Invited Article

Systematic Review on Interaction Studies of Synthetic Antidiabetic Drugs and Herbal Therapies

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ABSTRACT

Purpose: Complimentary and alternative therapies as well as traditional herbal home remedies are booming because they are perceived to be free of side effects and generally recognised as safe due to their natural origin. There are number of reports available on the interaction of anti diabetic drugs in vitro and in clinical trials. Diabetic patients are often treated with multiple synthetic drugs combination due to different co- morbidities and such patients should be informed regarding herb-drug interactions in clinical settings.

Approach: Informations from the published research articles available from MEDLINE, Cochrane and Pub med as well as additional data sources were obtained from manual searches of recent journal articles and textbooks and were used in the preparation of this review article.

Finding: Traditional home remedies and alternative therapies in treatment of *Diabetes mellitus* may pose concern or complications that would arise from these herbs on the pharmacodynamic and pharmacokinetic effects of synthetic drugs as they are used in combination therapy.

Conclusion: Herbal remedies are complex mixtures of bioactive entities which may interact with prescription drugs through pharmacodynamic or pharmacokinetic mechanism and sometimes result in serious clinical consequences. Patients and Physician should be familiar with the potential effects of commonly used herbal medications to prevent, recognise and treat potential adverse effect associated with their uses.

Keywords: Herb-drug interaction, Mechanism, Antidiabetic therapy, Clinical evidence, CYP

INTRODUCTION

Complementary and alternative therapies as well as traditional herbal home remedies are booming because they are perceived to be free of side effects and generally recognised as safe due to their natural origin. Due to high prices and potential side effects of synthetic drugs, people rely more on herbal drugs and this trend is growing, not only in developing countries but in developed countries too. Millions of people today use herbs either as food or in the form of medicine along with prescription and non prescription medications. This upsurge in the use of herbs is a global phenomenon. WHO estimates, demand for medicinal plants by the year 2050 would be ~US $5 trillion. Although considered natural and safe, many of these herbs can interact with other medications, causing either potentially dangerous side effects and/or reduced benefits from the medication.

The probability of herb–drug interactions can be higher than drug–drug interactions, as most herbal medicinal product (even single-herb products) contains mixtures of pharmacologically active constituents[1]. The use of alternative therapy is mostly not supervised by practitioners resulting in increased harm to patients, especially if they are using herbal and prescription medicines that have latent interactions[2].

Poor knowledge of pharmacokinetic of herbs

Reason behind the limited information is their existence in multi component mixtures. It is very difficult to quantify such a small amount in systemic circulation due to very low concentrations, that lead to the situation that most herb–drug interaction studies and case reports in literature only evaluate the outcome of adding a herbal medicinal product to an existing conventional drug therapy and monitoring changes in pharmacokinetics and/or clinical response of the orthodox drug. So, it is need of time to better understand the pharmacokinetics or pharmacodynamic mechanism of herbal medicines, which can support the predictability of herb-drug interactions.

Mechanisms of herb–drug interactions

The major reason for interactions is seen as the overlapping substrate specificity in the bio transformational pathways of the physiologic systems[3]. Mechanisms of drug interactions can be divided into two categories:

1) Pharmacokinetic interactions, which influence absorption, distribution, metabolism or excretion of a drug (ADME rule) and thus lead to increased or reduced plasma levels of a drug; and

2) Pharmacodynamic interactions, which alter pharmacologic efficacy of a drug while drug plasma levels remain unaltered[4].

Pharmacokinetic interactions

Herb-drug interactions at absorption level:

i) Influence of herbs on efflux transporters: Efflux of drugs against a steep concentration gradient is mediated by the ATP binding cassette (ABC) transporters, mostly located in the canalicular membrane of the intestinal epithelium, human liver, kidney or the endothelium of blood capillaries of the brain. ABC transporters are relatively easily modulated by factors such as therapeutic drugs and herbal medicines, foods and beverages[5]. The induction and inhibition of the efflux transporters by herbs would lead to treatment failure and to toxic level, respectively.

ii) P- Glyco protein (P-gp): P-gp is also known as multi-drug resistance protein 1 (MDR1) or ABC subfamily B. Modulation of P-gp by herbal constituents may; therefore, involve direct interaction with one or more binding sites on the P-gp molecule through competitive or non-competitive inhibition or induction of the efflux of drugs. Phytochemicals may also inhibit ATP binding, hydrolysis or coupling of ATP-hydrolysed molecules, therefore, depleting the energy which drives the translocation of P-gp bound substrate drugs[6].

iii) Herb interactions on gastrointestinal motility: Herbal induced diarrhoea, which results in a shorter transit time of the drug along the gastrointestinal tract, reduces contact time with the gastrointestinal epithelium and, therefore, leads to lower drug absorption.

b) Herb-drug interactions at distribution level: Alteration of plasma protein binding (only the free fraction of a drug in plasma is pharmacologically active, displacement from plasma protein binding can increase the active proportion of a drug), may affect overall distribution,causing increased efficacy / adverse effects of drugs,therefore may suggest for lowering of dose of synthetic drugs.

c) Herb-drug interactions at metabolism level: These interactions are performed primarily by the cytochrome P450 (CYP) family of metabolic enzymes (phase I enzymes) and non CYP enzyme systems (phase II enzyme). The most important CYP subfamilies responsible for drug metabolism are 1A1,1A2, 2A6, 2B6, 2C8,2C9, 2C19, 2D6, 2E1, 3A4, and 3A5 (Ono et al. 1996). Phase II metabolic enzymes including uridine diphosphoglucuronosyl transferase (UGT), N-acetyl transferase (NAT), glutathione S-transferase (GST), and sulfotransferase (ST) catalyze the attachment of polar and ionizable groups to phase I metabolites aiding their elimination. Induction of metabolic enzymes is a much slower process, in which herbal medicines promote gene activation and increase the gene or protein levels of the relevant metabolic enzyme. Inhibition of metabolic enzymes occurs when herbal medicines are able to decrease the expression or activities of metabolic enzymes in a

competitive or non-competitive manner. The CYPs induction is modulated by ligand-dependent transcription activation of nuclear receptors including pregnane X receptors (PXR) and constitutive androstane receptors (CAR), etc. Induction of CYP enzymes often results in therapeutic failure because of lower plasma concentrations of the drugs; whereas, inhibition of CYP enzymes would lead to an increase in plasma concentrations of the concomitant drug, and increased toxicity. The inhibition and induction process of enzymes are reversible and enzyme levels can return to the normal levels after stopping the administration of herbal medicines.

d) Herb-drug interactions at elimination level: Drugs that are chiefly excreted by the kidneys can get involved in herb-drug interactions by different mechanisms like competition at active transport sites, or alterations in glomerular filtration, passive renal tubular reabsorption or active secretion and urinary pH[7].

2. Pharmacodynamic interactions: Those interactions which cause changes in pharmacological responses of the drug through additive, synergistic or antagonistic actions[8]. Unfavourable effects may incur, causing target toxicity, if the effect of the drug in combination with the herbal medicine is enhanced synergistically or by additive effects.

3. Clinical Outcomes of Herb-Drug Interactions: The clinical outcome of an herb-drug interaction varies, being well tolerated, mild, or lethal.

a) Altered drug clearance: Herbs which modulate intestinal and hepatic CYPs and P-gp often alter the oral absorption, bioavailability, systemic exposure and clearance of co- administered drugs.

b) Altered drug efficacy: When the systemic exposure of a drug is significantly increased or reduced by herbal medicines, the clinical response to this drug may change. A direct additive, synergistic or antagonistic interaction between the drug and herbs will also alter the magnitude of drug response.

Diabetes Mellitus is a chronic disorder associated with high blood glucose level, either due to less production of insulin by the pancreas or due to inability of body cell to respond to the insulin produced. There are two types of diabetes: Type I and Type II. Type I is also called as insulin-dependent diabetes mellitus (IDDM) which is produced mainly due to less production of insulin and type II as non-insulin-dependent diabetes mellitus (NIDDM) which is produced mainly due to inability of body cells to respond to the insulin produced.

Diabetes is one of the most challenging health problems in the 21st century. Untreated diabetes can cause many complications like heart disease, stroke, nephropathy and neuropathy. International Diabetes Federation reports that diabetes affects about 382 million people world-widely and it is estimated that this number will rise to 592 million by 2035[9]. The hyperglycemia of type 2 diabetes mellitus (T2DM) patients is usually treated with oral antidiabetic drug monotherapy or combination therapy. Multitargeted treatments, including antihypertensive, lipid-lowering, and antiplatelet drugs, are prescribed to reduce cardiovascular morbidity and mortality especially common in the elderly[10]. However, the co-administered herbs may potentiate/ antagonize hypoglycaemic drug's pharmacological effects leading to serious effects.

Therefore, this paper reviewed herb–drug interactions with a focus on antidiabetic drugs, with their management strategies.

Antidiabetic–herb interactions

In antidiabetic therapy, either insulin therapy or oral hypoglycemic agents are commonly used. Oral hypoglycemic drugs are generally classified are as:

- Sulphonyl ureas: 1st generations (tolbutamide, chlorpropamide) and 2nd generations (glibenclamide, glipizide, gliclazide, glimipride).
- Biguanides: metformin
- Meglitinides: repaglinides, nateglinides
- Thiazolidine diones: rosiglitazone, pioglitazone
- Alpha-glucosidase inhibitors: acarbose, miglitol
- DPPH-4 inhibitors: sitagliptin
- GLP-1 analogue: exenatide

Commonly, these interactions interfere with the blood glucose levels. So, caution should be taking while using herbs and conventional antidiabetic therapy.

Sulfonyl ureas-Herbal Interactions

Aloe vera: A single-blind study in Thailand reported that 15mL of aloe juice with glibenclamide significantly reduced blood glucose level and lipid levels in the people with diabetes, but glibenclamide alone had not effectively controlled the diabetes in them[11]. Studies reported that treatment with aloesin and aloesinol could improve impaired glucose and insulin resistance in high-fat diet-induced and db/db non-insulin dependent diabetic mouse models. Similarly, chromone-standardized aloe-based composition enhanced improvement in plasma insulin levels and also provided statistically significant reduction in triglyceride levels in animals[12].

Allium sativum: It is commonly known as garlic and being used traditionally as spices in food. In diabetic patients, garlic not only help in lowering high blood sugar level, but can also provide a healthy blood circulation. It shows comparable effect as that of glibenclamide. It can be considered in combination but more trials are required[13].

Andrographis paniculata: Ethanolic and methanolic extracts of *A. paniculata* showed potent inhibitory effects on CYP3A4 and CYP2C9 activities[14]. Glibenclamide, glimepiride, glipizide are substrates of CYP2C9. In another study, rats were intragastrically dosed with 2g/kg/day APE (A. paniculata extract) or 50•mg/kg/day andrographolide for 5 days before a dose of 20mg/kg tolbutamide. APE and andrographolide significantly reduced the AUC_{0-12h} of tolbutamide compared with that in controls[15]. The protein and mRNA levels and enzyme activities of CYP2C6/11, CYP1A1/2, and CYP3A1/2 were increased by them.

Azadirachta indica: It may also act by increased release of insulin from beta cells of pancreas similar to sulfonylurea[16]. An antagonistic interaction is recorded when A. indica is co-administered with glibenclamide or glimepiride[17]. An oily extract of *Azadirachta indica* produces a marked decrease in blood glucose levels in alloxan diabetic rats[18].

Cassia auriculata L.: The leaf extract had shown an insulinogenic action in streptozotocin induced-diabetic rats[19]. The *Cassia auriculata* flower showed a comparable antidiabetic effect to glibenclamide in streptozotocin induced diabetic rats[20].

Coccinia indica: In Ayurveda, It is used from ancient times to treat diabetes. It has insulinomimetic properties. With glibenclamide, it has shown a significant hypoglycaemic, hypolipidemic, and antioxidant effect in diabetic rats and can be used safely in the treatment of diabetes[21].

Cyamopsis tetragonaloba L.: This is generally known as guar gum. In 9 healthy volunteers, 2.5 mg of glibenclamide plus 3.9 g of glucomannan(plant fibre) was given and after 6 hour period, the plasma concentration of drug was compared with the data obtained with the values found in the same individuals, who received the same dose of the drug, but not the fiber. Results showed a 50% reduction in plasma concentration of glibenclamide. The authors suggested that glucomannan may influence the intestinal absorption of glibenclamide, diminishing the bioavailability of the drug[23]. In other study, conducted in 10 healthy persons that received a single dose of 2.5 mg glipizide alone or with 4.75 g of guar gum, results depicted no change in insulin and glucose levels (calculated during 3 hours after ingestion). So, it did not affect the absorption of glipizide[24].

Ginkgo biloba: The extract increased hepatic clearance of insulin and oral hypoglycemic agents including glibenclamide[22].

Gymnema sylvestre: Its active constituent gymnemic acid IV shows the hypoglycemic effect. Pharmacokinetic and pharmacodynamic interactions with glimipride (0.8mg/kg) and *G. sylvestre* (400mg/kg) were studied in streptozotocin induced diabetic rats for 28 days. Results showed beneficial pharmacodynamic interactions whereas no major alterations in pharmacokinetics parameters of glimipride and *G. sylvestre* were observed[25].

Momordica charantia: Commonly known as karela. It produces significant improvement in glucose tolerance in T2DM patients when they were taking chlorpropamide, tolbutamide, and glibenclamide[26]. *Momordica charantia* inhibited CYP2C9 enzyme activity. Changes in hepatic phase I and phase II drug-metabolizing enzyme activities in streptozotocin (STZ)-induced diabetic animals may be associated with altered expression of CYP and glutathione S-transferase (GST) isozymes[27].

Pleurotus pulmonarius: It showed potent and synergistic antihyperglycemic effect in combination with glibenclamide in alloxan- induced diabetic mice. This combination could be effective[28]. Still, there is a need of human trials.

Trigonella foenum-graceum: In a study of 25 T2DM patients, when received 1g of hydro alcoholic extract of fenugreek seeds in combination with antidiabetics daily for 2 months, it improved glycemic control and decreased insulin resistance[29]. Glipizide monotherapy was more efficacious in controlling FBG and HbA1c levels than fenugreek monotherapy or in combination with fenugreek; whereas fenugreek monotherapy was more efficacious in controlling dyslipidaemia than in combination with glipizide. Both drugs as monotherapy or in combination were well-tolerated by the patients[30].

Zingiber Officinale: In vitro study in mouse myoblast and myotubes revealed that antidiabetic activity of ginger extract is due to its antioxidant activity, antiglycation activity, and it's potential to express or transport Glut4 receptors from internal vesicles[31]. Co-administration of glibenclamide (5mg/kg BW) and ginger crude extract at doses (25 or 50mg/kg BW) significantly reduced the nonfasting blood glucose level than glibenclamide alone in streptozotocin-(STZ-) induced diabetes. Further study is required to optimize the ratio of combination with glibenclamide[32].

Biguanide (Metformin) - Herbal interactions

Metformin is the only biguanide currently approved for the treatment of T2DM. It is recommended as first-line therapy because of good clinical efficacy and a low incidence of adverse events (American Diabetes Association, 2013). Metformin is partially absorbed in the small intestine, shows low plasma binding, and is excreted by renal elimination without hepatic metabolism. The elimination rate of the drug is mainly determined by renal function, in which several specific cation transporters are involved[33]. Thus, all drugs/herbs affecting renal function may also reduce the metformin clearance and may thereby increase the adverse effect of metformin. As metformin comes under Hard Drugs; drugs that are not metabolised by CYPs and not transported by PgP, so there are fewer chances of herb-drug interactions. Still, caution is advised.

Allium sativum: Its hypoglycaemic action may be due to an increase in pancreatic secretion of insulin from β-cells, enhancement of insulin sensitivity[34]. It alters the pharmacokinetics of metformin when given concomitantly in rats by increasing $C_{max,}$ $t_{1/2}$ and $AUC_{0\text{-}12h.}$ So, dose should be adjusted carefully while using garlic in diet[35].

Bridelia ferruginea: A reconstituted freeze dried extract of *B. ferruginea* leaves (30mg/kg) and metformin (7mg/kg) were administered concurrently as single dose to female Sprague-Dawley rats. Pharmacokinetic parameters of metformin were determined. Area under the curve (AUC), maximum whole blood concentration (Cmax) and half-life (T1/2) of metformin decreased significantly in the presence of *B. ferruginea*, whereas Tmax increased but insignificantly. So, patients should be advised on the implication of concurrent administration of metformin and *B. ferrruginea*[36].

Cassia auriculata: 250,500, and 1000 mg/kg Supercritical fluid extracts of *cassia auriculata* (CA-SFE) when co-administered with metformin, it decreased the AUC significantly than the metformin alone. The maximum concentration (Cmax) of metformin was also decreased. It was suggested that the CA-SFE interferes with the absorption of metformin which can be explained by the presence of non-polar components. The Hydroalcoholic extract (CA-HA) when co-administered with metformin did not interfere with pharmacokinetics[37]. Co-

administration of aqueous extract of *cassia auriculata* with metformin at varying dose showed a synergistic herb-drug interaction. Thus using the synergistic herb-drug interaction, the dose level of metformin may be reduced to produce the same therapeutic effect as when taken alone[38].

Emblica officinalis: Co-administration of metformin and amla in diabetic rats reduced the blood glucose levels much lower than metformin treatment alone. This pharmacodynamic interaction is beneficial[39].

Ginkgo biloba: The co-ingestion of 120 mg of extract of *ginkgo biloba* and 500 mg of metformin did not significantly affect the pharmacokinetic properties of metformin[40].

Cyamopsis tetragonaloba L.: When 10 g of guar gum were co-administered with 1.7 g of metformin to 6 healthy volunteers. Results depicted the delay in the absorption of the drug. Metformin plasma concentration was also decreased[41].

Momordica charantia: *Momordica charantia* fruit juice (MCFJ) potentiates the hypoglycemic effect of metformin in diabetic rats. This synergistic effect may help to reduce the dose of metformin[42].

Vernonia amygdalina: Researchers investigated the antidiabetic activity of various combinations of metformin and aqueous extracts of the leaves of *vernonia amygdalina* in normoglycemic and alloxan induced diabetic albino rats. No significantly change in the glucose level of the normoglycemic rats was found. The hypoglycemic effect of the combined agents suggested that their antidiabetic activities are additive. So dose of metformin should be monitored while consuming bitter leaves in diet[43].

Other antidiabetics-herbal interactions

Antidiabetic drugs like pioglitazone and repaglinide are substrates of CYP3A4, whereas nateglinide and rosiglitazone are substrates of CYP2C9. Herbs like *aloe vera*[44] showed (inhibitory effect) on CYP3A4 and

Table 1: Important herb-drug interactions with commonly used antidiabetics[50]

Herbs	Mechanism			Antidiabetic durgs
Aloe vera	Pharmacokinetic Pharmacodynamic	CYP3A4, CYP2D6 insulin sensitizing effect	inhibitor increased efficacy	pioglitazone, repaglinide additive effects with antidiabetic.in general
Allium sativum	Pharmacokinetic Pharmacodynam	icincrease Cmax, $AUC_{0\text{-}12h}$, $t_{1/2}$ increase insulin sensitivity	improvises rate, extent of absorption increased efficacy	Metformin additive effects with antidiabetic in general
Bredelia ferruginea	Pharmacokinetic	decrease Cmax, AUC, $t_{1/2}$	reduce and delay in absorption	Metformin
Andrographis paniculata	Pharmacokinetic Pharmacodynamic	CYP2C9,CYP2C19, CYP2D6, CYP3A4 glucose transporter (GLUT4)	inhibitor increased efficacy	glibenclamide, glipizide glimepiride, nateglinide, repaglinide, rosiglitazone, pioglitazone
Cassia	Pharmacokinetic Pharmacodynamic	CYP1A2,CYP2C9, CYP2D6, CYP3A4	inhibits the glucose absorption from the small intestine inhibitor	glibenclamide, glipizide glimepiride, nateglinide, rosiglitazone, repaglinide pioglitazone
Coccinia indica	Pharmacodynamic	insulin mimetic	increased efficacy	additive effect with glibenclamide
Cyamopsis tetragonaloba L.	Pharmacokinetic	decrease plasma conc.	delay in absorption	metformin

Emblica officinalis	Pharmacodynamic	insulin mimetic	increased efficacy	additive effect with metformin
P. Ginseng	Pharmacokinetic	CYP3A4	inducer	glibenclamide, glipizide, repaglinide, pioglitazone,meglitinides, sitagliptin, saxagliptin
	Pharmacodymanic	stimulate and increase in insulin action and secretion	increased efficacy	additive effects with antidiabetics
Ginkgo biloba	Pharmacokinetic	CYP2C9,CYP2C19	inhibitor	glibenclamide,glipizide, glimepiride, nateglinide, rosiglitazone
Gymnema sylvestre	Pharmacodynamic	increase insulin secretion	beneficial effect	Glimipride
Lycium barbarum	Pharmacokinetic	CYP2C9	inhibitor	glibenclamide, glipizide, glimepiride, nateglinide, rosiglitazone
	Pharmacodynamic	improved glucose transport and insulin signalling	probably increased efficacy	additive effect with antidiabetics
Momordica chirantia	Pharmacokinetic	CYP2C9	inhibitor	glibenclamide, glipizide, glimepiride, nateglinide, rosiglitazone
	Pharmacodynamic	stimulate insulin secretions	probably increased efficacy	additive effect in general
Pleurotus pulmonarius	Pharmacodynamic	Insulin sensitisation effect	synergistic effect with	glibenclamide
St. John's wort	Pharmacokinetic	CYP1A2,CYP2D6, CYP3A4, CYP2E1,CYP2C9,CYP2C19	inducer	sulfonylurea, thiazolidinediones, meglitinides, sitagliptin, saxagliptin
Vernonia amygdalina	Pharmacodynamic	Insulin mimetic effect		Synergistic effect with metformin

CYP2D6, *andrographis paniculata*[45] (inhibitory effect) on CYP2C9 and CYP2C19, *St. John Wort*[46] (inhibitory effect) on CYP2C8, CYP2C9, or CYP3A4, while *Panax ginseng* activated CYP3A4 in vitro[47]. Charantin and sterol glucoside mixture in fruits of *momordica chirantia* and the pyrimidine nucleoside vicine in their seeds are responsible for blood glucose lowering effect[48]. Co-administration of alcoholic extract of karela with 2 or 5 mg/kg rosiglitazone reduced serum glucose levels of rats at greater extent than rosiglitazone alone[49].

Miscellaneous herbs

Traditionally many herbs like dandelion, alfa-alfa, mistletoe, cocoa, coffee, sesame oil, cinnamon, flaxseed and holy basil, sweet neem are used for treatment of diabetes. But there are limited scientific evidences to support their safety and efficacy profiles. So, caution should be taken to co-administer these herbs with conventional antidiabetics.

CONCLUSION

Herbal remedies are complex mixtures of bioactive entities which may interact with prescription drugs through pharmacodynamic or pharmacokinetic mechanism and sometimes result in serious clinical consequences. Healthcare professionals should ask their patient about the use of herbal products consumed by them and consider the possibility of herb-drug interactions. Patient counsellor and Physician should be familiar with the potential effects of commonly used herbal medications to prevent, recognise and treat potential adverse effect associated with their uses. Hence, proper reporting of

cases, careful vigilance, evidence based appraisal and constantly updated reviews of herb- drug interactions is essential to guide practitioners involved in patient care.

Pharmaceutical research must go beyond focusing on pharmacological efficacy of botanicals but also in studies that improve their effectiveness in order for humanity to fully benefit from their inherent therapeutic potentials.

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