Herb-Drug Interaction of Traditional Indian Herbs Used for Treatment of Diabetes Mellitus: An Evidence-Based Review

Pushpa T.C.[1], Malathi H.[2], Sandeep V. Binorkar[3], Premalatha S.J.[4], Myrene Roselyn Dsouza[5], Vijayalaxmi Warad[6], and Sharangouda J. Patil,[7*]

[1]Department of Zoology, Maharani Cluster University, Bengaluru - 560001, Karnataka, India
[2]Department of Biotechnology and Genetics, Jain (Deemed-to be University), Bengaluru - 560002, Karnataka, India
[3]Department of Agadatantra, Government Ayurveda College, Vazirabad, Nanded - 431601, Maharashtra, India
[4]PG Department of Studies in Biochemistry, Maharani's Science College for Women, Mysuru - 570005, Karnataka, India
[5]Department of Biochemistry, Mount Carmel College, Bengaluru - 560052, Karnataka, India
[6]Department of Zoology, M.S.I Degree College, Kalaburagi - 585102, Karnataka, India
[*7]Department of Zoology, NMKRV College for Women, Bengaluru - 560011, Karnataka, India
*Corresponding Author Email:shajapatil@gmail.com

Abstract
The growing trend of nutraceuticals in diabetes management makes it imperative to document traditional knowledge of medicines under a single heading to help researchers formulate new functional foods. According to the World Health Organization, about 90% of the population in developing countries use plant products in primary health care either alone or in conjunction with western medicine. About 800 plants worldwide have been reported to possess powerful antidiabetic potential by enhancing insulin secretion, improving insulin resistance, α-glucosidase enzyme inhibitory activity, anti-inflammatory effects, regenerating pancreatic β-cells and mitigating diabetes-associated oxidative stress. Most natural remedies mediate enhancement of glucose uptake and suppression of hepatic glucose output by stimulating glycolysis, glucose oxidation and glycogenesis, along with reducing glycogen degradation and gluconeogenesis. Herbal treatment for managing diabetic symptomatologies has been a part of the Indian traditional system of medicine. This review evaluates the efficacy and safety of commonly used ethnomedicinal plants in India by providing an insight into the molecular and cellular mechanisms of action of key bioactives. As herbal remedies are complex mixtures of various bioactive entities, there is high probability of interaction with prescription drugs via pharmacokinetic or pharmacodynamic mechanisms. In addition, diabetic patients present different comorbidities and hence may be treated with multiple medications, increasing the chances of herb-drug interaction.
Keywords: Diabetes mellitus, Herbal-drug interaction, Insulin, Medicinal plants, Pharmacokinetic, Pregnancy

1. Introduction

The World Health Organization has described diabetes mellitus (DM) as a disease characterized by the inheritance and/or acquired defects in the biosynthesis of insulin by pancreas or the inefficiency of insulin produced (WHO, 1999). This is a metabolic disorder with high blood sugar levels over time causing the malfunctioning of most body organs. Diabetes is classified into insulin dependent disease (IDDM, T1DM) which is due to lack of

insulin production and Non-insulin dependent disease (NIDDM, T2DM) which is due to failure of cells to absorb insulin. Another form of diabetes, gestational diabetes is identified in pregnant woman who had no previous history of the disease but are diagnosed during pregnancy. DM is the major cause of these complication including blindness, renal failure, myocardial infarction and amputation of limbs. In India, there has been a record rise in diabetes patients. It rose from 7 million in 2000 to 72.96 million in the year 2019 (INDIAB, n.d.). A consequent rise in hypertension resulting in CVD in 70 % of such patients has been recorded (Dhaliwali et al., 2015). Depending on the mode of actions commercially available drugs can be classified into the following: insulin analogues, sulphonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, thiazolidiones, α-glucosidase inhibitors etc. But despite advanced research in DM, there is no single medicine that can end the disease in its tracks.

The application of traditional medicine in India has its source in 1000 BC. The scriptures in order to explain the course of supplementary extensive comprehensions inscribed ‘Ayurveda’ as an integrated science, which includes the control of mental, physical, spiritual and social plane of existence of human beings. This was made on the basis of correct techniques, procedures, regimen, diet and medicines that were used. According to Ayurvedic system the raw material largely used for preparing drugs are obtained from plants but metals, minerals, sea products and animal products are also used. Complementary and alternative medicine (CAM) is employed globally in the treatment of DM (Ningthoujam et al., 2018; Prabha et al., 2019; Dsouza, 2018a; Alisha et al., 2018) at an approximate of 72.8% (Li et al., 2017;); and usually employed alongside, or even instead of traditional medicine (Kiran et al., 2012; Modi & Patil, 2023). Herbal medicines are today enjoying wide acceptance all over the world because people are now convinced of the lack of side effects of these naturally made products. But herbal preparations are intricate concentrated solutions of organic volatile compounds which are scientifically proved to interact with synthetic drugs and other substances sometimes with lethal outcomes (Bent et al., 2005). These herb drug interactions during coadministration mostly influence the pharmacokinetic and or pharmacodynamic of the hypoglycemic agents either by augmenting or opposing their pharmacological actions (Tarirai et al., 2010; Hafner-Blumenstielet al., 2011; Cynthia et al., 2019; Bairagi et al., 2023; Giri et al., 2024; Devika et al., 2024). We thus find the associated risks worrisome mainly because therapy in diabetes is long term. As seen with most of the herbs compared to modern drugs, several uncharacterized bioactive molecules are present out of which one or several of these could provide therapeutic action. Another factor is variability of the bioactives subjective to the part of the plant used, the seasonality and the growing conditions. So, the goal of the paper is to review the data on the herb-drug interactions in terms of both the pathology and the conventional medicine, to reveal both the beneficial and detrimental effects of such interactions in terms of the mechanism, evidence, significance, and perspective of the problem along with the possibilities of its management.

2. Common anti-diabetic drugs

At present there are many pharmaceutical agents employed in diabetes treatment and they include long acting (6-24 h) sulfonylureas which stimulates insulin secretion, short acting (>6 h) meglitinides which also stimulate the secretion of insulin, thiazolidindiones which activates peroxisome proliferator activated receptor (PPAR) and reduces the hepatic glucose output and the biguanides which enhances the peripheral uptake of glucose. Further, the combination therapies employing the mentioned classes of diabetic agents might also be used to reduce side

effects and increase the number of therapeutic entities (Del Prato et al., 2007; Jovanovic et al., 2004; Dakshayini et al., 2023).

3. Antidiabetic Plants in Traditional Medicines

The NAPRALERT database have listed more than 1300 species, including higher plants, algae and fungi belonging to 750 genera in 190 families (Marles & Farnsworth, 1995). More than half of them is employed ethnopharmacologically in traditional medicine, especially against T2DM as a normative reference standard for health. Due to this increased reliance on such medicinal plants in cultures of industrialization complex carbohydrates, alkaloids, glycopeptides, terpenoids, peptides, amines, steroids flavonoids lipids, coumarins sulphur compounds and inorganic ions have been isolated (Chang et al., 2013). These compounds may act by direct insulinomimetic action, glycogenesis and hepatic glycolysis, blocker of pancreatic beta cell K^+ channel activity, activation of cAMP, adrenomimeticism in the absorption of glucose through the intestines (Patel et al., 2012; Gaede et al., 2008).

4. Mechanisms of Herb Drug Interaction

After the diagnosis of T2DM, the usual management is with oral antidiabetic drug monotherapy, but as the disease advances, multiple oral antidiabetic drugs may be needed. Furthermore, owing to difference in the type of diseases comorbid with DM, a multiple drug target intervention including antihypertensive, lipid low, and antiplatelet drugs appears logical particularly in the elderly (Gaede et al., 2008; Caughey et al., 2010). HDI also suggests that such patients are more likely to have dangerous dose–dose interactions and dose–herb interactions.

Herb–drug interactions (HDI) safety and efficacy clinically depends on the interactions between the various components of the herb and the molecules of the drug including additive or synergistic interactions or antagonism. Pharmacological interaction may manifest when any two or more of the following are ingested together or within a short period of time: herbs, drugs, nutrients, or foods leading to clinical effects that are more than the sum of the effects of each compound singly (Shediwah et al., 2019; Eramma et al., 2024; Darcia et al., 2024). Such interactions are established to change either the pharmacokinetic or pharmacodynamic of the drug making the severity or effectiveness of the result increase or decrease (Fig 1).

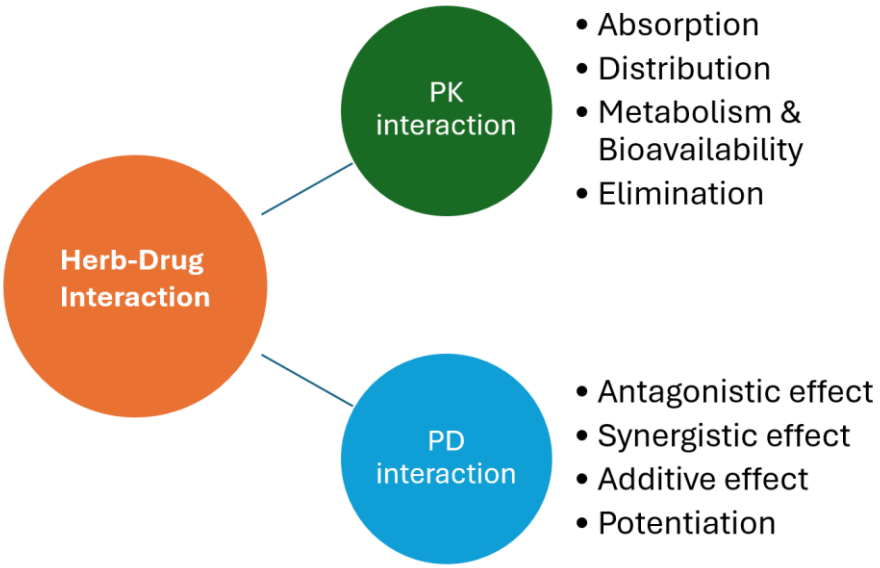

Fig 1: Mechanisms of action of herb–drug interactions

4. Pharmacokinetic herb–drug interactions

Pharmacokinetic interactions stem from changes in absorption (Mochiki et al., 2010), distribution (Rodriguez-Landa et al., 2003) and competition for and/or from metabolic and excretory processes (Isnard Bagnis et al., 2004; Yang et al., 2006). However, the principal pharmacokinetics mechanisms of drug–herb interaction involve the alteration of the activity or expression of the intestinal and hepatic metabolic enzyme of the CYP450 isoenzyme family, drug transporters, and efflux proteins (Nowack, 2008). The CYP referred to as cytochrome P450 is family of monooxygenase enzymes involved in phase I biotransformation such as oxidation, oxidative deamination, hydroxylation and S-and O-demethylation (Karyekar et al., 2002). Ingestion of some herbs and drugs may alter the activity of the same CYP isoenzymes since they may act as its substrate (Wang & Chou, 2010), for instance, CYP2C8 by pioglitazone, repaglinide and rosiglitazone; CYP2C9 by glibenclamide, glimepiride, glipizide, nateglinide and rosiglitazone (Gupta et al., 2107); St John's wort reduces CYP2C, CYP3A and several ABC efflux transporters (Whitten et al., 2006; Zhou & Lai, 2008). CYP3A4, CYP2C9 and CYP2C19 are thereby impaired by *Ginkgo biloba* (Fan et al., 2009). The primary cause of drug–drug, food–drug and herb–drug interactions lie in the fact that multiple drugs with similar substrate specificity compete for the biotransformation pathways available in a body (Colalto, 2010). Absorption of drugs may also occur arrested in presence of fibres, gums and mucilage examples of which are flaxseed, psyllium husk, aloe vera gel and rhubarb. Drugs that bind with protein can be displaced with components in the herbal preparations thus increasing the activity of the drug (Wang & Chou, 2010; Roy et al., 2023). There are so many herbs of which some have been reported to affect the renal clearance by altering the diuretic effect, tubular secretion, reabsorption as well as the glomerular filtration (Bagnis et al., 2004).

5. Pharmacodynamic herb–drug interactions

Pharmacodynamic percet HDIs alter the drug/herb effects in a qualitative way through the action of various chemical structures to bind to receptors, and thereby change the chemical

context (Izzo & Ernst, 2009). That is, they can produce antagonistic, additive, synergistic or potentiation effects. For instance, crude herbal medicines contain highly oxidant activities that could help to ameliorate the oxidative stress responsible for diabetes (Nasri et al., 2015). The documentation of these interactions is mostly safety-driven because beneficial drug interactions are rarely reported out of concern that positive drug interactions may cause enhancement of undesired pharmacological effect of HDI when the two are co-administered (Williamson et al., 2013). For instance, agrimony has blood glucose increasing effect if other antidiabetic drugs are present (Gray & Flatt, 1998). These are often referred to as antagonistic HDIs and could lead to a lowering of effect and ensuing therapy failure (Williamson et al., 2013). Therapeutic herbs like Ephedra or caffeine containing herbs when combined with other bioactives used in slendering herbs increase the cardiovascular activity that counteracts therapeutic effects of antihypertensive drugs (Williamson et al., 2013; Scott & Elmer, 2002).

6. Antidiabetic–herb interactions

Various types of HDIs are possible. However, the most common of these are the ones which result in a rise or fall in blood glucose levels, thereby disturbing the control of diabetes. Herb–drug interactions related to antidiabetic drugs are summarized in Table 1 while a detailed discussion of Indian herbs used in the control of DM are described below.

Table 1: Herb–drug interactions related to antidiabetic drugs

Interacting herb	Co-administered anti-diabetic drug	Observation	References
Hypericum perforatum (St. Johns wort)	Repaglinide	• No effect on blood glucose reduction and insulin elevation.	(Fan et al., 2011)
	Metformin	• Decreases renal clearance of metformin. • Improves glucose tolerance in males.	(Stage et al., 2015)
Allium Sativum (Garlic)	Metformin	• Increases the C_{max} and AUC of metformin • Potentiates hypoglycaemic effect • Attenuates tubular toxicity induced by gentamycin.	(Shikha et al., 2011; Poonam et al., 2013; Rafieian-Kopaei et al., 2013).
Zingiber officinale (Ginger)	Glibenclamide	• Greater reduction than glibenclamide alone.	(Al-Omari et al., 2012)
	Metformin	• Sub-optimal drug dose yields same	(Arshad et al., 2013)

		effects as full therapeutic dose. • Reduces hyperglycaemia and improves renal dysfunction. • Combination improves gentamicin nephrotoxicity.	
Gymnema sylvestre (Gymnema)	Metformin	• Reduces metformin bioavailability. • Induces pancreatic beta cell repair and regeneration. • Increases liver glucose uptake. • Antagonistic increase in serum glucose.	(Kumar & Ramakrishna, 2013; Srujan et al., 2014)
Aloe vera	Pioglitazone, repaglinide Glibenclamide	• Additive effects by inhibiting CYP3A4 and CYP2D6 along with insulin-sensitizing effects • Insulin release from β cells by inhibiting ATP sensitive K^+ channels and membrane depolarization	(Rheman et al., 2015) (Bunyapraphatsara et al., 1996)
Pongamia pinnata bark	Glibenclamide	• Synergistic action on hypoglycaemic activity and maintenance of insulin secretory response to the drug	(Heroor et al., 2015)
Flax seed	Metformin	• Increase in liver glucose-6-phosphate dehydrogenase enzyme activity • Normal glycogenesis • formation of new islets	(Dusane & Joshi, 2013)

AUC – area under the curve

6.1 Karela (*Momordica charantia*)

Karela, bitter melon, is a vegetable consumed in the tropical and subtropical regions for the treatment of diabetes, abdominal pain, jaundice, cough, respiratory diseases, skin diseases, wounds, ulcers, gout, and rheumatism (Dusane & Joshi, 2013). Contained sterols, glucoside

mixtures, and polypeptides which enhance the action of antidiabetics for raising blood glucose. The synergy between karela and antidiabetics was for the first time reported in a diabetic individual whose diabetes was not so manageable with diet control and chlorpropamide alone (Basch et al., 2003). Karela when taken together with the conventional oral anti-diabetics had better hypoglycemic effect. Its action is based on the sulfonylurea-like activity, the improvement of the glucose tolerance, the reduction of the insulin resistance. It has been demonstrated that Karela can suppress CYP2C9 and up-regule glutathione S-transferase for antidiabetic substrates (Kumar & Ramakrishna, 2013). However, its effectiveness is low, and people usually eat karela with or without the seeds in curries, extract, tablets or in powdered form (Izzo & Ernst, 2009).

6.2 Fenugreek (*Trigonella foenum-graecum*)

Spices such as fenugreek are used and widely documented to possess hypoglycemic and hypocholesterolemic effects. Saponins, alkaloids and trigonelline present in some of its seeds, husk and cotyledons interfere with intestinal glucose absorption (Dugoua et al., 2007). On administration with metformin, fenugreek has been observed to cause a decrease of plasma glucose concentrations in Type II diabetes patients. Co-treatment with glibenclamide provided better lipid peroxidation changes, lesser antioxidant activity (Ernst, 2002). Fenugreek monotherapy was superior for reduction of FBG and HbA1c comparing with fenugreek alone or in combination with glipizide.

The antidiabetic effects of seed extracts include the following; slowing down gastric emptying, the rate of glucose absorption, reducing glucose uptake and blood glucose levels, stimulating the regeneration of pancreatic β cells, increasing serum insulin levels, stimulation of glycogen synthetase, reducing the levels of proinflammatory cytokines and pancreatic enzymes, improving the restoration of glycogen stores, improving the serum lipid profiles, make cells more sensitive to insulin and improving Hb (Neha et al., 2015). It also has immunomodulatory and insulin stimulating effects when in the form of fenugreek oil. Hypoglycaemic activity of degummed seeds is significantly less than raw seeds, seed powder, cooked seeds and gum isolate and their percentile hypoglycaemic activity is as follows: It is wise to take whole seeds to cover the broad range of protection (Dsouza, 2021).

6.3 Cinnamon (*Cinnamomum zeylanicum*)

Cinnamon bark affords insulin mimetic activity which counteracts pancreatic enzymes, lowers insulin resistance, promotes glucose uptake and supresses gluconeogenesis (Adisakwattana et al., 2011; Quinn et al., 2004). Several papers reveal that cinnamon and metformin can augment the serum total cholesterol and HDL cholesterol in diabetic rats and cinnamon can decrease the activities of ALT, AST, and LDH (Kim et al., 2006; Khan et al., 2003; Dsouza, 2021). But both cinnamon and metformin cause DNA damage in hepatocytes that show elevated oxidative stress and poor glycaemia management. The study also found that cinnamaldehyde derived from cinnamon bark lowered the plasma glucose and HbA1c concentrations in diabetic rats through increased peripheral insulin sensitivity or decreased carbohydrate intake. It is further involved in phosphorylation of the insulin receptor β-subunit on adipocytes (Ashoor & Qusti, 2010). Indications exist that polyphenols in cinnamaldehyde may counteract some of the complications caused by oxidative stress. The suggested dose is 1-4 g cinnamon powder per day or 0. 05 to 0.2 g of cinnamon oil is proposed, although it is not recommended for pregnant women because of the stimulation of uterine contractions and premature labor (Babu et al., 2007).

6.4 Ginseng (*Panax ginseng* and *Panax quinquefolium*)

It has also been identified that ginseng and some of its ginsenosides namely Rg1, Rb1, Rb2, Rc, Re, Rg3, Rh2 and compound K have an antidiabetic effect on the body due to both insulin dependent and insulin independent mechanisms of action it has even been compared to metformin in the action is produces on the secretion of insulin (Khan et al., 2012). Panax notoginseng saponins (PNS) also have anti-hyperglycaemic and anti-obesity effects mediated by the enhancement of steps of insulin sensitivity. It is for this reason that ginseng has been reported to contribute to better glycaemic control for T2DM, raise plasma glucose levels and promote the regulation of insulin. To achieve the best glycaemic effect, ginseng should be consumed 40 minutes before a meal. As such, in non-diabetic clients, unintended hypoglycemia can be prevented if the said herb is consumed with food (Kim et al., 2017). It has been postulated that AG may attenuate postprandial hyperglycemia and hyperinsulinemia, increase glycogen and HDL concentrations and decrease plasma cholesterol and LDL levels (Vuksan et al., 2000a). It increases some functional aspects of β cell by promoting insulin synthesis, inhibiting apoptosis and enhancing insulin secretion, secretion and utilization of glucose, preventing hepatic gluconeogenesis, and by moderating the levels of circulating glucose and insulin levels (Vuksan et al., 2000b). The possible mechanism of the ginseng polysaccharides is that it promotes secretion of insulin, promotes glycogenesis and lowers the serum MDA levels on fasting blood glucose.

6.5 Green chireta *(Andrographis paniculata*)

Andrographis paniculata that is used traditionally for antidiabetic effect has the diterpene lactone compound andrographolide (Dsouza, 2020). They have decrease in glycosylated hemoglobin, improvement in peripheral insulin sensitivity, and activation of GLUT-4 in the muscle tissues (Yamashiro et al., 2006). Yet, it is seen that for lowering the blood glucose levels, 60 mg Andrographis powder may not be as effective as its extract as other components may also be contributing the change. It also has additive pharmacological interaction with antidiabetic drugs as well as with other medications used in its administration. Several works reveal that the action of Andrographolide in diabetic rats together with metformin and a significant reduction of the activity of metformin is indicated (Dsouza, 2020; Nugroho et al., 2012). If ethanolic extract of Andrographis was administered in conjunction with the curcuminoid fraction of *Curcuma xanthorriza*, there was better hypoglycaemic activity. This study showed that when high levels of Andrographolide and Asiaticoside – enriched extract of *Centella asiatica* was administered, the blood glucose levels was reduced by 68.13%. Andrographolide also stimulated glucose uptake in muscle of STZ-diabetic rats and at the same time TNBARS reduced, while SOD and CAT increased (Nugroho et al., 2014). Though, the exact action is still in a debate that rules out its use in clinical practice as part of combination therapy.

7. Conclusion

This review paper does not advocate the utilisation of conventional natural remedies without thorough understanding of the safety and efficacy of the therapy. In most cases, herbs are used by the physicians to supplement where the conventional medicines are deemed to be inadequate. There arises the need to compile a database of the natural products and record more clinical data as well as the PK/PD of these products. Many herbs are reported to interact with various drugs leading to the development of unwanted effects or reduced therapeutic efficacy

of the drugs involved. Knowledge of ideal treatment approaches to the likely interactions makes the use of the herbal remedies reasonable.

Diabetic patients are usually characterized by the presence of comorbidities that require prescription of many drugs or polypharmacy. These are often lifelong increasing the chance of drug-drug, drug-herb and herb-herb interactions. The findings described in this chapter can easily draw out positive and negative reactions elicited by herbs when administered along with the regular anti-diabetic medications. The interaction is highly complex because the target can vary, the herbal medicine is multicomponent, there are variations in batches due to climatic conditions, variation in processing criteria etc. Combination therapy can lead to add on or contrast effects. This may present as hypoglycaemia if it leads to enhancement of the glucose-lowering effect optimised by the HDI. In such cases diabetic patients require to frequently regulate their glucose level in the blood. As much as the current chapter does not involve a review of interactions with non-diabetic medicines a lot of precaution is required especially in patients with chronic ailments and the elderly.

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