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PHARMACOLOGICAL INTERACTION BETWEEN ANTI-DIABETIC DRUGS AND HERBS : AN OVERVIEW OF MECHANISM OF ACTION AND CLINICAL IMPLICATION

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Abstract

Pharmacological interaction between anti diabetic agents with herb poses a challenge for safety and efficacy for the management of diabetes. The population belief that the herbs are safe to human health as they are obtained from natural sources and contain many active constituents. Due to the great sources of medicinal agent in herbs, the various parts of herbs have been used in the treatment of diabetes mellitus. Sometime the antidiabetic active constituents of medicinal herbs and their secondary metabolites interacted with the synthetic standard drugs when combined together, action may be synergetic or antagonistic. Therefore in this review article we are emphasizing the mechanism of interaction between standard synthetic anti diabetic drug with medicinal herbs in relation to its pharmacokinetic and pharmacodynamics effect, the evidence of beneficial interaction were identified for future therapy to treat diabetes.

Key words: Anti-diabetic agent, drug- herb interaction, adverse effects, mechanism of action.

Introduction

Diabetic mellitus is commonly known as diabetes, defined as group of chronic metabolic disorders associated with high blood sugar, which slowly affect to different body parts. Diabetes is broadly classified into two types, type 1 diabetes mellitus (T1DM) or insulin-dependent diabetes mellitus (IDDM) and type 2 diabetes mellitus (T2DM) or non-insulin dependent diabetes mellitus (NIDDM). The pathophysiology behind T1DM is impaired insulin secretion from beta cell of pancreatic gland, on contrary for T2DM is the cells inability to respond to insulin or insulin resistance. It is observed that the occurrence of diabetes has been increasing on a worldwide. Data reported that, approximately 415 million adults were affected with diabetes as of 2015, the number increase in such way that the projected patient will reach about 642 million in 2040 (Rahelic, 2016), it was found that from the above report more than 70% adults living in developing countries like India and this percentage is continuously increasing annually (Rawal *et al*., 2012). Researcher reported that the global population from the last decade uses the complementary and alternative medicine (CAM) for the prevention and treatment of long term diseases such as diabetes, indicate more than 72.8% of the adults with diabetes used the herbal active constituents, dietary supplements and other CAM therapies (Chang *et al*., 2007). Ghorbani *et al*., reported that there are huge number of medicinal plants in the globe which contain anti diabetic ingredients have been consumed for the prevention and treatment of diabetes (Ghorbani, 2014). It is found that along with traditional agents and life style management, conventional agents are also being used to control diabetes mellitus. The interaction between herbs and synthetic drugs may lead to changes in pharmacological effect either produces the increase or decrease in therapeutic effect due to synergistic or antagonistic actions of antidiabetic agents. Hence in this review article we are highlighted the various reported herbs and conventional antidiabetic medicine interaction and detect their possible mechanism of action which will give new idea for future prospect.

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Herb–drug interaction and its mechanisms of action

Potential of chemical or pharmacological interactions has been observed among drugs, when two (or more) drugs administered together, which leads to change in outcome of any of the agent. Various chemical and

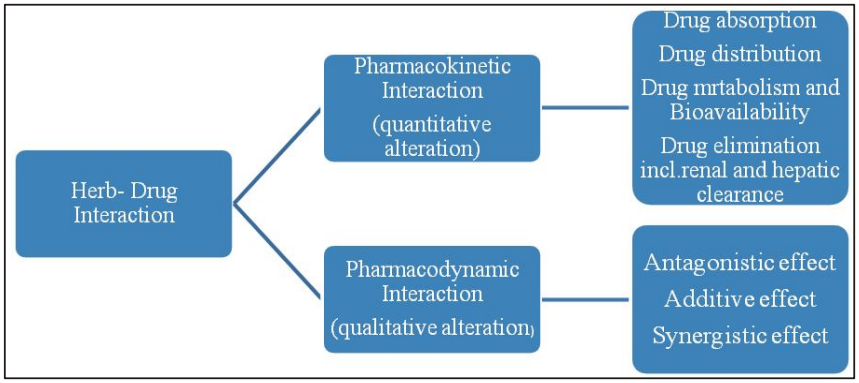

Fig. 1: Herb-Drug Interaction.

pharmacological factor such as physiochemical nature of the drug, pharmacokinetic and pharmacodynamics will determine the outcome of the interaction that is either decreases or increases the effectiveness or severity of adverse effects (Fig. 1).

In the modern era of treatment strategy of diabetes mellitus, various types of synthetic drugs are used through specific mechanism, for example sulfonylurea derivative act by binding to the sulfonylurea receptor subunit of pancreatic β-cell leads to inhibiting the K+-ATP channel to promote the release of insulin; biguanide derivatives (metformin and phenformin) acts by reducing the production of glucose from the hepatic cells, induces utilization of peripheral uptake of glucose and modify the insulin resistance; Piaglitazone, thiazolidinedione derivative, PPAR γ activator acts by stimulating the transcription of many insulin responsive gene lead to decrease in insulin resistance; the dipeptidyl peptitase-4 (DPP-4) inhibitor like vidagliptin and others act by inhibiting DPP-4 enzyme leads to degradation of incretin (glucagon like peptide -1); whereas α-glucosidase inhibitors such as acarbose and miglitol act by delaying the digestion of complex carbohydrates (Del *et al*., 2007; Krentz *et al*., 2005). It was found that combination of two or more synthetic antidiabetic drugs such as sulfonylureas with biguanides, thiazolidinedione with glucosidase inhibitors could increase the therapeutic targets in order to improve efficacy and to minimize side effects.

Commonly used Indian traditional medicine

Gymnema sylvestre Schult

Gymnema sylvestre Schult belongs to family Apocynaceae, leafs part having excellent pharmacological activity including diabetes, arthritis, hypercholestermia and snake bite in India and China (Zhu *et al*., 2008). From the structure elucidation, it was reported that the leaf extract of the *Gymnema sylvestre* contains many active components such as gymnemic acid, condurtiol-A and dihydroxygymnemic triacetate, different form of triterpinoid, saponins, including gymnemosides A-F, used as an herbal product for diabetic patients (Zhu *et al*., 2010). Literature review report found that the leaf or callus extract *Gymnema sylvestre*at the dose of 200 mg per kg body weight in oral route in alloxan induced diabetic mice, experimental result indicate hepatic glycogen concentration in plasma increase from 2.15 to 2.47 mg/g and increase in weight of pancreas and liver which specify there is increase secretion of insulin for pancreas (Ahmed, A.B. *et al*., 2010). In a another study it was found that acetone extract of *Gymnema sylvestre* at the dose of 600 mg per kg in oral route in streptozotocin induced rat, experimental finding showed after 45 days treatment there is decrease of plasma glucose level from 443 mg/L to 114 mg/L the probable mechanism of antidiabetic action due to dihydroxygmnemic triacetate the major active constituents of acetone extract regenerate more pancreatic β cells and increase the insulin level (Daisy *et al*., 2009).

Nahas and coworker reported in a clinical trial study that treatment of ethanol extract of *Gymnema sylvestre* at the dose of 200 mg for a period of 18 to 20 months, result indicates the fasting blood glucose and HbA1c levels were increased in diabetic mellitus patients (Nahas *et al*., 2009). In another clinical trial reported by Kumar *et al*., herbal extract of *Gymnema sylvestre* at the dose of 500 mg in oral route of administration for a period of three months, result found that subjects group showed reduced polyphagia, fatigue, blood glucose (fasting and postprandial) and HbA_{1C} in comparison to the control group (Kumar *et al*. 2010). Research team conducted an uncontrolled trial by using 800 mg daily dose of *Gymnema sylvestre* extract to group of 65 patients with both type (type 1 and type 2) of diabetic patients, result indicates the fasting blood sugar and HbA_{1C} levels were decreased 11% and 0.6%, respectively (Nahas, R. *et al*., 2009). Kamble and team revealed that the concomitant administration of *Gymnema sylvestre* extract with Glimepiride in streptozotocin induced diabetic rat showed no pharmacokinetic interaction (Kamble *et al*., 2016). This article also discuss the potential pharmacodynamics interactions of *Gymnema sylvestre* extract with glimperide and observed significant increases in anti hyperglycemic and anti hyperlipidemic activities (Kamble *et al*., 2016).

Momordica charantia

Momordica charantia (*M. charantia*) commonly

known as bitter melon or karela, belongs to family Cucurbitaceae, most extensively used for the treatment of diabetes mellitus in India, China, South America the Caribbean and East Africa (Leung *et al*., 2009). The seeds of *M. charantia* contains active constituents like eleostearic acid and stearic acid which accounts about 45% of total weight, along with stem and fruits contain various glycosidessuch as charantin and vicine, polypeptide-p, lipids, triterpenoids and alkaloids (Leung, L. *et al*., 2009).

Leung *et al.,* reported that methanol extract of *M. charantia* at the dose of 400 mg per kg in oral route in diabetic male ddY mice, result indicates the methanol extract of *M. charantia* exhibited significant hypoglycemic effects in diabetic male ddY due to inhibition of absorption of carbohydrates from the gastrointestinal tract (Leung *et al*., 2009). Research team reported that *M. charantia* studied in a clinical trial of type 2 diabetic patients, the outcome indicate a poor hypoglycemic effect was found might be a non-standardized extraction method (Leung *et al*., 2009). However, the juice from the fresh fruit of *M. Charantia* showed glucose-lowering effects in type 2 diabetes patients (Ahmad *et al*., 1999), but not the extract from the dried fruit (Tongia *et al*., 2004).

Research team reported that ethyl extract of *M.charantia* was studied in streptozotocin induced rats, experimental finding indicates the extract produces significant hypoglycemic effect could able to activate PPAR γ and hyperexpression of acyl CoA oxidase leads to enhanced insulin secretion in hepatic cell, active constituents of *M. charantia* known as momordicosides induces GLUT-4 transporter result more glucose uptake from the blood and decrease gluconeogenesis (Hafizur *et al*., 2011). Another published work revealed that concomitant administration of *M. charantia* extract with rosiglitazone was effective against hyperglycemia condition. However on prolonged use of this combination may lead to hypoglycemia hence further research should be studied (Nivitabishekam *et al*., 2009).

***Morus alba* L.**

Morus alba L.(*M. alba*)is known as mulberry tree, leafs of the plant have been used widely in the treatment of diabetes, hypertension, diuretic agent in Asian countries (Kim, H. *et al*., 2003), active constituents obtained from this plants are flavonoids, alkaloids (1-deoxynojirimycin) and polysaccharides. It was reported that the phyotoconstituents of *M. alba* inhibited CYP450 enzyme which leads to less antidiabetic drug-herb interaction (Kar, A. *et al*., 2015).

Tanabe *et al.,* reported the antidiabetic effect of *M. alba* extract in high sucrose fed KK-Ay mice for a period of 8 weeks, experimental finding indicates *M. alba* reduces the insulin resistance, fasting blood sugar and urinary glucose concentration in a dose dependent manner (Tanabe *et al*., 2011). In an another study lead by Park and his team that the extract of *M. alba* in Goto-kakizaki rats for type 2 diabetes study, result indicates the extract reduces post prandial blood glucose levels significantly (Park *et al.*, 2009). Kimura *et al*., exhibited the effect of food-grade mulberry powder in human subjects, result showed the powder which enriched with 1-deoxynojirimycin leads to suppression of postprandial blood glucose level (Kimura *et al*., 2007). *M. alba* extract studied in cells of adipocytes of db/db mice, result showed enhanced glucose uptake by stimulating the GLUT-4 transporter which increase the concentration from 5 µg to 45 µg per ml (Naowaboot *et al*., 2012). In a another study it was found that the extract of M. alba in db/db mice adipocytes cell produces significant induction of adipocytokines in white adipose tissue could be attributed by scavenging oxidative free radicals (Naowaboot *et al*., 2012), in addition to 1-deoxynorimycin the alkaloid of *M. alba* also remarkably inhibited the α-glucosidase which leads to antidiabetic effect (Oku *et al*., 2006).

***Trigonella foenum-graecum* L.**

Trigonella foenum-graecum L. (*T. foenum-graecum*) belongs to family Fabaceae, seed of this plant is widely used traditionally for the prevention and management of diabetes mellitus by ancient Indian, China and Egyptians (Bawadi *et al*., 2009). The major chemical constituents of the seed of *T. foenum-graecum* are polysaccharide such as galactomannan, saponin such as diosgenin, yamogenin, gitogenin, tigogenin and neotigogens, beside it also contain minor active constituents include mucilage, volatile oils and alkaloids (Mandegary *et al*., 2012). Literature review found that antidiabetic activity of seed extract of *T. foenum-graecum* studied in diabetic rats, result indicate the isolate product of the seed, 4-hydroxyisoleucine stimulate the secretion of insulin result more peripheral utilization of glucose (Mishkinsky *et al*., 1974; Vijaykumar *et al*., 2005). It was reported that the seed of *T. foenum-graecum* studied in diabetic rats, the experimental finding indicate that seed extract reduces the activities of hepatic enzymes action includes hexokinase, glucokinase, G6P and fructose 16-bisphosphatse (Vijayakumar *et al*., 2008). Report found that in a placebo treatment of seed of *T. foenum-graecum* in both diabetic and non-diabetic patients, result showed the level of insulin significantly ($p=0.03$) increased in diabetic patients than control, regulate the HbA1c levels up to 1.13 percentage (Sharma

et al., 1990; Suksomboon *et al*., 2011).

Barringtonia racemosa

Barringtonia racemosa (*B. racemosa*) is commonly known as putat, geographically distributed west costal belt of India, Bangladesh and Sri Lanka with diverse ethno botanical use such asdiabetes, arthritis, hypertension, cancer and antimicrobial agents. The decoction of bark and leave was used for snake bites, rat poisoning, boils and gastric ulcers (Patil *et al*., 2011). The chemical constituents of *B. racemosa* was found to be contain terpenoids such as di, tri terpenoids along with it contain active components known as barringtonia and bartogenic acid (Gowri *et al*., 2009). Literature review found that hexane, ethanol and methanol extract of *B. racemosa* and bartogenic acid in the concentration range from 0.02 to 0.2 µg per ml was studied by using *in vitro* enzymatic assay, experimental finding indicates inhibition of intestinal α-glucosidase. In addition to methanol extract of *B. racemosa* studied in vivo maltose treated rat, result showed increase insulin secretion (Gowri *et al*., 2007).

***Syzygium cumini* (L.) Skeels**

Syzygiumcumini (L.) Skeels (*S. cumini*), is commonly known as skeels, distributed to India, China, brazil and Indonesia with wide ethnopharmacological use especially in the management of diabetes mellitus (Gowri *et al*., 2007; Oliveira *et al*., 2005). The major constituents of *S. cumini* was found to be anthocyanins, glucoside, ellagic acid, isoquercetin, kaemferol and myrecetinetc, play a vital role in prevention and treatment of diabetes mellitus. Literature report found that extract of *S. cumini* showed reductions in blood glucose, post prandial glucose, cholesterol and free fatty acid (Prince *et al*., 2004). Shinde *et al.*, reported that *S. cumini* extract in diabetic rat showed hypoglycemic activity by inhibiting the α-glucosidase, hence decreases the blood sugar in diabetic rat (Shinde *et al*., 2008). Research team investigated that extract *of S. cumini* in diabetic animal, result found that glucokinase and fructokinase enzyme activity in hepatic cell reduces significantly, therefore control the glucose metabolism (Achrekar *et al*., 1991). Teixeira and coworker reported about *S. cumini* extract in diabetic patients, result found that erythrocytes collected from both diabetic and non-diabetic patients showed reduction of activity of adenosine deaminase. However, favorable results have not been produced by two double-blind, randomized clinical trial, it was found that there was no significant reduction of fasting blood glucose levels when compared with tea consumption in diabetic patients (Teixeira *et al*., 2000). Chaudhari *et al.*, reported that aqueous extract of *S. cumini* seeds in combination with Glipizide showed possible drug interaction by increasing the AUC of drug through inhibition of CYP3A using *in-vitro* analysis (Chaudhari *et al*., 2019).

Tinospora cordifolia

Tinospora cordifolia (*T. cordifolia*) is commonly known as guduchi, belongs to family Menispermaceae, geographically distributed to India, Myanmar and Sri Lanka, having diverse ethnopharmacological uses include diabetes, antipyretic, anti-inflammatory, immunomodulatory and gastric pain (Grover *et al*., 2002; Sengupta *et al*., 2012). The chemical constituents of *T. cordifolia* are alkaloids, diterpenoid lactone, glycosides, steroids and polysaccharides.

Research team investigated the antidiabetic activity of *T.c ordifolia* extract of aqueous and alcoholic at a dose of 400 mg per kg using diabetic rat, result found that *T.cordifolia* extract modulate the glucose tolerance and diabetic neuropathy (Nadia *et al*., 2012). Patel *et al.*, investigated antidiabetic activity of 70% ethanol extract of *T. cordifolia* at the oral dose of 100 and 200 mg per kg. in diabetic rat, result found that after 14 days of treatment of extract there was significant reduction of blood glucose levels in both group (Patel *et al*., 2011). Further the ethanol extract at the dose of 250 mg per kg prevent the chance of diabetic retinopathy in rat model (Agrawal *et al*., 2012). The probable mechanism of antidiabetic activity of different extract of *T. cordifolia* is decrease the production of thiobarbituric acid reactive substance by improving the oxidative stress, modify the metabolism of carbohydrate, lead to inhibition of enzyme activity of G6P and fructose 1,6 diphosphate result reduction of gluconeogenesis (Sangeetha *et al*., 2011), increases the secretion of insulin and inhibit the enzyme activity of α-glucosidase accumulates a potential antidiabetic agent (Chougale *et al*., 2009). Sahu *et al*., has revealed the pharmacokinetic interaction on concomitant administration of aqueous-alcoholic extract of *T. cordifolia* with glibenclamide, result found that *T. cordifolia* extract inhibited the effect of CYP2C9 with IC50 less than 0.1 mg/ml which leads to prolong bioavailability of glibenclamide (Sahu *et al*., 2018).

Ocimum basilicum

Ocimum basilicum (*O. basilicum*) *is commonly known as* basil or sweet basil, a culinary herb belongs to family Lamiaceae, geographically distributed in Southern Asian countries and India with diverse ethno botanical use like potent antiseptic, mild sedative effect, upper respiratory tract infection, antiviral activity and diabetes (Bora *et al*., 2011). The active chemical constituents of *O. basilicum* was found to be apigenin, ursolic acid and linalool having wide medicinal value (Chiang *et al*., 2005).

The anti diabetic activity of aqueous extract of Basil was investigated in rat model, result found that the extract produce antidiabetic activity by inhibiting the enzyme activity of sucrose, pancreatic α-amylase therefore reduces the blood sugar level (El-Beshbishy *et al*., 2012). Agrawal *et al*., investigated clinical trial of leaf extract of basil in diabetes patients of India, outcome found that leaf extract showed reduction of fasting blood glucose by 21 mg/dl and postprandial blood glucose fell by 15.8 mg/dl, suggest dietary therapy of basil can be useful for the managing mild to moderate type 2 diabetes (Agrawal *et al*., 1996). The antidiabetic activity of Basil was investigated in hypercholesteromic rat, result found that the plant extract reduces the diabetic associated co morbidities by increasing the lipid metabolism (Harnafi *et al*., 2009). In addition to ethanol extract of basil *in vitro* cell line study using human macrophages, there is decrease in cholesterol synthesis (Bravo *et al*., 2008).

Berberis aristata

Berberis aristata (*B. aristata*) is commonly known as Zarshik belongs to family Berberidaceae, distributed in many parts of Asian countries, having huge ethnopharmacological use since from ancient times for the improvement of hepatic and cardiovascular function (Potdar *et al*., 2012). It was found that the root of the *B. aristata* contain major constituents like berberine, berbamine and palmatine (Singh *et al*., 2009). Literature review found that the root extract *B.aristata* have potential ability for regulating glucose balance by decreasing the gluconeogenesis and oxidative stress, in this contest the antidiabetic activity of extract was investigated in diabetic rat, result found that it showed hypoglycemic activity by decreasing the G6P and increasing the glucokinase activity (Singh *et al*., 2009). It was reported in clinical trial that the treatment of 90 days with *B. aristata* extract showed significant reduction of HbA1c and decrease insulin resistance alongwith the reduction of low density lipoprotein and triglycerides, suggest antidiabetic activity (Di Pierro *et al*., 2012). In another study conducted by Bahadur *et al* revealed that co-administration of *B.aristata* with glimperide andgliclazide showed significant low inhibitory effect on metabolizing enzyme (Bahadur *et al*., 2017).

Conclusion

In conclusion we have explored the effects of drug interaction between anti diabetic agent and herbal formulation. It was found from the above discussion that most of the herbs use in the management of diabetes having lack of safety and standard of manufacture. The prospective randomized clinical trials are require for assessing antidiabetic drug-herb interaction in a urgent basis for getting effective dosage for the diabetes.

References

Ahmed, A.B., A.S. Rao and M.V. Rao (2010). *In vitro* callus and *in vivo* leaf extract of Gymnema sylvestre stimulate β-cells regeneration and anti-diabetic activity in Wistar rats. *Phytomedicine*., **2010 Nov 1, 17(13):** 1033-9.

Ahmad, N., M.R. Hassan, H. Halder and K.S. Bennoor (1999). Effect of *Momordica charantia* (Karolla) extracts on fasting and postprandial serum glucose levels in NIDDM patients. *Bangladesh Medical Research Council bulletin*., **1:** 11-13.

Achrekar, S., G.S. Kaklij, M.S. Pote and S.M. Kelkar (1991). Hypoglycemic activity of *Eugenia jambolana* and *Ficus bengalensis*: mechanism of action. *In Vivo*., **2:** 143-147.

Agrawal, S.S., S. Naqvi, S.K. Gupta and S. Srivastava (2012). Prevention and management of diabetic retinopathy in STZ diabetic rats by *Tinospora cordifolia* and its molecular mechanisms. *Food and Chemical Toxicology*., **9:** 3126-3132.

Agrawal, P., V. Rai and R.B. Singh (1996). Randomized placebo-controlled, single blind trial of holy basil leaves in patients with noninsulin-dependent diabetes mellitus. *International Journal of Clinical Pharmacology and Therapeutics*., **9:** 406-409.

Bawadi, H.A., S.N. Maghaydah, R.F. Tayyem and R.F. Tayyem (2009). The postprandial hypoglycemic activity of fenugreek seed and seeds' extract in type 2 diabetics: a pilot study. *Pharmacognosy Magazine*., **18:** 134-138.

Broca, C., R. Gross and P. Petit *et al*., (1999). 4-hydroxyisoleucine: experimental evidence of its insulinotropic and antidiabetic properties. *American Journal of Physiology*., **4:** 617-623.

Broca, C., V. Breil and C. Cruciani-Guglielmacci *et al*., (2004). Insulinotropic agent ID-1101 (4-hydroxyisoleucine) activates insulin signaling in rat. *American Journal of Physiology*., **3:** 463-471.

Berić, T., B. Nikolić, J. Stanojević, B. Vuković-Gačić and J. Knežević-Vukčević (2008). Protective effect of basil (*Ocimum basilicum* L.) against oxidative DNA damage and mutagenesis. *Food and Chemical Toxicology*., **2:** 724-732.

Bora, K.S., S. Arora and R. Shri (2011). Role of *Ocimum basilicum* L. in prevention of ischemia and reperfusion-induced cerebral damage and motor dysfunctions in mice brain. *Journal of Ethnopharmacology*., **3:** 1360-1365.

Bravo, E., S. Amrani, M. Aziz, H. Harnafi and M. Napolitano (2008). Ocimumbasilicum ethanolic extract decreases cholesterol synthesis and lipid accumulation in human macrophages. *Fitoterapia*., **7-8:** 515-523.

Bahadur, S., P.K. Mukherjee, S. Pandit, S.M. Ahmmed and A. Kar (2017). Herb-drug interaction potential of *Berberis aristata* through cytochrome P450 inhibition assay. *Synergy*., **4:** 1-7.

Bunyapraphatsara, N., S. Yongchaiyudha, V. Rungpitarangsi and O. Chokechaijaroenporn (1996). Antidiabetic activity of *Aloe vera* L. juice II. Clinical trial in diabetes mellitus patients in combination with glibenclamide. *Phytomed. Int. J. Phytother. Phytopharmacol.*, **3:** 245-8.

Chang, H.Y., M. Wallis and E. Tiralongo (2007). Use of complementary and alternative medicine among people living with diabetes: literature review. *J. Adv. Nurs.*, 4307-19.

Chougale, A.D., V.A. Ghadyale, S.N. Panaskar and A.U. Arvindekar (2009). Alpha glucosidase inhibition by stem extract of *Tinospora cordifolia*. *Journal of Enzyme Inhibition and Medicinal Chemistry*., **4:** 998-1001.

Chiang, L.C., L.T. Ng, P.W. Cheng, W. Chiang and C.C. Lin (2005). Antiviral activities of extracts and selected pure constituents of *Ocimum basilicum*. *Clinical and Experimental Pharmacology and Physiology*., **10:** 811-816.

Chaudhari, S., S. Zambad and M. Ali (2019). Pharmacokinetic and Pharmacodynamics Interaction between *Syzygium cumini* and Glipizide: Role of Cytochrome P450 Enzyme. *Indian Journal of Pharmaceutical Education and Research*., **53(3):** S273-S279.

Del Prato, S., C. Bianchi and P. Marchetti (2007). Beta-cell function and anti-diabetic pharmacotherapy. *Diabetes Metab Res Rev.*, **7:** 518-27.

Daisy, P., J. Eliza and K.A.M. Mohamed Farook (2009). A novel dihydroxy gymnemic triacetate isolated from *Gymnema sylvestre* possessing normoglycemic and hypolipidemic activity on STZ-induced diabetic rats. *Journal of Ethnopharmacology*., **2:** 339-344.

Devi, B.A., N. Kamalakkannan and P.S.M. Prince (2003). Supplementation of fenugreek leaves to diabetic rats. Effect on carbohydrate metabolic enzymes in diabetic liver and kidney. *Phytotherapy Research.*, **10:** 1231-1233.

Di Pierro, F., N. Villanova, F. Agostini, R. Marzocchi, V. Soverini and G. Marchesini (2012). Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control. *Diabetes, Metabolic Syndrome and Obesity*., **5:** 213-217.

El-Beshbishy, H. and S. Bahashwan (2012). Hypoglycemic effect of basil (*Ocimum basilicum*) aqueous extract is mediated through inhibition of alpha-glucosidase and alpha-amylase activities: an *in vitro* study. *Toxicology and Industrial Health.*, **28(1):** 42-50.

Ghorbani, A. (2014). Clinical and experimental studies on polyherbal formulations for diabetes: current status and future prospective. *J. Integr. Med*., **12(4):** 336-45.

Grover, J.K., S. Yadav and V. Vats (2002). Medicinal plants of India with anti-diabetic potential. *Journal of Ethnopharmacology*., **1:** 81-100.

Gowri, P.M., S.V. Radhakrishnan, S.J. Basha, A.V.S. Sarma and J. Madhusudana Rao (2009). Oleanane-type isomeric triterpenoids from *Barringtonia racemosa*. *Journal of Natural Products.*, **4:** 791-795.

Gowri, P.M., A.K. Tiwari, A.Z. Ali and J.M. Rao (2007). Inhibition of α-glucosidase and amylase by bartogenic acid isolated from *Barringtonia racemosa* Roxb. seeds. *Phytotherapy Research.*, **8:** 796-799.

Grover, J.K., V. Vats and S.S. Rathi (2007). Anti-hyperglycemic effect of *Eugenia jambolana* and *Tinospora cordifolia* in experimental diabetes and their effects on key metabolic enzymes involved in carbohydrate metabolism. *Journal of Ethnopharmacology.*, **3:** 461-470.

Grover, J.K., S. Yadav and V. Vats (2002). Medicinal plants of India with anti-diabetic potential. *Journal of Ethnopharmacology.*, **1:** 81-100.

Gilani, A.H., K.H. Janbaz and N. Aziz *et al*., (1999). Possible mechanism of selective inotropic activity of the n-butanolic fraction from *Berberis aristata* fruit. *General Pharmacology*., **5:** 407-414.

Hermann, L.S., G. Lindberg, U. Lindblad and A. Melander (2002). Efficacy, effectiveness and safety of sulphonylurea-metformin combination therapy in patients with type 2 diabetes. *Diabetes. Obes. Metab.*, **5:** 296-304.

Hafizur, R.M., N. Kabir and S. Chishti (2011). Modulation of pancreatic β-cells in neonatally streptozotocin-induced type 2 diabetic rats by the ethanolic extract of *Momordica charantia* fruit pulp. *Natural Product Research*., **4:** 353-367.

Harnafi, H., M. Aziz and S. Amrani (2009). Sweet basil (*Ocimum basilicum* L.) improves lipid metabolism in hypercholesterolemic rats. *e-SPEN*., **4:** 181-186.

Jovanovic, L., D.R. Hassman, B. Gooch, R. Jain, S. Greco, N. Khutoryansky and P.M. Hale (2004). Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone. *Diabetes. Res. Clin. Pract.*, **2:** 127-34.

Krentz, A.J. and C.J. Bailey (2005). Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs.*, **3:** 385-411.

Kumar, S.N., U.V. Mani and I. Mani (2010). An open label study on the supplementation of *Gymnema sylvestre* in type 2 diabetics. *Journal of Dietary Supplements*., **3:** 273-282.

Kim, H., M.H. Jang and M.C. Shin *et al*., (2003). *Folium mori* increases cell proliferation and neuropeptide Y expression in dentate gyrus of streptozotocin-induced diabetic rats. *Biological and Pharmaceutical Bulletin*., **4:** 434-437.

Kimura, T., K. Nakagawa and H. Kubota *et al*., (2007). Food-grade mulberry powder enriched with 1-deoxynojirimycin suppresses the elevation of postprandial blood glucose in humans. *Journal of Agricultural and Food Chemistry*., **14:** 5869-5874.

Kar, A., P.K. Mukherjee, S. Saha, S. Bahadur, S.K. Ahmmed and S. Pandit (2015). Possible herb-drug interaction of *Morus alba* L.-a potential anti-diabetic plant from Indian Traditional medicine.

Kamble, B., A. Gupta, I. Moothedath, L. Khatal, S. Janrao, A. Jadhav and B. Duraiswamy (2016). Effects of *Gymnema sylvestre* extract on the pharmacokinetics and pharmacodynamics of glimepiride in streptozotocin

induced diabetic rats. *Chemico-biological interactions.*, **245:** 30-38.

Leung, L., R. Birtwhistle, J. Kotecha, S. Hannah and S. Cuthbertson (2009). Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review. *British Journal of Nutrition*., **12:** 1703-1708.

Mandegary, A., M. Pournamdari and F. Sharififar *et al*., (2012). Alkaloid and flavonoid rich fractions of fenugreek seeds (*Trigonella foenum-graecum* L.) with antinociceptive and anti-inflammatory effects. *Food and Chemical Toxicology*., **7:** 2503-2507.

Mishkinsky, J.S., A. Goldschmied and B. Joseph (1974). Hypoglycaemic effect of *Trigonella foenum graecum* and *Lupinus termis* (Leguminosae) seeds and their major alkaloids in alloxan diabetic and normal rats. *Archives Internationales de Pharmacodynamie et de Therapie.,* **1:** 27-37.

Madar, Z., R. Abel, S. Samish and J. Arad (1988). Glucose-lowering effect of fenugreek in non-insulin dependent diabetics. *European Journal of Clinical Nutrition*., **1:** 51-54.

Mathern, J.R., S.K. Raatz, W. Thomas and J.L. Slavin (2009). Effect of fenugreek fiber on satiety, blood glucose and insulin response and energy intake in obese subjects. *Phytotherapy Research*., **11:** 1543-1548.

Nahas, R. and M. Moher (2009). Complementary and alternative medicine for the treatment of type 2 diabetes. *Canadian Family Physician*., **6:** 591-596.

Naowaboot, J., C.H. Chung and P. Pannangpetch *et al*., (2012). Mulberry leaf extract increases adiponectin in murine 3T3-L1 adipocytes. *Nutrition Research*., **1:** 39-44.

Naowaboot, J., P. Pannangpetch and V. Kukongviriyapan *et al*., (2012). Mulberry leaf extract stimulates glucose uptake and GLUT4 translocation in rat adipocytes. *The American Journal of Chinese Medicine*., **1:** 163-175.

Nadig, P.D., R.R. Revankar, S.M. Dethe, S.B. Narayanswamy and M.A. Aliyar (2012). Effect of *Tinospora cordifolia* on experimental diabetic neuropathy. *Indian Journal of Pharmacology*., **5:** 580-583.

Nivitabishekam, S.N., M. Asad and V.S. Prasad (2009). Pharmacodynamic interaction of *Momordica charantia* with rosiglitazone in rats. *Chemico-Biological Interactions.*, **177(3):** 247-253.

Oku, T., M. Yamada, M. Nakamura, N. Sadamori and S. Nakamura (2006). Inhibitory effects of extractives from leaves of *Morus alba* on human and rat small intestinal disaccharidase activity. *British Journal of Nutrition*., **5:** 933-938.

Oliveira, A.C.P., D.C. Endringer, L.A.S. Amorim, M.D.G.L. Brandão and M.M. Coelho (2005). Effect of the extracts and fractions of *Baccharis trimera* and *Syzygium cumini* on glycaemia of diabetic and non-diabetic mice. *Journal of Ethnopharmacology*., **3:** 465-469.

Park, S.C., H.S. Yoo and C. Park *et al*., (2009). Induction of apoptosis in human lung carcinoma cells by the water extract of *Panax notoginseng* is associated with the activation of caspase-3 through downregulation of Akt. *International Journal of Oncology*., **1:** 121- 127.

Pang, X., L. Kang and H. Yu *et al*., (2012). Rapid isolation of new furostanol saponins from fenugreek seeds based on ultra-performance liquid chromatography coupled with a hybrid quadrupole time-of-flight tandem mass spectrometry. *J. of Separation Science*., **12:** 1538-1550.

Patil, K.R., C.R. Patil, R.B. Jadhav, V.K. Mahajan, P.R. Patil and P.S. Gaikwad (2011). Anti-arthritic activity of bartogenic acid isolated from fruits of *Barringtonia racemosa* Roxb. (Lecythidaceae) *Evidence-based Complementary and Alternative Medicine*., 2011785245.

Prince, P.S.M., N. Kamalakkannan and V.P. Menon (2004). Antidiabetic and antihyperlipidaemic effect of alcoholic *Syzigium cumini* seeds in alloxan induced diabetic albino rats. *Journal of Ethnopharmacology*., **2-3:** 209-213.

Prince, P.S.M., V.P. Menon and L. Pari (1998). Hypoglycaemic activity of *Syzigium cumini* seeds: effect on lipid peroxidation in alloxan diabetic rats. *Journal of Ethnopharmacology*., **1:** 1-7.

Patel, M.B. and S. Mishra (2011). Hypoglycemic activity of alkaloidal fraction of *Tinospora cordifolia*. *Phytomedicine*., **12:** 1045-1052.

Potdar, D., R.R. Hirwani and S. Dhulap (2012). Phyto-chemical and pharmacological applications of *Berberis aristata*. *Fitoterapia*., **5:** 817-830.

Qi, L.W., E.H. Liu, C. Chu, Y.B. Peng, H.X. Cai and P. Li (2010). Anti-diabetic agents from natural products—an update from 2004 to 2009. *Curr Top Med Chem*., **10(4):** 434-57.

Rahelic, D. (2016). 7th edition of Idf diabetes Atlas-call for immediate action. *LijecVjesn.*, **(1-2):** 57-8.

Rawal, L.B., R.J. Tapp, E.D. Williams, C. Chan, S. Yasin and B. Oldenburg (2012). Prevention of type 2 diabetes and its complications in developing countries: a review. *Int. J. Behav. Med*., **2:** 121-33.

Samad, A., M.S. Shams, Z. Ullah, M. Wais, I. Nazish, Y. Sultana and M. Aqil (2009). Status of herbal medicines in the treatment of diabetes: a review. *Curr Diabetes Rev*., **2:** 102-11.

Sharma, R.D., T.C. Raghuram and N.S. Rao (1990). Effect of fenugreek seeds on blood glucose and serum lipids in Type I diabetes. *European J. of Clinical Nutrition*., **4:** 301-306

Suksomboon, N., N. Poolsup, S. Boonkaew and C.C. Suthisisang (2011). Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes. *Journal of Ethnopharmacology*., **3:** 1328-1333.

Shinde, J., T. Taldone and M. Barletta *et al*., (2008). Alpha-Glucosidase inhibitory activity of *Syzygium cumini* (Linn.) Skeels seed kernel *in vitro* and in Goto-Kakizaki (GK) rats. *Carbohydrate Research*., **7:** 1278-1281.

Sangeetha, M.K., H.R. Balaji Raghavendran, V. Gayathri and H.R. Vasanthi (2011). *Tinospora cordifolia* attenuates oxidative stress and distorted carbohydrate metabolism in experimentally induced type 2 diabetes in rats. *Journal of Natural Medicines*., **3-4:** 544-550.

Singh, J. and P. Kakkar (2009). Antihyperglycemic and antioxidant effect of *Berberis aristata* root extract and its role in regulating carbohydrate metabolism in diabetic rats. *Journal of Ethnopharmacology*., **1:** 22-26.

Sahu, R., T. Ahmed, R. Sangana, R. Punde and B.B. Subudhi (2018). Effect of *Tinospora cordifolia* aqua-alcoholic extract on pharmacokinetic of Glibenclamide in rat: An herb-drug interaction study. *Journal of pharmaceutical and biomedical analysis.*, **151:** 310-316.

Turner, R.C., C.A. Cull, V. Frighi and R.R. Holman (1999). Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *J.A.M.A.*, **21:** 2005-12.

Tongia, A., S.K. Tongia and M. Dave (2004). Phytochemical determination and extraction of *Momordica charantia* fruit and its hypoglycemic potentiation of oral hypoglycemic drugs in diabetes mellitus (NIDDM) *Indian Journal of Physiology and Pharmacology*., **2:** 241-244.

Tanabe, K., S. Nakamura, K. Omagari and T. Oku (2011). Repeated ingestion of the leaf extract from *Morus alba* reduces insulin resistance in KK-Ay mice. *Nutrition Research*., **11:** 848-854.

Teixeira, C.C., F.D. Fuchs, L.S. Weinert and J. Esteves (2006). The efficacy of folk medicines in the management of type 2 diabetes mellitus: results of a randomized controlled trial of *Syzygium cumini* (L.) Skeels. *Journal of Clinical Pharmacy and Therapeutics*., **1:** 1-5.

Teixeira, C.C., C.A. Rava and P. Mallman Da Silva *et al*., (2000). Absence of antihyperglycemic effect of jambolan in experimental and clinical models. *Journal of Ethnopharmacology.*, **1-2:** 343-347.

Vijayakumar, M.V., S. Singh, R.R. Chhipa and M.K. Bhat (2005). The hypoglycaemic activity of fenugreek seed extract is mediated through the stimulation of an insulin signalling pathway. *British Journal of Pharmacology*., **1:** 41-48.

Vijayakumar, M.V. and M.K. Bhat (2008). Hypoglycemic effect of a novel dialysed fenugreek seeds extract is sustainable and is mediated, in part, by the activation of hepatic enzymes. *Phytotherapy Research*., **4:** 500-505.

Welihinda, J., E.H. Karunanayake, M.H.R. Sheriff and K.S.A. Jayasinghe (1986). Effect of *Momordica charantia* on the glucose tolerance in maturity onset diabetes. *Journal of Ethnopharmacology*., **3:** 277-282.

Zhu, X.M., P. Xie, Y.T. Di, S.L. Peng, L.S. Ding and M.K. Wang (2008). Two new triterpenoid saponins from *Gymnema sylvestre*. *Journal of Integrative Plant Biology*., **5:** 589-592.