Pharmacogn. Res., 2025; 17(2):385-401.
https://www.phcogres.com

Review Article

Interaction between Anti Diabetic Drugs and Herbs: A Review

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ABSTRACT

Diabetes is a long-term medical disorder characterized by elevated blood glucose levels due to inadequate insulin use. It is caused by a pathogenic process that results in insulin insufficiency due to the death of β-cells. Uneven insulin secretion and use contribute to diabetes mellitus. Pancreatic beta cell loss is a primary cause of diabetes mellitus, which is associated with both insulin insufficiency and insulin resistance. Herbal medicines have been used for treating illness since ancient times, with over 800 plants having potential anti-diabetic properties. These plants have numerous pharmacological and therapeutic applications, including lowering blood glucose levels and enhancing beta-cell function. It is a common trend in Asian countries specifically in India that herbal medicine/s along with allopathic medicine/s is used. Herbal drug interactions can occur when conventional medications and herbal remedies are used together, leading to elevated toxicity or pharmacological effects. Xenobiotic substrates can affect the biological activity of xenobiotic substrates and other compounds, leading to increased oral bioavailability and decreased clearance and excretion. Cytochrome induction, triggered by AhR and PXR receptors, can improve the activity of intestinal and hepatic enzymes, affecting oral bioavailability and plasma concentration. The therapeutic benefit of herbal drugs that induce cytochrome induction is reduced when taken concurrently, hence in the present review interactions (pharmacodynamic and pharmacokinetic) of 27 plants having anti-diabetic property with oral anti-diabetic agents have studied.

Keywords: Anti-diabetic effect, Cytochrome (cyp), Herbal drug interaction, *In vitro* study, *In vivo* study, Pharmacodynamic study, Pharmacokinetic study, Plant extract.

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Received: 12-08-2024;
Revised: 05-11-2024;
Accepted: 21-01-2025.

INTRODUCTION

Diabetes is a long-term medical disorder characterised by elevated blood glucose levels (hyperglycemia) brought on by inadequate insulin use or level. Elevated blood sugar levels are associated with organ damage and tissue breakdown.[1] Diabetic Mellitus (DM) is caused by a pathogenic process that result in insulin insufficiency due to the death of β-cells Improper utilisation and metabolism of glucose results in insulin resistance. Uneven insulin secretion and use is a major contributor to diabetes mellitus.[2] A WHO 2021 report states that between 1980 and 2014, there were 422 million more diabetic patients than there were in 1980. Between 2000 and 2016, the number of early deaths linked to diabetes increased by 5%.[3] One of the primary causes of diabetes mellitus is the pancreatic beta cell loss. It is associated with both insulin insufficiency and insulin resistance. Insulin resistance may result from the down regulation of GLUT-4 in muscle and adipose tissue because it improves glucose absorption to these tissues. The main site of glucose utilisation is skeletal muscle. It is thought that oxidative stress contributes to the development of pancreatic-cell dysfunction in type 2 diabetes.[4] Excessive formation of ROS destroys the beta cells in the pancreas and impacts cellular activity, leading to cell death in many organs and blood vessels. Insulin deficiency results from beta cell loss.[5]

Since ancient times, herbal medicines have been utilised for treating illness. There are more than 800 plants with possible anti-diabetic properties. The natural remedies work to alleviate illnesses. There are numerous pharmacological and therapeutic applications for the phytochemicals that exist in plants, including polysaccharides, alkaloids, glycosides, lipids, terpenoids and steroids. The action of the plants' herbs lowers blood glucose levels and enhances beta-cell function (Table 1). Most synthetic medications are made from plants and herbs.[6] Many plants have traditionally been used to treat DM because they have less adverse effects when used long term.[7]

When a conventional medication and herbal remedy are used together, there may be positive or negative interactions

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Manuscript TECHNOMEDIA

DOI: 10.5530/pres.20252023

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between the two. These are known as herbal drug interactions. Drug interactions with herbal treatments may result in elevated toxicity or pharmacological effects.[8] Pharmacokinetic interaction is the term for when cytochrome enzyme inhibition impacts biotransformation or pharmacokinetic factors such drug absorption, bioavailability, distribution, metabolism and elimination.[9] The drug's clinical and therapeutic effects changed; this is known as pharmacodynamic interaction. These are two forms of herbal drug interactions: Pharmacokinetic interaction and pharmacodynamic interaction.[10] Herbal drug interactions may occur due to a lack of knowledge about the pharmacological mechanisms of medicinal plants.[11] Inhibition and induction of cytochrome have a role in herbal drug interaction processes. CYP450 enzymes are ham proteins that belong to a super family. Each one is identified by the letters CYP, followed by a number and a letter. Three of the 74 CYP gene families have been identified as being involved in drug metabolism in the human liver (CYP1, CYP2 and CYP3).[12] By catalyzing the process, the cytochrome plays a critical role in drug metabolism. The cytochrome P450 enzyme has been responsible for the oxidative, per oxidative and reductive metabolic transformations of drugs and natural compounds.

The biological activity of xenobiotic substrates and other compounds can be affected when xenobiotic substrates impair CYP enzymatic activity.[13] Because drug absorption and distribution increase while clearance and excretion decrease when cytochrome is inhibited, the pharmacokinetic properties of the drug are altered. This results in high oral bioavailability because drug absorption and distribution increase while clearance and excretion decrease. The accumulation of drugs is also a source of concern. This improves the drug's therapeutic impact, but co-administration of herbal drugs with drugs having a narrow therapeutic window can have substantial side effects.[14] The activation of various receptors causes cytochrome induction. The AhR (Aryl hydrogen Receptor) and PXR (Pregnane Nuclear Receptor) receptors, which belong to the orphan nuclear receptors/steroids receptors super family, trigger CYP1A/B and CYP3A isozymes.[9] Some xenobiotics improve the activity of intestinal and hepatic enzymes by enhancing mRNA transcription, resulting in higher enzyme levels than usual and speeding up drug metabolism. This has an impact on oral bioavailability as well as plasma concentration. The therapeutic benefit of herbal drugs that induce cytochrome induction is reduced when they are taken concurrently.[14]

Abelmoschus esculentus

Okra is the scientific name for *Abelmoschus esculentus*.[15] The anti-diabetic action of the *A. esculentus* has been demonstrated through glycogenesis, delayed intestinal glucose diffusion, increased glucose adsorption capacity and pancreatic islet cell regeneration. In the study, all of these pathways were discovered to reduce the post-meal glucose level. The glucose level in the blood is reduced by *A. esculentus*.[16] The major chemical constituents of *A. esculentus* are flavonoids, which number seven in number. Rutin, hypersoside, hibifolin, isoquercitin, myricetin, quercetin and qurectin-3-o-robinobioside are among the compounds.[17] In *A. esculentus*, β-sistostenol, oleanolic acid, myricetin and kaempferol have indeed been demonstrated to have anti-diabetic action. Myricetin has been discovered as an anti-diabetic compound which might be isolated from various plant components.[15] The inhibitory concentrations of α-amylase and α-glucosidase are 125±2 μg/mL and 110±1 μg/mL respectively. Metformin absorption from the small intestine is suppressed in an *in vivo* investigation of water-soluble okra extract with metformin. Dietary fibers are found in the highest concentration in okra, followed by carbs and protein. Metformin is entrapped by fibers, which inhibits absorption.[18,19] It was indicated that metformin should not be used with okra in this case. Because it has the potential to lower metformin levels at the target location.

Phyllanthus emblica

In Hindi, *Phyllanthus emblica* is known as amla and in English, Indian gooseberry. Emblicanin A and Emblicanin B, pedunculagin and punigluconin are some of the primary tannins found in *P. emblica*. Gallic acids, amlaic acid, arginine, aspartic acid, astragallin, carotene, sitosterol, chebulagic acid, chebulic acid, chebulaginic acid, chebulinic acid, chebulinic acid, corilagic acid, corilagin, cysteine, ellagic acid, emblicol, kaempferol, leucodelphinidin[20] Gallic acid, Ellagic acid, Estradiol, Sesamine, Kaempferol, Zeatin, Quercetin and Leucodelphinidin have all been identified as possible anti-diabetic substances in a computer simulation.[21] Inhibition of diasaccharidase activity reduces glucose and sucrose absorption from the gut.[22] *P. emblica* inhibits glycogenolysis and hepatic glucogenesis by increasing insulin secretion via pancreatic β-cell stimulation or by having an insulin-sensitizing action.[23] In an *in vitro* investigation, aqueous extracts of *P. emblica* were found to inhibit cytochrome 450 isoforms CYP1A2 (IC_{50} value=310.28±5.07μg/mL), CYP2C9 (IC_{50} value=194.72±2.94 μg/mL), CYP2D6 (IC_{50} value=589.52±14.32 μg/mL), CYP2E1 (IC_{50} value=310.27±15.06 μg/mL), CYP3A4 (IC_{50} value=325.54±7.44 μg/mL), the metabolisms of tolbutamide and metformin may affect due to inhibition of CYP2C9 and CYP3A4.[24] The co-administration of metformin (200 mg/kg) with the herbal formulation of Nisha amlaki, a combination of turmeric and Indian gooseberry, increases C_{max}, AUC_t and AUC by 62.06%, 45.64%and 46.69%, respectively and decreases clearance and Vd by 109.6% and 119% in diabetic rats, according to Shengule *et al.*,[25] but the AUC for glucose level reduces by 37.79% and decreases TC level by 25.7% in diabetic rats. The Nisha amlaki reduces metformin excretion by reducing metformin transportation by the Organic Action Transporter (OCT). This could be the cause of metformin pharmacokinetic parameter variation.

Andrographis paniculata

Kalmegh is a popular name for *Andrographis paniculata*. *Kalmegh* is a natural antidiabetic with insulin secretagogue action that has been shown to stimulate insulin secretion *in vitro* studies.[26] The HepG2 hepatoma cell line was used to investigate the effects of *A. paniculata* on cytochrome inhibition. The andrographolide (60 μM) reduced the CYP1A2 expression. CYP2D6 and CYP3A4 were both inhibited by andrographolide and 14 deoxy 11, 12 didehydro androgapholide.[27] In treated human hepatocytes. The expression of CYP1A2, CYP2C9and CYP3A4 mRNAs was significantly reduced (>2-fold) by andrographolide and *A. paniculata* extract. The cytochrome inhibitory action of Andrographolide extracts in different solvents varies. The highest inhibitory activity shown in androgapholide ethanol and methanol extract IC_{50} value 21.1±1.4 μg/mL and 27.8±1.9 μg/mL respectively for CYP3A4, IC_{50} value 52.6±0.8 μg/mL and 87.8±2.6 μg/mL for CYP2D6, IC_{50} value 41.3±3.5 μg/mL and 76.7±2.0 μg/mL for CYP2C9. In comparison to ethanol and methanol extract andrographolide aqueous and hexane extract had a modest inhibitory impact on CYP3A4, CYP2D6and CYP2C9. All solvent extractions have shown that CYP2C9-mediated tolbutamide 4 hydroxylation is Inhibited.[28] The *A. paniculata* extract and andrographolide magnify the ethoxyresorufin-O-deethylation, methoxy resorufin-O-demethylation, diclofenac-4-hydroxylation and testosterone 6β-hydroxylation in rat liver. The andrographolide affects the pharmacokinetic of the tolbutamide, it lowers the plasma concentration of tolbutamide in serum and the *A. paniculate* extract reduces the $AUC_{0\text{-}12h}$ by 18%. *A. paniculate* extract and andrographolide is a PXR and AhR activator, it increases the DNA binding activity of PXR and AhR which magnify the gene transcription and enzymatic activities of CYP1A1, CYP1A2, CYP2C6, CYP2C11, CYP3A1, CYP3A2. The increased action of CYP2C maximizes the metabolisms of tolbutamide. CYP isozymes and P-glycoprotein expression elicitation has been seen in *A. paniculate* extract (APE) treated rats. The co-administration of APE andrographolide with tolbutamide doesn't show any significant synergistic effect. They don't alter the blood glucose sugar.[29] The APE inhibits the human liver microsomal CYP1A2, CYP2C, CYP3A4 cytochrome.[30] As earlier shows that the andrographolide inhibits the CYPEA4. Co-administration of glyburide with andrographolide maximize the bioavailability and the pharmacokinetic parameters such as $C_{max,}$ $AUC_{0\text{-}n,}$ $AUC_{total,}$ $t_{1/2}$ MRT. There is no change in T_{max} of glyburide, it indicate that andrographolide has no effect on rate of absorption of the glyburide. The tolbutamide and *A. paniculate* together shows a synergestic effect[31] Co-medication of gliclazide with *A. paniculate* increases the $C_{max,}$ AUC, $kd_{,}$ $t_{1/2}$ and bioavailability of gliclazide by 63.39%. The increase in pharmacokinetic parameter may be due to decreased metabolism of gliclazide via CYP2C9 and CYP3A4 enzyme inhibition by *A. paniculate*.[32]

Boswellia serrata

Salai guggal is the common name for *Boswellia serrata* (Family-*Burseraceae*). *Boswellia serrata* improves insulin sensitivity and reduces insulin resistance.[33] Using baculovirus-infected cells and PHLM (pooled human liver microsome), the researchers have found that the 50 g/mL *B. serrata* extract has an 84% and 98% inhibitory impact on CYP2C9 and CYP3A414 respectively, with IC_{50} values of 11 μg/mL and 1.4 μg/mL.[34] Frankincense (10 g/mL), a Boswellia tree oleo gum resin, inhibits CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19and CYP3A4. The CYP2C8, CYP2C9and CYP3A4 enzymes are inhibited by boswellic acid, KBA and AKBA, with IC_{50} values in the 5-10 M range.[35] In STZ induced diabetic rats, Samla S. and Veersham C.[36] discovered that Boswellic Acid (BA) and extract of *B. serrata* (BSE) showed an increase in pharmacokinetic parameters such as C_{max}, $AUC_{0\text{-}n}$, AUC_{Total}, $T_{1/2}$ and MRT of glimepiride and a decrease in clearance and Vd of glimepiride, but no change in T_{max} of glimepiride. Glimepiride with BSE and glimepiride with BA reduced glucose levels by 52.95% and 53.04%, respectively. The BSE and BA with glimepiride lower triglyceride levels while increasing insulin levels in the blood. The BSE and BA may inhibit CYP2C9 and interact pharmacokinetically with glimepiride. In both normal and diabetic rats, boswellic acid had a somewhat stronger impact than *B. serrata* extract. In a pharmacokinetic study of metformin with boswellic acid, researchers discovered an increase in C_{max}, $AUC_{0\text{-}n}$, AUC_{Total}, $T_{1/2}$ and MRT, as well as a decrease in clearance and Vd in normal and diabetic rats. Because BA inhibits CYP3A4 in human liver microsomes and enhances metformin bioavailability, there is no effect on T_{max} and rate of absorption. After 28 days, BA and metformin lower GOT, GPT and glucose levels while increasing insulin levels in the blood.[37]

Aloe barbadensis Miller

In India, *Aloe barbadensis Miller* is known as *Aloe vera*. Aloin, barbaloin, isobarbaloine, aloetic acid, aloe-emodin, emodin, cinnamic acid, crysophanic acid glucomannan, cellulose, mannose and glucosamines have antihyperglycemic action. *Aloe vera* raises insulin levels and lowers glucose absorption from the gut[38] and inhibits the AGE formation.[39] The two separate brands of *Aloe vera* juice A and B, respectively, with IC_{50} values of 8.35±0.72 mg/mL and 22.4±5.4 mg/mL for CYP3A4 and 12.5±2.1 mg/mL and 43.0±2.0 mg/mL for CYP2D6.[40] The enzymes CYP3A4 and CYP2D6 may be inhibited by *Aloe vera*. The co-administration of glibenclamide and *Aloe vera* reduces glucose and lipid levels at modest doses within 2 to 4 weeks in a clinical investigation.[41] The interaction of *Aloe vera* and other antihyperglycemic medications has potential. Because *Aloe vera* is a widely used herbal medicine, the interaction between the two should be investigated.

Bridelia ferrugenia

'Ira' is the common name for *B. ferrugenia* (family: *Euphorbiaceae*). *B. ferrugenia* increases insulin sensitivity in tissue and decreases glucose absorption from the gut via stimulating insulin secretion and glp-1.[42] α-Amyrin acetate, cymene, β-Amyrin 4-Phenylbenzophenone, Lupenon, Lupeol acetate, 2, 3, 6-Trimethylhept-3-en-1-oland 2, 3,6-Trimethylhept-3-en-1-ol have antihyperglycemic properties.[43] Metformin pharmacokinetics was affected when metformin and *B. ferrugenia* were given together. C_{max}, T_{max} and AUC have all dropped. It means that the bioavailability of metformin in the body is reduced. Vd grew as the absorption rate constant (Ka) increased. Metformin's elimination constant, clearanceand $T_{1/2}$ (half-life time) all increased. It is thought that *B. ferrugenia* reduces the impact of metformin via increasing metformin elimination.[44] To corroborate this research, coadministration of metformin (250 mg/kg p.o. and 1000 mg/kg p.o.) with *B. ferrugenia* (30 mg/kg p.o. and 300 mg/kg p.o.) had a lesser antihyperglycemic impact in rats than *B. ferrugenia* (30 mg/kg and 300 mg/kg p.o.).[45]

Cassia ariculata (L)

Cassia ariculata (L), popularly known as avaram senna, is a plant in the *Fabaceaceae* (*Leguminosae*) family. Qurecitin, cyanidin, spermidine and N8-acetylspermidine, hesperidine and nitexin-2-o-rhamnoside are phytochemicals found in *C. ariculata* that have anti-diabetic properties.[46] *C. ariculata* increases insulin levels in the blood and glycogen production, stimulates beta cell insulin release and regenerates them[47] and inhibits AGE formation.[48] With IC_{50} values of 28.5 µg/mL, 165.5±7.50 µg/mL and 158.8±9.62 µg/mL, *Cassia alata* inhibits CYP1A2, CYP2D6 and CYP3A4 correspondingly.[49] Metformin (90 mg/kg) and *C. ariculata* have a synergistic impact for glucose reducing action, while metformin (45 mg/kg) and *C. ariculata* had a similar effect to metformin alone. Metformin (90 mg/kg) enhanced the C_{max} by 11.46% and the AUC_{0-24} by 4.6% in *C. ariculata*. Metformin's half-life was doubled, however T_{max} stayed the same. The half-dose of metformin (45 mg/kg) with *C ariculata*, on the other hand, resulted in a 17.72% reduction in C_{max} and a 42.42% reduction in AUC_{0-24}.[50] The pharmacokinetic and pharmacodynamic interaction of a medicine may be affected by its dose. Therefore, dose determination should be studied in order to achieve a favorable therapeutic impact.

Catharanthus roseus

Periwinkle is a common name for *Catharanthus roseus* (family: *apocynacea*).[51] *In vivo* and *in vitro* studies, vindoline,[52] vincristine and vinblastine have significant anti diabetic and anticancer effects.[53] The *C. roseus* maximize the glucose utilization via escalate the GLUT-2 and GLUT-4 gene expression in muscle tissue and alleviate the blood glucose level[51] Augment the insulin secretion from beta cells.[54] Vindoline, an alkaloid found in *C. roseus*, is an inhibitor of CYP2D6 (IC_{50} value 15.9 M) and CYP3A4 (IC_{50} value 20.1 M). Ajmalicine is a potent reversible inhibitor of CYPD26. The methanol extract of *C. roseus* has been shown to inhibit CYP2D6 with an IC_{50} of 11 g/mL.[55] *C. roseus* can impact the pharmacokinetics and pharmacodynamics of drugs metabolised by CYP3A4 and CYP2D6, such as metformin, sitagliptin and sexagliptine. According to Ohadoma and Michael's research,[56] *C. roseus* (250 mg/kg) plus metformin (100 mg/kg) exhibited a 64.86% drop in blood glucose levels when taken together. This occurred because of *C. roseus* inhibiting CYP3A6, which increased metformin bioavailability. However, when glibenclamide was combined with *C. rosea*, there was no significant difference in blood glucose levels compared to the normal medicine.

Table 1: Mechanisms of action of herbs.

Mechanisms of action	Plants
Inhibition of AGE formation	*Aloe barbadensis miller, Cassia ariculata.*
Increase GLP secretion	*Coctus pictus, Bridelia ferrugenia, Cinnamomum verum.*
Regeneration of pancreatic cells	*Cassia ariculata, Zingiberis offinalis roscoe, Glycyrrhiza glabra* L.
Glycogen synthesis	*Cassia ariculata, Cinnamomum verum, Curcuma longa, Momordica charantia.*
Increase insulin secretion	*Bridelia ferrugenia, Phyllanthus emblica, Andrographis paniculate, Cassia aricuata, Catharanthus rosea, Coctus pictus, Trigonella foenum graecum, Allium sativum* L., *Momordica charantia, Ginkgo biloba* L., *Gymnema sylvestre, Azadirachta indica.*
Decrease glucose absorption	*Aloe barbadensis miller, Abelmoschus esculentus, Phyllanthus emblica, Bridelia ferrugenia, Cinnamomum verum, Trigonella foenum graecum, Tinospora cardiofolia, Opuntia* spp., *Gymnema sylvestre, Azadirachta indica, Ginkgo biloba* L.
Regulation of glycolysis and Krebs cycle	*Tinospora cordifolia, Syzigium cumini.*
Insulin resistance	*Boswellia serrata, Cinnamomum verum, Costus pictus, Curcuma longa, Trigonella foenum graecum, Allium sativum* L., *Zingibereris officinale roscoe, Gingko biloba, Opuntia* spp., *Gymnema sylvestre, Syzigium cumini, Azadirachta indica.*
Inhibition of gluconeogenesis	*Phyllantus emblica, Cinnamomum verum, Panax ginseng.*

Cinnamomum verum

Dalchini is the Indian name for *Cinnamomum verum* (family: *lauraceace*). *C. verum* is widely used as condiment all over the world. Cinnamaldehyde, eugenol, caryophyllene, cinnamyl acetate and -humulene are the primary phytochemicals.[57] According to a placebo clinical study, *C. verum* increases GLUT 4 translocation and PPAR gene expression, improves insulin sensitivity and raises GLP-1 levels, while inhibiting glucose absorption through α- glucosidase inhibition and increasing glucose metabolism through stimulation of glycogen synthesis and inhibiting gluconeogenesis.[58] *C. verum* suppresses the activity of the CYP2D1 enzyme in both type 1 and type 2 diabetes mellitus.[59] An herbal-drug interaction may occur when a drug is processed by the CYP2D enzyme.[60] The co -administration of metformin with *C. verum* in low and high doses improved G6PDH activity in diabetic rats, but that there was no significant difference in glucose reduction between the metformin-treated group and the metformin+cinnamon with low and high dose treated group. In comparison to the metformin-only group, the co-administration of metformin and *C. verum* improved HDL cholesterol levels in the blood. *C. verum* and metformin have been found to have a synergistic effect on cholesterol lowering.[61]

Costus pictus

Spiral flag and step ladder are popular names for *Costus pictus* (family: *Costaceae*)[62] belongs to Central America and is known in South India as the insulin plant.[63] The major phytochemicals present in *C. pictus* are isoquercetin, astragalin, kaempferol, quercetin, isovitexin, naringenin, galanin, genistin, licochalcone A, 2, 5-dihydroxy benzoic acid, gentisic acid, o-coumaric, melilotic, α-resorcyclic acid, 3,5-dihydroxy benzoic acid, p-hydroxy benzoic acid, cis and trans-p-coumaric acid.[62] Insulin secretory action has been demonstrated *in vitro* and *in vivo* in several investigations and it is utilized as a herbal medication. Through activation of the incretin hormone GLP-1 release, the insulin plant reduces insulin resistance, enhances pancreatic insulin secretion and lowers postprandial blood glucose levels.[63] The combination of metformin and the methanol extract of *C. pictus* (400 mg/kg) have a synergistic effect on the fasting blood sugar and lipid profile of diabetic rats. The extract and metformin have been shown to help with renal and liver problems.[64] The herbal medication interaction of *C. pictus* with anti- diabetic drugs should be investigated in the future.

Curcuma longa

The rhizomes of *Curcuma longa* (*zingiberaceae*) are known as turmeric in English and haldi in Hindi. Curcumin, bisdemethoxycurcumin and demethoxycurcumin, as well as tumerone, atlantone and zingiberene, are diarylheptanoids found in curcuma species.[65] *C. longa* increases hepatic glucose synthesis, GLUT2, GLUT3and GLUT4 gene expression, glucose uptake in tissue, activates AMPK and lowers insulin resistance by increasing hepatic glucose production, GLUT2, GLUT3and GLUT4 gene expression and decreasing insulin resistance.[66] Both dexomethoxycurcumin and curcumin have been proven to inhibit CYP3A4, CYP1A2, CYP2C9 and CYP2D6. Demethoxycurcumin inhibited CYP3A4 (11.1±1.6 μM), CYP1A2 (1.4±0.2 μM), CYP2C9 (36.7±2.1 μM) and CYP2D6 (34.0±14.2 μM), while curcumin inhibited CYP3A4 (54.4±18.3 μM), CYP1A2 (6.0±1.4 μM), CYP2C9 (175.0±47.0 μM) and CYP2D6 (104.6±22.1 μM). In comparison to curcumin, demethoxycurcumin has a stronger inhibitory effect.[67,68] Curcumin inhibited the production of p-gp in the intestine[69] UGT and SLUT activities were suppressed by the curcuminoid extract.[70] The curcuminoids may influence the enzymes that metabolize the drugs, resulting in a herbal drug interaction. In diabetic rats, the combination of curcumin from curcuma species plus glyburide, a sulfonyl urea derivative, had a considerable impact on blood glucose levels and lipid profiles. The bioavailability of glyburide is reduced by Pgp effluxand curcumin is a powerful Pgp inhibitor that increases glyburide bioavailability. The kinetics of glyburide is affected by curcumin. In contrast to the clearance, the AUC has increase.[71] In diabetic rats, the combination of curcumin with glimepiride influences the pharmacokinetic characteristics of glimepiride, with an increase in C_{max}, AUC_{0-n}, AUC_{total}, $t_{1/2}$, MRT and a decrease in clearance and volume of distribution. This could be due to suppression of the CYP2C9 enzyme, but there was no change in T_{max}, indicating that the rate of glimepiride absorption has not changed.[72] Curcumin (30 mg/kg) combined with metformin (50 mg/kg) resulted in a maximum decline in blood glucose levels and a positive rise in serum insulin levels. Undale V.R. *et al.*,[66] have observed beta cell reincarnation.

Trigonella foenum graecum L.

Fenugreek (*Trigonella foenum graecum*) belongs to the *Leguminosae* family. Fenugreek seed contains mainly mucilaginous fiber (galactomannans), alkaloids mostly trigonelline, choline, gentianine and carpaine. Flavonoids are apigenin, luteolin, orientin, quercetin, vitexin and isovitexin. Saponins are diosgenin, yamogenin, tigogenin, neotigogenin, cholesterol and sitosterol. Other constituents are coumarin, fenugreekine, nicotinic acid, phytic acid, scopoletin, vitamins A, B1, C and nicotinic acid. GLUT4 translocation reduces glucose absorption and aberrant lipid metabolisms via inducing the insulin signaling pathway.[73] The *Trigonella foenum graecum* extract had greater inhibitory activity on CYP3A4, CYP2D6 than trigonelline in cytochrome P450-carbon monoxide complex assay and fluorogenic assay. There are dose-dependent effects.[74,75] The CYP2C11 activity was decreased by 43% at a high dose of fenugreek (600 mg/kg) and the protein expression was reduced by 80%. At a high dose, CYP2C9 was suppressed by 50%.[76] The blood glucose level is reduced when fenugreek (1 g/kg) is combined with glimepiride (4 mg/kg) and insulin (4 u/kg). After 6 to 8 weeks of administration, they have a synergistic effect.[73] Researchers discovered that

when metformin 300 mg/kg was compared to 500 mg/kg using non-compartment pharmacokinetic analysis, the drug's C_{max} and AUC increased by 74.68% and 148.55%, respectively. Vd and clearance fall, but metformin's T_{max} rises from 1 to 2 hr. The shift in T_{max} is attributable to a decrease in the drug's solubility. Metformin's bioavailability is increased by fenugreeks.[76,77] After coadministration of aqueous extract of fenugreek and gliclazide, blood glucose levels in normal and diabetic rabbits were lowered by 56.96% and 45.81%, respectively. After coadministration of aqueous extract of fenugreek and gliclazide, blood glucose levels in normal and diabetic rabbits were lowered by 56.96% and 45.81%, respectively. The pharmacokinetic parameter of gliclazide has not been changed by fenugreek.[78] In clinical research conducted in China, the combination of fenugreek (0.35 g/pill) and sulfonyl urea reduced blood glucose levels by 80.43% more than the control group (43.48%) and the CSQS and HbA1c levels in diabetes patients decreased dramatically.[79]

Allium sativum L.

Garlic is the common name for the *Allium sativum* L. (Alliaceae) plant. The major biological active constituents of *A. sativum* are Alliin, allicin, allixin, adenosine, Allyl1,5-hexadienyl trisulphide, Allyl methyl trisulphide, s-allyl2-pro pene thiosul phinate, ajoene, Diallyl disulfide, 1,5-hexa dianyl trisulfide, Methyl allyl trisulfide, 2-vinyl 1,3-dithiene, 3-vinyl 1,3-dithiene, S-allyl merc aptocysteine, Se-methyl selenocysteine, Allyl propyl disulfide, Sodium 2-propenyl thiosulphinate, s-methyl1-cysteine sulfoxide.[80] Garlic improves insulin sensitivity and production from beta cells, whereas allicin protects insulin from the SH group reaction and prevents insulin inactivation.[81] Several researches on various allium products in various solvents have been conducted. In an *in vitro* investigation, garlic products or extracts block CYP3A, CYP2A and Pgp trafficking.[82] In a clinical trial, diabetic volunteers who ingested 10 g of raw garlic each day for 42 days had their blood cholesterol levels, FBS and HB1C levels drop dramatically, while their HDL-C levels raise significantly.[83] Garlic raises intestinal Pgp expression by 131% and decreases the bioavailability of Pgp substrate saquiravair over 21 days in a clinical investigation. On CYP3A4, no effect was detected.[84] Garlic 100 µg/mL decreased CYP2C9 activity but not CYP3A4 activity on the fourth day of therapy.[85] Garlic oil helps with blood sugar control, diabetic nephropathy and blood pressure.[86] The co-administration of metformin with *A. sativum* the AUC_{0-12} and C_{max} increases the bioavailability of the drug.[81] In diabetic rats, co-administration of aqueous extract of *A. sativum* (500 mg/kg) with metformin (50 mg) resulted in a greater reduction in blood glucose levels than metformin (100 mg).[87] Giving T2DM patients garlic tablets (300 mg) with metformin (500 mg) for 24 weeks resulted in a significant reduction in fasting blood glucose and total cholesterol levels.[88] In STZ-induced diabetic rats, orally co-administration of aqueous extract of garlic (500 mg/kg) with glibenclamide (0.5 mg/kg) lowered blood glucose levels by 55.5%. It also helped diabetic rats lose weight, according to Tripathi P. *et al*.[89]

Tinospora cordifolia

Tinospora cordifolia (family: *Menispermaceae*) is known in Sanskrit as amrita and in Hindi as *giloy*. Phytochemicals of *giloy* are tinosporine, cardiofolide, tinosporide, cardifole, columbin, barberin.[90] magnoflorine, tinosporicide, manispermacide, tiniosinen.[91] Amrita inhibits the synthesis of cholesterol and glycolysis. Inhibition of the DPP 4 enzyme enhances glucose transport and decreases carbohydrate digestion and absorption.[90] *T. cardifolia* has been demonstrated to have an inhibitory effect on the CYP3A4, CYP2D6and CYP1A2 isoenzymes at high concentrations in DMSO and ethanol (5%), but no interaction was identified at low concentrations (0.1%), indicating that the effect is concentration dependant. CYP3A4 (IC_{50}=136.45 g/mL), CYP2D9 (144.37 g/mL), CYP29 (127.55 g/mL)and CYP1A2 (141.82 g/mL) have been demonstrated to be inhibited by *T. cardifolia* constituents and extracts, but the inhibitory impact is smaller than the positive control group.[92] *T. cardifolia*extract (400 mg/kg) combined with metformin (90 mg/kg), sitagliptin (10 mg/kg)and glibenclamide (1 mg/kg) lowered FBS levels to 148.8, 147.4and 188.5 mg/dL, respectively, with no hypoglycemia impact observed after 28 days. There was no interaction between metformin and sitagliptin pharmacokinetic parameters; however, *T. cardifolia* increases the C_{max} and AUC of glibenclamide by 1.2 times, a clinically insignificant impact. *T. cardifolia* combined with the above medicine lowered TC, TG and BUN levels in diabetic rats.[93] The C_{max}, AUC and bioavailability of glibenclamide (1 mg/kg) with *T. cardifolia* extract (400 mg/kg) increased at high dose, but not $T_{1/2}$ of glibenclamide significantly, T_{max} increased from 3.5 hr to 6.5 hr significantly decreased in clearance at dose of 400 mg *T. cardifolia* extract with 1 mg/kg glibenclamide, according to Sahu R *et al.*[94] *T. cardifolia* hydroalcoholic extract (100 mg/kg) plus glimepiride (20 mg/kg) Glimepiride's C_{max}, AUC_{0-t} and MRT_{0-t} all increased dramatically, but Vd and clearance decreased.[95]

Zingiberis officinale Roscoe

Zingiberis officinalis Roscoe (Zingiberaceae) is an herb that has been used to treat a variety of ailments. *Zingiberis officinalis Roscoe* is a plant that contains mostly gingerols and is often referred to as ginger. [6]-Gingerol, [8]-gingerol and [10]-gingerol are the most common gingerols. Methylgingerol and gingerdiol, dehydrogingerdione, [10]-dehydrogingerdione, gingerdiones, diarylheptanoids, diterpenlactones and galanolactone are some of the other gingerols. Gingerol has a pancreatic beta cell protective action, promotes glucose consumption in tissue and maintains blood glucose homeostasis by increasing insulin release and sensitivity and decreasing blood glucose levels.[96] The ginger extract ethyl extract fraction inhibits the CYP2A6 and CYP2A13 enzymes with IC_{50} of 1.80±0.07 µg/mL and 11.81±0.18 µg/mL, respectively.[97] The gingerols in ginger suppressed the

activity of CYP2C9, CYP2C19, CYP3A4and CYP2D6. The 8-gingerol showed the most powerful inhibitory activity for CYP2C9 (6.8 μmol/l), CYP2C19 (12.5 μmol/l)and CYP2D6 (42.7 μmol/l).[98] The 6-shogal a chemical constituent present in the ginger, inhibits the CYP2C9 (29.20 μM), CYP2C19 (18.78 μM), CYP2E1 (99.58 μM) CYP2E1 (99.58 μM).[99] *In vitro* studies showed that 6-gingerol had a substantial inhibitory impact on CYP2C19 (IC_{50} 36 μM) and CYP1A2 (IC_{50} 51 μM), but a modest inhibitory effect on CYP3A4 (IC_{50} 108μ M), CYP2D6 (IC_{50} 235 μM)and CYP2E1 (IC_{50} 104 μM).[100] When ginger extract (4 mL/kg) and sitagliptin (20 mg/kg) were given simultaneously, there was no interaction.[101] Concomitant administration of (5 mg/kg) glibenclamide and ginger extract at doses of 25 mg/kg and 50 mg/kg lowered blood glucose levels, but the higher doses of 100 mg/kg of extract raised blood glucose levels. In diabetic rats, ginger extract (50 mg/kg) reduced blood glucose level more than insulin.[102]

Ginkgo biloba L.

Ginkgo biloba L. (family: *Ginkgoaceae*) is a living fossil that is used in traditional Chinese medicine. Flavone glycosides, ginkolides and bilobalides, rutin, quercitrin and hyperosid are the bioactive components of *G. Biloba*.[103] (ginkgolides A, B, C and J and bilobalide) kaempferol, quercetin, apigenin, myricetin, tamarixetin, which yielded IC_{50} values for CYP1A2 or CYP3A of less than 10 μg/mL.[104] The extract of *G. biloba* stimulates beta cell secretion and lowers insulin resistance.[105] *G. biloba* extract inhibits CYP2C9((K_i=14±4 μg/mL), CYP1A2 (K_i=106±24 μg/mL), CYP2E1(K_i=127±42 μg/mL)and CYP3A4 (K_i=155±43 μg/mL), flavonoidic fraction of EGb 761 inhibited CYP2C9 (K_i=40±12 μg/mL), CYP2C9 (K_i=4.9±0.6 μg/mL), CYP3A4 (K_i=43±9 μg/mL)and CYP2E1 (K_i=55±11 μg/mL). And terpenoid fraction EGb 761 inhibited only CYP2C9 (K_i=15±6 μg/mL).[106] A clinical study done by Geaorge B Kudolo,[105] the *G biloba* extract (EGb 761, 120 mg for 3 month) have been reduced the glucose and insulin level in NIDDM subjects with pancreatic exhaustion (FBG 152±46 mg/dL, FPI 16±8 μU/mL) with oral hypoglycemic treatment. The *G. biloba* augmented the hepatic metabolic clearance rate of insulin and hypoglycemic agents; it may be anti-hyperinsulinemia in nature. The *G. biloba* extract inhibited CYP activity in small intestine (IC_{50}=50 μg/mL) and in liver (IC_{50}=182±13μg/mL).[107] In comparison to alpha amylase inhibitory effect, ethanolic and aqueous extracts (50 g/mL) had a high alpha glucosidase inhibitory impact.[108] After taking tolbutamide and GBE together, healthy volunteers' blood glucose levels dropped by 16%. There was no significant change in C_{max} and $AUC_{0-\infty}$.[109] In a double-blind, placebo-controlled, cross-over study, co-administration of 120 mg of EGb 761 with metformin (500 mg) had no significant effect on metformin pharmacokinetic parameters in diabetic patients, but the highest dose of extract (9850 mg) had a significant effect on AUC and metformin excretion in 4 days.[110]

Panax ginseng

Asian or Korean red ginseng is the common name for *Panax ginseng*.[111] The main component of *P. ginseng* is ginsenoside, which is divided into two groups: protopanaxatriol (Re, Rg1, Rh1 and Rg2) and 20(S) protopanaxadiol (Rg3, Rd, Rb3, Rc, Rb1, Rb2). Improve perturbation of hepatic glucose uptake by GLUT 4 into peripheral tissue. Increases glucose absorption in muscles, lowers blood glucose and lowers HbA1c via activating AMPK and suppressing gluconeogenesis.[112] Ginsenoside Re (20 mg/kg) decreased the fasting blood glucose level after 2 weeks of treatment in diabetic rat. It also has a protective effect against oxidative stress in the kidneys and eyes.[113] After 1 hr of treatment with ginsenide Rh2 (1.0 mg/kg), plasma insulin levels rise from 211.42±13.84 to 342.34±12.23 pmol/L.[111] In stz-induced diabetic rats, the extract and metformin reduce blood glucose levels up to 200 mg/dL after 35 days of treatment.[112] In a 12-week randomised double-blind, placebo-controlled research of *P. ginseng* in diabetic patients, oral anti diabetic medication reduced blood glucose levels by 8-11% and plasma insulin levels by 33-38% after the oral glucose tolerance test.[114] Compound K, a metabolite of protopanaxadiol ginsenosides, was combined with metformin (10 mg/kg) to lower plasma insulin and glucose levels.[115] The pharmacokinetic parameter of metformin and the rate of absorption of metformin were not affected by the coadministration of *P. ginseng* 2g/kg with metformin 50 mg/kg.[112] The urine excretion rate is altered by repeated administration of red ginseng extract and the AUC and C_{max} of metformin are enhanced.[116] BST204 is a ginseng extract that is dry. With IC_{50} values of 17.4, 26.8, 31.5and 49.7l g/mL, BST204 mildly reduced the activity of CYP2C8, CYP2D6, CYP2C9and CYP2B6, respectively.[117]

Glycyrrhiza glabra L.

Liquorice plant (*Glycyrrhiza glabra* L.) belongs to the *Fabaceae* family. Glycyrrhizin, glycyrrhctinic acid, glabrene, formononetin, glabroi, isoliquiritigenin and liquiritigenin are phytoconstituents of *G. glabra*.[118] Liquorice plant increases pancreatic cell number and improves tolerance to oral loading.[119] *G. Glabara* and glycyrrhizin have an inhibiting impact on the cytochrome isozyme. Ethanol extract of *G. Glabara* affect the CYP3A4 and CYP2D6 with IC_{50} value 140.95±4.80 μg/mL and 132.49±1.07 μg/mL and the IC_{50} value for DMSO solvent of *G. Glabra* are 129.47±2.41 μg/mL and 125.16±0.88 μg/mL. The glycerrhizin in ethanol and DSMO inhibit CYP3A4 and CYP2D6 with IC_{50} value174.62±2.30 μg/mL, 156.25±3.48 μg/mL and 172.33±1.92 μg/mL, 153.38± 1.98 μg/mL. The crude extract has more potent action compared to bioactive compounds.[120] Licorice extract and glycerrhin increased the expression of CYP2B1, CYP2B9and CYP3A by 1.8-4.4 times, 1.8-2.2 times and 2 times, respectively. CYP2E1 and CYP1A1 activity have been reduced.[121] The activities of CYP2C9, CYP2C19and CYP3A4 were all inhibited by glycyrhhetinic acid. On the activity of CYP1A2, CYP2D6and CYP2E1, a modest inhibitory effect has been seen, with an IC_{50}

Table 2: Summary of Herbal Drug Interaction.

Sl. No.	Name of plant	Type of study	CYP/P-gp inhibition/induction	Interacting drug	Pharmaco-kinetic Interaction	Pharmaco-dynamic interaction
1.	*Abelmoschus esculentus*	*In vitro* study and *in vivo*	-	Metformin	Yes	-
2	*Phyllanthus emblica*	*In vitro* study and *in vivo*	Inhibition of CYP1A2, CYP2C9, CYP2D6, CYP2E1, CYP3A4.	Metformin	Yes	Yes
3.	*Andrographis paniculata*	*In vitro* study and *in vivo*	Inhibition of CYP3A4, CYP2D6 and CYP2C9.	Tolbutamide, Glyburide, gliclazide	Yes Yes Yes	No Yes -
4	*Boswellia serrata*	*In vitro* and *in vivo* study	Inhibition of CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4.	Glimepride, metformin	Yes Yes	Yes Yes
5	*Aloe barbadensis Miller*	*In vitro, in vivo* study and human study	Inhibition of CYP3A4 and CYP2D6.	Glibenclamide	-	Yes
6	*Bridelia ferrugenia*	*In vitro, in vivo* study	-	Metformin	Yes	Yes
7	*Cassia ariculata* (L).	*In vitro, in vivo* study	Inhibition of CYP1A2, CYP2D6 CYP3A4.	Metformin	Yes	Yes
8	*Catharanthus roseus*	*In vitro, in vivo* study	Inhibition of CYP2D6 and CYP3A4.	Metformin, Glibenclamide	- -	Yes No
9	*Cinnamomum verum*	*In vitro, in vivo* study	Inhibition of CYP2D1.	Metformin	-	Yes
10	*Costus pictus*	*In vitro, in vivo* study	-	Metformin	-	Yes
11	*Curcuma longa*	*In vitro, in vivo* study	Inhibition of CYP3A4, CYP1A2, CYP2C9 and CYP2D6, Pgp inhibitor.	Glyburide Glimepiride Metformin.	Yes Yes -	Yes - Yes
12	*Trigonella foenum graecum*	*In vitro, in vivo* study and human study,	Inhibition of CYP2C9, CYP3A4, CYP2D6, CYP2C11.	Glimepiride Insulin Metformin Gliclazide.	- - Yes -	Yes Yes - Yes
13	*Allium sativum* L	*In vitro, in vivo* study and human study,	Inhibition of CYP3A, CYP2A CYP2C9, induction of Pgp.	Metformin	Yes	Yes
14	*Tinospora cordifolia*	*In vitro* and *in vivo* study	Inhibition of CYP3A4, CYP2D9, CYP1A2, CYP29.	Metformin Sitagliptin Glibenclamide Glimepiride.	No No Yes Yes	Yes Yes Yes -
15	*Zingiberis officinale Roscoe*	*In vitro* and *in vivo* study	Inhibition of CYP2C9, CYP2C19, CYP3A4 and CYP2D6.	Sitagliptin Glibenclamide.	No -	No Yes

Sl. No.	Name of plant	Type of study	CYP/P-gp inhibition/induction	Interacting drug	Pharmaco-kinetic Interaction	Pharmaco-dynamic interaction
16	*Ginkgo biloba* L.	*In vitro, in vivo* study and human study	Inhibition of CYP2C9, CYP1A2 CYP2E1, CYP3A4.	Tolbutamide Metformin.	Yes No	- -
17	*Panax ginseng*	*In vitro, in vivo* study and human study	Inhibition of CYP2C8, CYP2D6, CYP2C9 and CYP2B6.	Metformin	Yes	Yes
18	*Glycyrrhiza glabra* L.	*In vitro* and *in vivo* study	Inhibition of CYP3A4, CYP2D6, CYP2E1.	Glibenclamide	Yes	-
19	*Opuntia* spp.	Human study	-	Glipizide Metformin	- -	Yes Yes
20	*Gymnema sylvestre*	*In vitro* and *in vivo* study	Inhibition of CYP1A2, CYP2C9, CYP3A4 and CYP2C8.	Sitagliptin Gliclazide Glimepiride Metformin Glibenclamide.	Yes Yes No Yes Yes	- No Yes Yes No
21	*Syzigium cumini*	*In vitro* and *in vivo* study	Inhibition of CYP3A4, CYP2D6 induction of Pgp.	Gliclazide Sitagliptin Glipizide.	- Yes Yes	Yes Yes Yes
22	*Scutellaria baicalensis*	*In vitro* and *in vivo* study	Inhibits only CYP1A2	Metformin	-	Yes
23	*withania somnifera*	*In vitro in vivo* study and human study	Induction of CYP1A.	Glimepiride	Yes	Yes
24	*Swertia chirata*	*In vito* and *in vivo* study	Inhibition of CYP3A4, CYP2D6.	Tolbutamide	-	Yes
25	*Azadirachta indica*	*In vito* and *in vivo* study	Induction of CYP3A4.	Gliclazide Glipizide	- No	Yes Yes
26	*Momordica charantia*	*In vito* and *in vivo* study	Inhibition of Pgp, CYP2C9 CYP2C19, CYP1A2, CYP3A4, CYP2A6.	Rosiglitazone Metformin Glibenclamide.	- - -	Yes Yes Yes
27	*Moringa Oleifera,* Lam.	*In vito* and *in vivo* study	Inhibition of CYP1A2, CYP2D6, CYP2E1, CYP3A4.	Metformin Pioglitazone	- Yes	Yes -

value of around 500 M.[122] When 18- glycyrrhizin (25 mg/kg i.p.) and glibenclamide (1 mg/kg i.g.) were given together, C_{max}, AUC_{0-14} hand elimination half time $T_{1/2}$, ke were all elevated by 18%, 59%and 63%, respectively, while glibenclamide elimination was reduced by 38%.[123]

Opuntia spp. (Prickly pear cactus)

Opuntia, popularly known as prickly pear cactus, is a cactus that belongs to the *cactaceae* family.[124] *Opuntia* spp. is a medicinal plant that is used to treat a variety of chronic diseases. It thrives in arid climates with harsh environmental conditions.[125] *In vivo* research has discovered that *Opuntia spp.* have alpha glucosidase inhibitory action. The glucose absorption has declined in small intestine after the administration of *opuntia* spp. The blood glucose level of streptozocine induced rat has been reduced. After receiving an aqueous extract of *Opuntia ficus indica*, the AUC of blood glucose was reduced by 33.10%.[126] The stimulation of the AMPK/P38 MAPK pathway in L6 myoblast cells by *Opuntia ficus indica* and enhanced GLUT-4 translocation and glucose absorption.[127] The *Opuntia* spp. contain 14.25%±0.062

pectin fiber[128] which reduces the glucose absorption,[129] phenols, flavonoids, dietary fibers, betalains, taurine linolic acid, vitamins, minerals and free amino acids are some of the bioactive compounds found in *Opuntia* spp.[130] The alkaloids Indica xanthin, neobatanin, fibre, flavonoids and poly saccharides have been proven to have anti-diabetic and anti-glycation property.[131] In clinical investigations, *Opuntia ficus indica* combined with leucine produced a synergistic effect in males after a vigorous workout.[132] With the *Opuntia* spp., glipizide and metformin were given together. The results revealed an additive impact that resulted in hypoglycemia in diabetic patients.[133]

Gymnema sylvestre

In Hindi, *Gymnema sylvestre* (family: *Asclepiadaceae*) is called as gur-mar.[134] A new extract of *G. sylvestre* known as OSA improved glucose tolerance by reducing intestinal glucose absorption after an oral glucose load, decreasing insulin resistance, or increasing plasma insulin levels. OSA functioned to preserve insulin reserves by boosting insulin production through an increase in PPI mRNA. *Gymnema sylvestre* extracts have been shown to limit glucose absorption in the gut.[135] Gymnemic acids, gymnemosides, gymnemasaponins, gurmarin, gymnemanol, stigmasterol, d-quercitol, amyrin related glycosides, anthraquinones, lupeol, hydroxycinnamic acids and coumarols are among the plant's bioactive ingredients. Anti-diabetic action has been found in gymnemic acids, gymnemasaponins and Gurmarin.[136] The extracts of *G. sylvetre* in chloroform, n-hexane and ethyl acetate decrease the activities of CYP1A2, CYP2C9 and a modest inhibition of CYP3A4 and CYP2C8.[137] When sitagliptin (20 mg/kg) was co-medicated with *G. sylvestre* extract (400 mg/kg), the bioavailability and AUC of sitagliptin (20 mg/kg) decreased.[138] The reduction found in bioavailability by 43%, in C_{max} by 75%, the absorption rate constant by 95% and an increment in clearance of gliclazide (40 mg/kg p.o.) when combine with *G. sylvestre* extract (30 mg/kg p.o.). There was a maximum hypoglycemic effect observed but less than gliclazide alone.[139] No significant pharmacokinetic interaction found between glimepiride (0.8 mg/kg) and *G. sylvestre* (400 mg/kg) in the study. On a 28-day treatment, the levels of FBGL and Hb1Ac were reduced by 63.38% and 4.82%, respectively, a more potent effect than the individual effects of glimepiride and *G. sylvestre*.[140] *G sylvestre* (100 mg/kg and 500 mg/kg p.o.) and metformin (50 mg/kg and 100 mg/kg p.o.) interact, *G. sylvestre* (100 mg/kg) and metformin (50 mg/kg) decreased $AUC_{0-\infty}$, C_{max} and K_a by 27%, 34% and 37%, respectively and increased clearance by 38%, while *G. sylvestre* 500 mg/kg and metformin 100 mg/kg decreased AUC, C_{max} and Ka by 47%, 53% and 41%, respectively and increased clearance by 88%. The combination of metformin and *G. sylvestre* dramatically reduced the FBGL to 140.4±3.4 mg/dL.[139] Taking *G. sylvestre* 500 mg/kg with glibenclamide 0.5 mg/kg together reduced $AUC_{0-\infty}$ by 17%, C_{max} by 19%, Ka by 24% and increased clearance by 14%. The second combination of *G. sylvestre* 500 mg/kg and a high dose of glibenclamide (0.6 mg/kg) lower $AUC_{0-\infty}$ by 8-7% increases C_{max} by 13%, Ka by 9% and increases clearance by 29%. This combination lowers blood glucose and cholesterol levels, but it has a smaller effect than glibenclamide (0.6 mg/kg).[141]

Syzigium cumini

Eugenia jambolana Lam. (syn. *Syzigium cumini* (L.), Family: *Myrtaceae)*, often known as black plum in English or Jamun in Hindi, is a plant that grows in the Myrtaceae family. Ellagic acids, isoquercetin, quercetin, kampferol, myricetin anthocyanins, delphinidin, petunidin, malvidin-diglucosides, jambosine, gallic acid, corilagin, -sitosterol, betulinic acid, mycaminose are phytochemicals found in plants.[142] Mycaminose has anti-diabetic properties. Aqueous extract of seed (2.5 g/kg) was given to diabetic rats for 30 days, the results were observed that, seed extract increases the glycolysis and decreases glucose formation by increment in hexokinase activity and reduces insulin sensitivity by augmentation of glucose utilization. Extract administration also decreases the tissue damaged by oxidative stress.[143] The interaction of crude seed extract of *S. cumini* with CYP isoenzymes was examined .*S. cumini* crude extract inhibited CYP3A4 with an IC_{50} of 76.69 µg/mL, whereas CYP3A4 (IC_{50}=359.02 µg/mL) and CYP2D6 (IC_{50}=493.05 µg/mL) were only weakly inhibited.[144] The methanolic extract of *S. cumini* (500 mg/kg) with gliclazide 2 mg/kg reduced the blood glucose level by 35% in 12 hr of administration.[145] Combining sitagliptin and aqueous seed extract of *E. jambolana* (400 mg/kg) effectively lowered FBL to 298.74 mg/dL after 28 days of treatment. C_{max} and AUC_{0-24}, both pharmacokinetic parameters, were lowered by 38.70% and 22.40%, respectively. The decrease in absorption could be related to increased P-gp expression or stimulation of the CYP enzyme. The pancreatic tissue was able to recover from oxidative injury in a considerable way.[146] The combination of *S. cumini* seed extract (250 mg/kg and 400 mg/kg p.o.) and glipizide enhances the AUC, C_{max} and $T_{1/2}$ of glipizide, while the *S. cumini* (100g) extract suppresses the CYP3A enzymatic activity. The *S. cumini* extract at 250 mg/kg and 400 mg/kg in combination with glipizide dramatically lowers blood glucose levels.[147]

Scutellaria baicalensis

Scutellaria baicalensis, often known as Scutellariae radix or skullcap root. Baicalin, baicalein, wogonin, chalones, flavanonols and anthocyanidines are active phytoconstituents of *S. Baicalensis.*[148] *S. baicalensis* (3.52 g) and metformin (500 mg) together enhanced insulin resistance and hepatic enzymatic activity, as well as glucose tolerance.[149] The *S. baicalensis* extract inhibits solely CYP1A2 with an IC_{50} value of 0.5 µM to 19.9 µM.[150] When *S. baicalensis* is used with a drug metabolized by CYP1A2, it may induce an herbal drug interaction. To test this, more research is required. A pharmacokinetic interaction between metformin (500 mg/kg) and *S. baicalensis* (400 mg/kg) given to STZ induced diabetic rats for 30 days, which reduced

38.2% blood glucose levels and plasma TC levels (99.733 mg/dL) with a greater effect than the metformin and *S. baicalensis* groups treated separately.[151]

Withania somnifera

Ashwagandha or Indian ginseng is the way of referring to *Withania somnifera* (L.) Dunal (family: *solenaceae*). Isopelletierine, anaferine (alkaloids), tamanolides', withaferins (steroidal lactones), sitoindoside VII and VIII and sitoindoside IX and X are the biologically active chemical ingredients.[152] A research study found increases of 2.13, 1.95, 1.35and 1.20 times in C_{max}, $AUC_{0-\infty}$, $T_{½}$ and MRT and decreases of 0.51 and 0.69 folds in clearance and volume of distribution, in glimepiride pharmacokinetic parameter, the oral bioavailability by 33.5%. The combination of ashwagandha (500 mg/kg) with glimepiride (1 mg/kg) resulted in a 55.46% reduction in glucose levels after 6 hr, compared to glimepiride (46.06%).[153] The inhibitory impact of crude extract of *W. somnifera* (10-640 µg/mL) and active ingredient (1-32 µM) on cytochrome isoenzyme. *In vitro* studies revealed that crude extract and phytoconstituent had no inhibitory effect on CYP1A, with IC_{50} values of ˃500 µg/mL and ˃32 µM, respectively. *In vivo* studies revealed that the methanolic extract of *W. somnifera* and phenacetin reduced $AUC_{0-\infty}$ by 31%, increased elimination constant by 48% and decreased half-life $T_{1/2}$ by 43%, with no significant difference in C_{max} of phenacetin. These findings could point to an increase in the CYP1A isoenzyme, which could reduce the therapeutic efficacy of a medicine metabolized by the CYP1A enzyme.[154] In a clinical trial on patients with mild hyperglycemia and hypercholesteremia, after 30 days of treatment, NIDDM patients who were administered ashwagandha 500 mg capsules, 6 capsules per day (3 g/day), saw a 12% reduction in blood glucose levels. Ashwagandha has been shown to boost insulin levels. Serum cholesterol, triglycerides, LDL and VLDL cholesterol levels were reduced by 10%, 15%, 6% and 15%, respectively.[155]

Swertia chirata

Chirata or Buch-Ham is the common name for *Swertia chirata* (family: Gentianaceae). It's a type of Chinese medicine that dates back thousands of years.[156] Amarogentin, mangiferin and swertia merin are phytochemicals of *Swertia chirata*. Mangiferin is proven to lower blood glucose levels while also lowering lipid levels.[157] The ethanlic and DSMO extract of *Swertia chirata* inhibited CYP3A4 (197.49±2.68 and 193.63±2.87) and CYP2D6 (211.45±3.54 and 208.34±1.26) respectively. The hexane extract of *S. chirata* (250 mg/kg) given to tolbutamide pre- treated rats, a decrement in blood sugar level at 4 hr.[158]

Azadirachta indica

Azadirachta indica (family: *Meliaceae)* is a plant that is generally referred to as neem in Hindi and is utilized in Ayurveda and Unani medicine.[159] *A. indica* stimulates beta cell insulin release, improves glucose utilization and insulin sensitivity and prevents glucose absorption in the gut.[160] The aqueous and acetone extracts of *A. indica* inhibited α amylase and α glucosidase with IC_{50} values of 9.15 mg/mL and 5.00 mg/mL, respectively.[161] After 21 days of treatment, chloroform extract of *A. indica* lowers fasting blood glucose (109.65 mg/dL). The activity of the glucosidase enzyme was reduced by 51% and 35%, respectively, after administration of chloroform and aqueous neem extract. After 21 days of *A. indica* administration, plasma insulin secretion from cells and G6PD activity were shown to be enhanced.[162] In diabetic rats and normal rabbits, the co-administration of aqueous neem extract (30 mg/kg) with gliclazide (2 mg/kg) lowered blood glucose levels by 28.1 and 1.2%, respectively. After administration of *A. indica*, there was no significant pharmacokinetic interaction in gliclazide.[163] The co-administration of *A. indica* (250 mg) with glipizide (5 mg/kg) had no significant effect on gliclazide pharmacokinetic parameters, but *A. indica* (500 mg/kg p.o.) decreased AUC and $T_{1/2}$, but had no effect on C_{max}, MRT significantly increased and T_{max} significantly increased, indicating that *A. indica*. The *A. indica* extract (100 µg) caused induction of CYP3A4 enzymatic activity. No significant difference was found in the blood glucose level when treated with combination of *A. indica* 250 mg+5 mg/kg and 500 mg/kg+5 mg compared to gliclazide (5 mg/kg p.o.) alone. The AST and ALT level decreased in *A. indica* (500 mg/kg) and gliclazide (5 mg/kg). Glucose load has been decreased after 120 min of treatment.[160] Because of the elevation of CYP3A4 enzymatic activity, *A. indica* has an herbal medication interaction with gliclazide.

Momordica charantia

Momordica charantia (Family: *Cucurbitaceae)* is commonly known as bitter gourd. Neuropathy, retinopathy, cardiomyopathy, nephropathy, exocrine gland insufficiency and various other diabetes problems are all treated with *Momordica charantia. Momordin charantin* and momordicin are bioactive phytochemicals. These compounds have anti-diabetic properties.[164] *M. charantia* stimulated beta cells, which increased glucose uptake and insulin levels.[165] In H411EC3 hepatoma cells, an ethyl acetate extract of *M. charantia* activates PPARγ and PPARα.[166] Glycogen synthesis was induced by *M. Charantia*.[167] *M. charantia* inhibits P-gp with IC_{50} value of 16±0.4 and raise the induction of PXR activity by 2 times. Methanolic extract of *M. charantia* inhibits CYP2C9 and CYP2C19 strongly, CYP1A2, CYP3A4 and CYP2A6 weakly.[168] The glucose load and blood glucose level have been reduced by the combination of rosiglitazone (2 mg and 5 mg) and *M. charantia* (500 mg/kg) methanolic extract.The potent effect shown by the high dose of rosiglitazone (5 mg) with MC.[169] In clinical study, the carbon tetrachloride+hexene extract of *M. charantia* with metformin (2.5 mg/kg .po.) reduced 11% FBS and 17% PPBS and extract with glibenclamide (2.5mg/kg p.o.) reduced 13% FBS and 15% PPBS in diabetic patient, the combination of *M. charantia* extract with metformin (2.5 mg) and glibenclamide 2.5 mg have reduced 13%

FBS and 21% PPBS, *Momordica charantia*+antihyperglycemic drug showed synergistic effect.[170]

Moringa oleifera, Lam

Moringa oleifera, Lam (family: *Moringaceae*) is commonly known as drumsticks.[171] The phytochemicals are 4(α L-rhamnosyloxy)-benzyl isothiocyanate, niazimicin, 3-O-(6′-O-oleoyl-β-D-glucopyranosyl)-β-sitosterol, β-sitosterol-3-O-β-D-glucopyranoside, niazirin, β-sitosterol and glycerol-1-(9-octadecanoate),[172] chlorogenic acid, rutin, quercetin glucoside and kaempferol rhamnoglucoside.[173] Ethanolic and aqueous extract of *M. oleifera* inhibited human CYP1A2, CYP2D6, CYP2E1 and CYP3A4 activities with IC_{50} value 13.8 to 1500 µg/mL. Ethanolic extract of *M. oleifera* shown specific inhibition of CYP1A2 with IC_{50} 13.8 µg/mL and CYP3A4 with IC_{50} 101 µg/mL.[174] and A study has found a synergistic effect of met (150 mg/kg) and ethanolic extract of MO 375, 750 and 1500 rmg/kg in alloxan induced diabetic rat, the blood glucose level and serum lipid level have been reduced in 28 days.[175] Aqueous extract of *M. oleifera* leaves (200 µg/mL) inhibited α-amylase and α- glucosidase activity by 80.5% and 75.65% respectively. Intestinal absorption inhibited by extract at 100 µg/mL by 86.25%.the glucose uptake increased by 24.3% at the dose of 100 µg/mL.[171] Mukharjee *et al.*[176] resulted that, hydroalcoholic extract of *Moringa oleifera* and chlorogenic acid weak inhibitor of CYP3A4 and CYP2D6 compared to positive inhibitors. The co- administration of pioglitazone (3 mg/kg) and moringa (800 mg/kg) have reduced the glucose levels and body weights on contrast the half dose of pioglitazone 1.5 mg/kg and 400 mg/kg have produced significant interaction with the Pharmacokinetic parameter AUC, $T_{1/2}$, Ke, CL, Vd administered to diabetic and normal rabbit. The single dose decreased AUC and in opposite multiple doses increased AUC.[177]

DISCUSSION

Herbal medicines are widely utilised and various formulations are available as Over-The-Counter (OTC) and prescription pharmaceuticals. Patients are encouraged to take herbal medications in addition to their allopathic treatment. This could result in an herbal drug interaction and a lack of understanding of HDI could worsen the patient's condition. Cytochrome inhibition or induction is the mechanism of pharmacodynamic and pharmacokinetic interactions. *Andrographis paniculata* and *Catharanthus roseus* exhibited no impact when taken together with tolbutamide and glibenclamide respectively. Metformin's bioavailability and therapeutic and pharmacological effects were lowered by *Bridelia ferugenia*. Before combining allopathy with herbs, they should be researched thoroughly. Plant phytochemicals interfere with cytochrome activity, promoting cytochrome induction or inhibition. It is necessary to investigate phytoconstituents and cytochrome induction or inhibition activity to improve therapeutic and pharmacological effects, safety, efficacy and dose adjustment. The phytoconstituents present in medicinal plants are responsible for the herbal drug interaction. The phytoconstituents alter the cytochrome activities by inhibition or induction. Cytochrome induction and inhibition distress the pharmacokinetic and pharmacodynamic effects. These are major concerns when we combine herbs with allopathy. The safety and efficacy of drug should be study for better therapeutic effect. The researcher should pay attention towards this. Herbal drug interaction should be measured for better treatment and mitigation of diabetes Mellitus.

CONCLUSION

The exploration of interactions between herbal remedies and conventional antidiabetic medications presents significant implications for diabetes management. Herbal treatments, with a long-standing history of use in managing chronic conditions, offer promising benefits when integrated properly with allopathic therapies. As highlighted in the findings of the study, numerous plants exhibit pharmacological properties that can enhance glycemic control and improve metabolic profiles in diabetic patients.

However, the potential for herb-drug interactions remains a critical concern, primarily due to the involvement of cytochrome P450 enzymes and other metabolic pathways. Understanding the pharmacokinetics of both herbal and conventional medications is essential for optimizing therapeutic efficacy while minimizing adverse effects. The research indicates that certain herbal compounds can modulate the bioavailability and effectiveness of antidiabetic drugs, such as metformin and glimepiride.

Future research should focus on elucidating the mechanisms underlying these interactions and establishing comprehensive guidelines for patients seeking to incorporate herbal remedies into their diabetes management strategies. By fostering a collaborative approach between traditional and modern medicine, we can create a more effective, safe, and holistic framework for treating diabetes, ultimately enhancing patient outcomes and quality of life.

ACKNOWLEDGEMENT

The authors are grateful to the School of Pharmacy, Devi Ahilya Vishwavidyalaya, Indore for providing necessary research facilities. RM is grateful to the All-India Council of Technical Education (AICTE), New Delhi, for PG scholarship.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AUC: Area Under the Curve; **AUC_0:** Area Under the Curve from 0 to the last measurable concentration; **AUC_{total}:** Total Area Under the Curve; **AMPK:** AMP-Activated Protein Kinase; **C_{max}:**

Maximum Plasma Concentration/Peak Plasma Concentration; **CYP:** Cytochrome; **DSMO:** Dimethyl Sulfoxide; **FBS:** Fasting Blood Sugar; **GOT:** Glutamic Oxaloacetic Transaminase; **GLUT:** Glucose Transporter; **GPT:** Glutamic Pyruvate Transaminase; **HbA1c:** Hemoglobin A1c; **LDL:** Low-Density Lipoprotein; **MRT:** Mean Residence Time; **PgP:** P-Glycoprotein; **PPAR:** Peroxisome Proliferator-Activated Receptor; **T1/2:** Half-life; **T2DM:** Type 2 Diabetes Mellitus; $\mathbf{T_{max}}$**:** Time to reach maximum concentration; **TC:** Total Cholesterol; **Vd:** Volume of distribution.

SUMMARY

This review article investigates the complex interplay between herbal remedies and oral antidiabetic medications. Focusing on 27 antidiabetic plants highlights the increasing prevalence of diabetes mellitus globally, characterized by high blood glucose levels due to insufficient insulin function. The extensive use of herbal supplements alongside conventional treatments necessitates a thorough understanding of potential Herb-Drug Interactions (HDIs). The review details the diverse mechanisms by which these 27 plants may impact blood glucose, including AGE inhibition, GLP-1 stimulation, beta-cell regeneration and glucose metabolism modulation (Table 1). However, this article emphasizes the critical role of Cytochrome P450 (CYP) enzymes in mediating pharmacokinetic and pharmacodynamic HDIs. CYP inhibition can enhance drug bioavailability, potentially causing adverse effects, while induction diminishes therapeutic efficacy. The study meticulously examines the individual interactions of each plant with specific antidiabetic drugs, documenting CYP involvement and resultant changes in pharmacokinetic and pharmacodynamic parameters (Table 2). The authors conclude that a comprehensive understanding of HDIs is paramount for safe and effective diabetes management. They stress the need for further research focusing on dose-dependent effects and identifying specific phytochemicals responsible for these interactions to optimize therapeutic outcomes and minimize adverse events. This necessitates a shift towards more rigorous safety and efficacy testing of herbal remedies used concomitantly with conventional antidiabetic medications.

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Cite this article: Mourya R, Sharma R. Interaction between Anti Diabetic Drugs and Herbs: A Review. Pharmacog Res. 2025;17(2):385-401.