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Review Article

Interactions Between Herbs and Antidiabetic Drugs: A Systematic Review

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- Antidiabetic drugs
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Abstract

Herbal medicine practice has gained acceptance around the globe especially in developing countries because of ease of accessibility, afford-ability, presumed safety and the notion that it is without adverse effect. This is not necessarily true as herbal medicine practices have its own challenges and limitations so Physicians need to know which herb their patients take along with antidiabetic medications as some combinations may be beneficial, harmful or have no effect. In this study, it was summarized the report available on the interaction of herbs and various classes of antidiabetic drugs whether pharmacodynamic (beneficial, harmful or no effect), pharmacokinetic (whether the herb affect absorption, distribution, metabolism or elimination of the drug) and a brief description of the study.

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INTRODUCTION

Medicinal herbs and their active ingredients are used globally and they have become an essential part of clinical medicine (Liu *et al*., 2011).

Evidence suggested that application of traditional methods including medicinal plants is the first means used therapeutically by man to address illness and medicinal plants constitute an essential component of various traditional medicine practices worldwide (Rehman *et al*., 2015).

Currently, the use of herbal medicine is on the rise globally as a result of the high prevalence of chronic illnesses such as hypertension, diabetes, obesity, anxiety, pain syndromes, as well as due to the craving for good health (Rehman *et al*., 2015).

Herbal medicines are rapidly gaining importance as a result of their natural origin and the belief that they are free from side effects. However, they are a complex mixture of organic chemicals that can have varied adverse effects due to their active ingredients (Rehman *et al*., 2015).

Most patients often make use of herbs and prescribed medications without the knowledge of their health care provider and the fact that these health care providers are less informed of herb-drug interactions and resultant adverse effects is a serious cause for concern (Nduka *et al*., 2015).

There are so many people who are using herbal medicines for the treatment of chronic diseases like diabetes mellitus. Many people often combine herbal medicines with oral antidiabetic drugs without medical advice (Rehman *et al*., 2015).

The combined use of herbs and antidiabetic drugs increases the likelihood of pharmacokinetic and pharmacodynamic interactions (Liu *et al*., 2011).

Evidence from clinical studies has shown that the combined use of herbs and antidiabetic drugs can increase or decrease the efficacy and toxicity of the drugs (Liu *et al*., 2011).

It is, therefore, imperative that clinicians, herbalists and patients understand the nature of herb and antidiabetic drug interactions, so as to prevent any adverse effects resulting from co-administration of herbs and antidiabetic drugs (Nduka *et al*., 2015).

Pharmacokinetic interactions between herbs and antidiabetic drugs may occur at the level of absorption (Islam *et al*., 2012), distribution (Brew-Daniels *et al*., 2015), metabolism (Mouid, 2016) and elimination (Wang *et al*., 2010).

Pharmacodynamic interactions include potentiation, additivism (Michael *et al*., 2010) or synergism (Badole *et al*., 2008).

Diabetes is a chronic metabolic disease characterized by high blood sugar levels over a prolonged period (Rehman *et al*., 2015).

Complications arising from inadequate or lack of treatment of the condition may be acute (e.g., diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome) or more seriously blindness, stroke, heart disease, kidney failure and foot ulcer (Rehman *et al*., 2015).

It is, therefore, important to keep blood sugar under control in patients with diabetes and this can be achieved by non-pharmacologic means (e.g., diet modification or exercise) and pharmacologic means (insulin or oral antidiabetic).

However, when herbs are co-administered with antidiabetic drugs, they may alter the pharmacokinetic or pharmacodynamic properties of the drug rendering it less effective or potentiating its activity and producing an adverse effect.

Therefore, the aim of this study was to provide an overview interaction between herb remedies and antidiabetic drug.

MATERIALS AND METHODS

The following databases were employed during literature searches, Google scholar, MEDLINE (via PubMed), Cochrane library, biological abstract (all from their inception to August, 2017). All human, animal and *in vitro* studies related to herb and antidiabetic drug interactions were included in **Table 1-5**.

Each search term yielded >100 articles and only articles related to herb antidiabetic drug interactions were selected. Only articles written in English were included Human, animal and *in vitro* studies included randomized and non-randomized controlled trial.

RESULTS AND DISCUSSION

Selected herb sulphonyurea interactions: *Azadirachta indica* (Indian Lilac, Neem tree, dogon-yaro in Hausa) from the family Meliaceae is a tropical evergreen tree. Its active extract is ferulic acid. It is used globally because of its numerous medicinal properties (Nduka *et al*., 2015).

Studies have been carried out on its antidiabetic effects and have been shown to treat lesions of pancreatic islets and normalize blood sugar in streptozocin induced diabetic rats (Nduka *et al*., 2015).

Table 1: Summary of herb-sulphonyurea interaction

Name of herb	Type of interaction with sulphonylureas		Description	References
	Pharmacodynamic	Pharmacokinetic		
Withania somnifera	Synergistic effects with Glibenclamide		Extract+Glibenclamide administered orally to insulin resistant rat model	Sudheendra (2012)
Gymnema sylvestre		↓ Absorption of glibenclamide and hence↓ bioavailabiity	Extract at 500 mg kg^{-1}+Glibenclamide at 0.5 and 0.6 mg kg^{-1} at 0.5 and 0.6 mg kg^{-1} given orally to STZ-induced diabetic rats	Dholi and Raparla (2015)
Azadirachta indica	Antagonism, ↓ activity of Glibenclamide		500 mg kg^{-1} of extract+5 mg kg^{-1} Glibenclamide orally at single dose and 10 days extract+Glibenclamide on 11th day to STZ-induced diabetic rat	Nduka *et al*. (2015)
Hypericum perforatum		↓ Half-life and AUC of gliclazide	Single dose of 80 mg gliclazide+300 mg St John's wort administered either alone or on the last day (Day 15) to 21 healthy volunteer	Xu *et al*. (2008)
Ficus glomerata	Synergistic effects with Glibenclamide		200 mg kg^{-1} of methanolic bark extract+300 and 600 µg kg^{-1} of Glibenclamide in normal and alloxan induced diabetic rats	Heroor *et al*. (2014)
Tinospora cordifolia	Synergistic effects with glibenclamide		200 mg of aqeous extract+2 mg kg^{-1} of Gliclazide administered orally to STZ-induced diabetic rats	Santhivardhan (2015)
Xiaoke pills	Enhances the hypoglycaemic effects of antidiabetics			Chan *et al*. (2016)
Swietenia macrophylia king	Additive effects with glibenclamide		250 mg kg^{-1} aqueous-methanolic extract of seed and endocarp+Glibenclamide at 5 mg kg^{-1} given orally for 3 weeks to STZ and NAD-induced diabetic rat	Kumar *et al*. (2014)
Fenugreek and coffee	Enhances the hypoglycaemic effects of glimepiride		Glimepiride at 4 mg kg^{-1}+fenugreek at 0.5 and 1 g and Glimepiride at 4 mg kg^{-1}+coffee at 0.5 and 1 g administered orally daily for 30 days to Alloxan-induced diabetic rats	Mai Abd Al-Khalik (2016)
Fenugreek	Positive interaction with glimepiride in improving the liver parameters in rats		Glimepiride (4 mg kg^{-1})+Fenugreek seed powder treatment (1 g kg^{-1}) orally once daily for 8 weeks in STZ-induced diabetic rats	Chiluka *et al*. (2015)
Allium sativum	Synergistic effects with Glibenclamide		Glibenclamide at 0.25 and 0.5 mg kg^{-1} and *A. sativum* extract at 500 mg kg^{-1} given to STZ-induced diabetic rats	Poonam *et al*. (2013)
Curcumin		↑ t 1/2, MRT and Vds of Glibenclamide	Curcumin 50 mg kg^{-1}+GL 6 mg kg^{-1} given orally once daily to diabetic rats	Devi *et al*. (2015)
Eugenia jambolana	Synergistic effects with Glibenclamide		400 mg kg^{-1} of extract+Glibenclamide at 0.6 mg kg^{-1} given orally once daily for 14 days to STZ-induced diabetic rats	Santhivardhan (2015)
Andrographis paniculata	Enhances the hypoglycaemic effects of Glimepiride	↑Cmax, AUC 0 to n, AUC total, t1/2 and MRT of Glibenclamide	Ethanolic extracts of AD (4.5 mg kg^{-1}) and Glimepiride (1 mg kg^{-1}) administered orally daily for 28 days to STZ-induced diabetic rats	Mouid (2015)
Pueraria lobata extract		↑ In AUC, MRT and ↓ in Cl and Vd of Glibenclamide	615 mg kg^{-1} of Aqueous-methanolic extract and Glibenclamide (10 mg kg^{-1}) given orally to male wister rats	Li *et al*. (2013)
Carica papaya	Initial delay in onset of action of Glimepiride followed by synergism	↓onset of action of Glimepiride	Ethanolic Leaf extract at 10 mg kg^{-1} and Glimepiride at 0.4 mg kg^{-1} given to alloxan induced diabetic rats for 7 days	Fakeye *et al*. (2007)

Table 1: Continue

Name of herb	Type of interaction with sulphonylureas: Pharmacodynamic	Pharmacokinetic	Description	References
Ginkgo biloba	Antagonism, decreases the effects of tolbutamide	↓(AUC0-∞) for tolbutamide	Tolbutamide 125 mg given to 10 male healthy volunteers before and after GBE intake at 360 mg day^{-1} for 28 days	Sugiyama *et al*. (2004)
Gymnema sylvestre	Enhances the hypoglycaemic effects of Glimepiride		Con-comitant oral administration of *G. sylvestre* extract (400 mg kg^{-1}) and Glimepiride (0.8 mg kg^{-1}) in STZ induced diabetic rats for 28 days	Kamble *et al*. (2016)
Boswellia serrata	Enhances the hypoglycemic effect of Glimepiride	↑Cmax, AUC0-n, AUCtotal, t1/2 and MRT,↓CL and VD of Glimepiride	Extract at 100 and 200 mg kg^{-1}+Glimepiride 1 mg kg^{-1} given orally to STZ-induced diabetic rats	Samala and Veeresham (2013)
Gongronema latifolium	Additive effects with Glibenclamide		Methanolic leaf extract at 400+5 mg kg^{-1} glibenclamide and 500+5 mg kg^{-1} glibenclamide given orally to Alloxan-induced diabetic rats	Gabriel *et al*. (2014)
Aloe vera	Enhances the hypoglycaemic effects of Glipizide		Ethanolic leaf extract given to STZ-induced diabetic rats daily at 20, 40 and 80 mg kg^{-1}+0.18 Glipizide for 28days and sugar checked on day 0, 7, 14, 21 and 28	Naveen *et al.* (2016)
Trigonella foenum-graecum	Prolong the effects of Gliclazide	Decreases serum conc of Gliclazide	Aqueous extract of seed powder at 30+2 mg kg^{-1} of drug to normal albino rats and Alloxan-induced diabetic rat	Satyanarayana *et al*. (2007)
Cinnamomum cassia	Enhances the effects of Glibenclamide at higher doses		Daily dosing of hydroalcoholic extract of stem bark at 285.7/666.66 and 1 mg kg^{-1} of glibenclamide to alloxan-induced diabetic rats for 21days	Bugudare *et al*. (2011)
Syzygium cumini seeds	Prolongs and sustains the effects of Gliclazide		500 mg kg^{-1} of methanolic seed extract+2 mg kg^{-1} of Gliclazide in alloxan-induced diabetic rats	Mastan *et al*. (2009)
Commiphora molmol	Synergistic effects with Glibenclamide		Extract administered at 500 and 1000 mg kg^{-1}+ Glibenclamide at 0.6 mg kg^{-1} to groups of diabetic rats	
Pleurotus pulmonarius	Synergistic effects with Glyburide		500 mg kg^{-1} of aqueous extract+Glyburide 10 mg kg^{-1} given orally daily for 28days to Alloxan induced diabetic mice	Badole *et al*. (2008)
Zingiber officinale	Enhances the hypoglycaemic effects of Glibenclamide		Crude extract of root at dose of 25-50 mg kg^{-1}+ Glibenclamide at 5 mg kg^{-1} given orally to STZ-induced diabetic rats for 4.5 h	Rai *et al*. (2012)
Cassia auriculata	Enhances the hypoglycaemic effects of Glibenclamide		Leaf extract at dose of 0.45 g kg^{-1} for 30 days to STZ-induced diabetic rat	Rai *et al*. (2012)
Allium sativum	Together with Gliclazide prevents beta cells degeneration		Aqeuos extract 250 mg kg^{-1}+Gliclazide 10 mg kg^{-1} given orally for 10 days to alloxan induced diabetic rats	Asdaq (2015)
Salvia miltiorrhiza		↑ Tolbutamide CL, ↓ AUC, ↑ Vd following single dose and ↑ T1/2 and Vd following 3 days treatment	50 or 200 mg kg^{-1} i.p given as single dose and 3 days treatment (200 mg kg^{-1}/day, i.p.)+Tolbutamide in rats	Wang *et al*. (2010)

Table 1: Continue

Name of herb	Type of interaction with sulphonylureas		Description	References
	Pharmacodynamic	Pharmacokinetic		
Prickly pear cactus	Additive effects with Glipizide		A case study of adverse effect in a 58 year old Mexican male taking the extract, 1g of Metformin twice a day and 10 mg Glipizide daily	Sobieraj and Freyer (2010)
Aloe vera	Enhances the hypoglycaemic effects of Glibenclamide		15 mL of aloe juice+glibenclamide at 5mg given to human subjects with diabetes	Rai *et al*. (2012)
Tinospora cordifolia	Enhances the hypoglycaemic effects of Gliclazide		400 mg kg^{-1} Methanolic extract+2 mg kg^{-1} Gliclazide administered orally to STZ-induced diabetic rats	Raju and Satynarayana (2014)
Gymnema sylvestre	Enhances the hypoglycaemic effects of Gliclazide	Decreases bioavailability of gliclazide	Aqeous extract at 100 and 500 mg kg^{-1}+Gliclazide 20 and 40 mg kg^{-1} given orally to STZ-induced diabetic rats	Raju *et al*. (2014)
Zingiber officinale roscoe	Inhibits the effects of Glibenclamide		Aqueous extract of root at doses of 25, 50 mg and 100 mg kg^{-1}+Glibenclamide 5 mg kg^{-1} STZ-induced diabetic rats for 4.5 h	Al-Omaria *et al*. (2012)
Boswellia serrata		↑ Absorption and decrease clearance of Glibenclamide	Extract+Glibenclamide administered to insulin resistant rat model	Sudheendra (2012)
Pongamia pinnata	Synergistic effects of Glyburide		50 mg kg^{-1} Petroleum ether extract of stem bark with 10 mg kg^{-1} Glyburide to alloxan-induced diabetic mice for 21 days	Badole and Bodhankar (2009)
Madhumehari	Additive effects with Glimepiride		Extract at 100, 200 mg kg^{-1}+Glimepiride at 4 mg kg^{-1} given orally to alloxan induced diabetic rats	Anitha and Mamatha (2013)
Pterocarpus marsupium	Additive effects with Glibenclamide		Extract at 400 mg kg^{-1}+Glibenclamide at 0.6 mg kg^{-1} given orally for 14 days to STZ-induced diabetic rats	Santhivardhan (2015)

Table 2: Summary of herb-biguanide interaction

Name of herb	Type of interaction with biguanides: Pharmacodynamic	Type of interaction with biguanides: Pharmacokinetic	Description	References
Andrographis paniculata	Auguments the effects of Metformin	↑Cmax, AUC0 to n, AUCtotal,t1/2 and MRT of metformin	Ethanolic extract administered orally twice daily for 14 days to at dose of 1.5 mg kg^{-1} to STZ –induced diabetic rat	Mouid (2015)
Albemoschus esculentus		↓ Intestinal absorption of metformin		Ezuruike and Prieto (2016)
Carica papaya	Synergistic effects with metformin		5 mg kg^{-1} low dose and 10 mg kg^{-1} high dose Ethanolic leaf extract+metformin 50 and 100 mg kg^{-1} to alloxan induced diabetic male rats for 7 days	Fakeye *et al.* (2007)
Cinnamomum cassia	No effects combined with metformin		Extract at 285.71 and 666.66 mg kg^{-1}+metformin at 300 mg kg^{-1} given orally for 21 days to alloxan induced diabetic rats	Bugudare *et al.* (2011)
Prickly pear cactus	Additive hypoglycaemic effects with metformin		A case study of adverse effect in a 58 years old Mexican male taking the extract, 1g of metformin twice a day and 10 mg glipizide daily	Sobieraj and Freyer (2010)
Vernonia amygdalina	Additive effects with metformin		80 mg kg^{-1} Aqueous extract of leaf+metformin at 50 mg kg^{-1} in ratio 1:1, 1:2 and 2:1 given orally to alloxan induced diabetic rats over 6 h	Michael *et al.* (2010)
Cassia auriculata L.	Synergistic effects with metformin	Enhanced time to Cmax, AUC	500 m kg^{-1} of aqueous extract of seed+metformin at 45 and 90 mg kg^{-1} given orally STZ-induced diabetic wister albino rats for 14 days	Elango *et al.* (2015)
Moringa oleifera	Additive effects with metformin		375, 750 and 1500 mg kg^{-1} of Ethanolic leaf extract+ metformin at 150 mg kg^{-1} to given orally to alloxan-induced diabetic rats for 28 days	Idakwoji *et al.* (2015)
Allium sativum		↑ Cmax, AUC 0-12 and T 1/2 of metformin	Extract at 500 mg kg^{-1}+metformin at 320 mg kg^{-1} given orally to rats for 8 days	Chourey *et al.* (2011)
Pleurotus pulmonarius	Synergistic effects with metformin		Aqueous extract at 500 mg kg^{-1}+metformin at 250, 500 mg kg^{-1} given orally once daily for 14 days to alloxan induced diabetic mice	Badole and Bodhankar (2008)
Abroma augusta L.	Antagonistic effects with metformin	↓ Absorption of metformin	0.5 mL of extract+0.2 mL of metformin at 500 mg kg^{-1} given orally to alloxan induced diabetic rats	Islam *et al.* (2012)
Gymnema tea	Antagonistic effects with metformin	↓ Plasma metformin concentrations	Gymnema tea+metformin at 50 mg kg^{-1} given orally to diabetic rats for 28 days	Raja *et al.* (2013)
Bridelia ferruginea		↓ Cmax, AUC, t ½, ↑ Kel, Cl, Ka, Vd, of metformin	30 mg kg^{-1} Aqueous leaf extract+metformin at 7 mg kg^{-1} given orally to sprague dawley rat at 1, 2, 4, 8, 24 h	Brew-Daniels *et al.* (2015)
Cinnamic acid derivatives	Synergistic effects with metformin		Ferulic acid 25 µM or p-coumaric acid 25 µm+metformin 20 µM to 3T3-L1 adipocytes	Prabhakar and Doble (2011)
Pongamia pinnata	Synergistic effects with metformin		50 mg kg^{-1} of petroleum ether extract of stem bark with 250 mg kg^{-1} of metformin for 21 days to alloxan-induced diabetic mice	Badole and Bodhankar (2009)
Eugenia jambolana	No effect on metformin		400 mg kg^{-1} of extract+metformin at 200 mg kg^{-1} given orally once daily for 14 days to STZ-induced diabetic rats	Santhivardhan (2015)

Table 2: Continue

	Type of interaction with biguanides			
Name of herb	Pharmacodynamic	Pharmacokinetic	Description	References
Gymnema sylvestre	Synergistic effects with metformin		20 mg kg^{-1} of extract+metformin at 200 mg kg^{-1} given orally once daily for 14 days to STZ-induced diabetic rats	Santhivardhan (2015)
St John's wort		↓ CL of metformin	Metformin 1g bd for 1 week to 20 healthy male with or without 21 days of concomitant treatment with St john's wort	Stage *et al*. (2015)
Withania somnifera	Synergistic effects with metformin	No effect on met pharmacokinetics	Extract+Glibenclamide administered orally to insulin resistant rat model	Sudheendra (2012)

Table 3: Summary of herb-insulin interaction

	Type of interaction with insulin			
Name of herb	pharmacodynamic	Pharmacokinetic	Description	References
Cinnamon	↑ Glycaemic control and insulin sensitivity		3 g single dose of cinnamon on human	Solomon and Blannin (2009)
Zingiber officinale roscoe	Enhances the hypoglycaemic effects of insulin		Aqueous root extract at doses of 25, 50 and 100 mg kg^{-1} +insulin 1.2 IU kg^{-1} i.p., to STZ-induced diabetic rats for 4.5 h	Al-Omaria *et al*. (2012)
Trigonella foenum-graecum	Enhances the effects of insulin		0.1-1 mg mL^{-1} of aqueous ethanolic extract on isolated pancreatic islet from rat	Satyanarayana *et al*. (2007)
Fenugreek	Positive interaction in improving the liver parameters in rats		Insulin (4 U kg^{-1})+Fenugreek seed powder treatment (1 g kg^{-1}) orally once daily for 8 weeks in STZ-induced diabetic rats	Chiluka *et al*. (2015)

Table 4: Summary of herb-thiazolidinediones interaction

Name of herb	Type of interaction with thiazolidinedione: Pharmacodynamic	Type of interaction with thiazolidinedione: Pharmacokinetic	Description	References
Spirulina		No change in Tmax, Cmax, AUC0-α, t1/2 and Kel of Glitazones	500 mg kg^{-1} of aqueous extract+Pioglitazone at 10 mg kg^{-1}, Rosiglitazone at 10 mg kg^{-1} given orally to insulin resistant rat model	Gupta *et al*. (2013)
Ginkgo biloba	Enhances the hypoglycaemic effect of Pioglitazone	↑ AUC, ↑ bioavailability, of Pioglitaone	120 mg day^{-1} of ginkgo given orally for 3months, thereafter single dose of 15 mg Pioglitaone+ginkgo 120 mg to 8 healthy human volunteers	Wang *et al*. (2007)
Piper cubeba Linn	Synergistic effects with Pioglitazone		400 mg kg^{-1} Methanolic extract given over 7days+Pioglitazone 10 mg kg^{-1} on day 8 to alloxan induced diabetic rats	Mouid (2016)
Curcumin	Enhances the hypoglycaemic effects of Pioglitazone	↑ AUC, ↓ CL of Pioglitazone	60 mg kg^{-1} of extract for 7 days and on the 8th day curcumin (60 mg kg^{-1} PO) followed by 1 h pre-dosing with Pioglitazone (10 mg kg^{-1} PO) to alloxan induced diabetic rats	Neerati and Kanwar (2013)
Cinnamic acid derivatives	Synergistic effects with Thiazolidinediones		Ferulic acid 25 μM or p-coumaric acid 25 μ+thiazolidinedione 20 μM to 3T3-L1 adipocytes	Prabhakar and Doble (2011)
Cassia auriculata	Enhances the hypoglycaemic effects of Thiazolidinediones		450 mg kg^{-1} of extract orally+10 mg kg^{-1} pioglitazone at 100:100, 50:50 and 75:25% for 28 days to alloxan induced diabetic rat	Grover and Bafna (2013)
Add-on preparations		↑ AUC0–1, T1/2, MRT, bioavailability of pioglitazone	Extract at 2, 10, 20 mg kg^{-1}+pioglitazone at 10 mg kg^{-1} to female Sprague-Dawley rats for 24 h	Umathe *et al*. (2008)
Pleurotus pulmonarius (FR.)	Synergistic effects with rosiglitazone		500 mg of aqueous extract+6 mg kg^{-1} of roziglitazone orally to alloxan induced diabetic mice and checked after 24 h	Badole *et al*. (2006)
Pongamia pinnata	Synergistic effect with Pioglitazone		50 mg kg^{-1} of petroleum ether extract of stem bark+50 mg kg^{-1} pioglitazone to alloxan-induced diabetic mice for 21 days	Badole and Bodhankar (2009)
Raw Radix Rehmanniae		↑ Cmax, ↓V/F, T1/2 of pioglitazone	7.8 g kg^{-1} of extract given orally daily for 14 days then thereafter 1.5 mg kg^{-1} pioglitazone on day 15 to STZ-induced diabetic rats	Shi *et al*. (2014)

Table 5: Summary of herb-glucosidase interaction

Name of herb	Type of interaction with thiazolidinedione: Pharmacodynamic	Type of interaction with thiazolidinedione: Pharmacokinetic	Description	References
Pleurotus pulmonarius	Synergistic effects with acarbose		500 mg kg^{-1} aqueous extract+50 mg kg^{-1} acarbose given once daily for 28 days to alloxan-induced diabetic mice	Badole and Bodhankar (2007)
Tea and wine	Enhances the hypoglycaemic effects of acarbose		Extract+Acarbose 25μM at ratio 25:75, 50:50 and 75:25	Ogunbadejo and Ganiyu (2015)
Anogeissus leiocarpus	Additive effects with acarbose on α-amylase, synergistic effects with acarbose on α-glucosidase		1 mg mL^{-1} aqueous extract+1 mg mL^{-1} of acarbose mixed at 50:50v/v and tested on α-amylase and α-glucosidase *in vitro*	Adefegha *et al*. (2016)

It was reported that after the administration of a single dose of azadirachta indica extract at 500 mg kg^{-1}+ Glibenclamide at 5 mg kg^{-1} and the extract for 10 days followed by Glibenclamide, there was a continuous decrease in blood glucose for 30 min.

However, antagonistic interactions were noticed in both forms of extract-Glibenclamide combinations. The induction of CYT P450 enzyme especially CYT P2C9 led to reduction in activities of Glibenclamide (Nduka *et al*., 2015).

Allium sativum (garlic) belongs to the family Amaryllidaceae. It is known for its nutritional and medicinal properties and has been employed in the treatment of diabetes (Asdaq, 2015).

Its anti-platelet property is due to its high content of adenosine and this has a major role in myocardial infarction (Asdaq, 2015).

It was reported that the hypoglycemic effect observed with combinations of glibenclamide and *Allium sativum* extract was greater than either of the drugs given alone, therefore, *Allium sativum* extract shows a synergistic effect with Glibenclamide in streptozocin induced diabetic rats (Poonam *et al*., 2013).

Zingiber officinale (ginger) belongs to the family Zingiberaceae. Its rhizome (underground stem) is used as spice and is also medicinal (Al-Omaria *et al*., 2012).

Its aqeous extract is employed traditionally in Jordan for the treatment of diabetes. Its interaction with glibenclamide was found to be beneficial in reducing blood glucose level in streptozotocin-(STZ-) induced diabetes rats. The combinations of Glibenclamide (5 mg kg^{-1} b.wt.) and ginger crude extract at doses (25 or 50 mg kg^{-1} b.wt.) significantly reduced the non-fasting blood glucose level by 26.3% ($p<0.001$) and 25.1% ($p<0.01$), respectively, after 4.5 h which was better than the reduction by glibenclamide treatment alone (7.9%) (Al-Omaria *et al*., 2012).

***Carica papaya* Linn:** Paw paw and papaya belongs to the family Cariaceae. It is abundant in tropical and subtropical countries. Active extracts include chymopapain and papain (Fakeye *et al*., 2007).

Its leaf extract is taken alongside oral antidiabetic drugs and extract gotten from unripe fruits have been used as a treatment modality by some diabetics (Fakeye *et al*., 2007).

Administration of *Carica papaya* leaf extract with glimepiride or metformin led to decrease in onset of action of glimepiride and augumentation of the effects of metformin and glimepiride in alloxan induced diabetic rats (Fakeye *et al*., 2007).

***Moringa oleifera*:** (Drumstick tree, horseradish tree) is of the family Moringaceae. The plant is known to grow fast even in dry weather.

Components of the plant (leaf, flower and seed) have been used in the treatment of diabetes (Idakwoji *et al*., 2015). It was reported that *Moringa oleifera* extract and metformin co-administration produced additive anti-hyperglycaemic and hypolipidaemic effects compared to either *Moringa oleifera* extract or Metformin alone in alloxan-induced diabetic rats and may be useful in the therapeutic management of diabetes mellitus that is associated with dyslipidaemia (Idakwoji *et al*., 2015).

Albemoschus esculentus (okra, lady's finger, gumbo) from the family malvaceae, is an essential vegetable known for its nutritional and therapeutic value and is widely used in Africa, Asia, Europe and America (Sabitha *et al*., 2011).

It contains fibers which control sugar absorption from the gastrointestinal tract. It is also used in treatment of ulcers, lung inflammation, sorethroat and irritable bowel (Sabitha *et al*., 2011).

It was reported that *Albemoschus esculentus* extract decreases intestinal absorption of metformin when co-administered with metformin in humans (Nduka *et al*., 2015).

***Vernonia amygdalina*:** Chusar-doki, bitter leaf of the family Astereaceae, is commonly used because of its therapeutic and nutritional value. It exist as a shrub of 2-5 m tall with petiolate leaves of about 6.0 mm wide (Ojiako and Nwanjo, 2006). Its use in soup making is prominent among the Ibos in South East Nigeria. The leaf is used in folk medicine as anti-malaria, purgative, antiparasitic, treatment of eczema and as antidiabetic agent (Nwanjo and Nwokoro, 2004).

It was reported that the combination of *Vernonia amygdalina* extract and metformin in ratio 1:1 and 2:1 exhibited significant ($p<0.05$) reduction in FBS with the latter ratio being higher (-38%) as against distilled water (-9.32%), metformin alone (-8.77%) and extract alone (+0.9%) in alloxan induced diabetic rats (Michael *et al*., 2010).

CONCLUSION

Herbal medicine practice has gained acceptance around the globe especially in developing countries because of easy accessibility, afford-ability and it is widely perceived as natural, safe and without adverse effect.

This is not necessarily true as herbal medicine practice have its own challenges and limitations.

From the result above it can be said that interactions exist between herb and antidiabetic drugs which may be pharmacodynamic (synergistic additive or antagonism) or pharmacokinetic.

As patients often combine herbs with antidiabetic drugs, physicians should be meticulous enough to find out which herb their patients consume with prescribed antidiabetic medications and to watch out for possible interactions.

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