanism of Action of Herbal Antidiabetics

The mechanism of action of herbal anti-diabetic could be given as-

- Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2nd messenger) stimulation Inhibition in renal glucose reabsorption.
- Reduction in insulin resistance and Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells. Regenerating and repairing pancreatic beta cells.
- Increasing the size and number of cells in the islets of Langerhans.

- Stimulation of insulin secretion, glycogenesis and hepatic glycolysis from beta cells of islets and inhibition of insulin degradative processes.
- Protective effect on the destruction of the beta cells.
- Improvement in digestion along with reduction in blood sugar and urea.
- Prevention of pathological conversion of starch to glucose.

Conclusion:

Herbal plants are playing a significant role in the treatment of various diseases. Plants have been traditionally used for their various purposes. They exhibit more reliable criterias for their usage as the natural source of medicaments which are free from side effects and pertain longer shelf life. Due to these features, plant drugs are being used on larger scale nowadays for the treatment of Diabetes. They are available in the form of poly herbal formulations which are very effective in the control of Diabetes.

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