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Potential Herb Drug Interactions in antidiabetic Drugs and Herbal Drugs

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Abstract

Home grown items are considered as more secure and patients are frequently blend it with the oral Antidiabetic tranquilizes in the treatment diabetes. But various reports state that merging of different parts of herbs and drugs are not safe. A few combinations might be valuable and some might be not safe. So before taking any natural herbs with oral Antidiabetic drugs, patient ought to counsel restorative specialist. In this paper we are abridging the reports accessible on the cooperation of home grown solutions for a portion of the oral hypoglycemic operators and ordering the result of the blend is significant and risky. An endeavor has been made to outline the collaboration of natural solution to that of the antidiabetic drugs.

Keywords: Diabetes Mellitus, Oral hypoglycemic drugs, Herbal drugs and Herb drug interactions.

1. Introduction

Diabetes Mellitus (DM) is a noteworthy unending perilous issue, in which homeostasis of starch and lipid digestion is inappropriately directed by the pancreatic hormone, insulin; bringing about an expanded blood glucose level. [1] The effects of diabetes mellitus consolidate whole deal hurt, brokenness and disillusionment of various organs. [2]

Diabetes was first portrayed in Egyptian culture in fifteenth century as "excessively extraordinary exhausting of pee". Hindu doctors in the Ayurveda built up the primary clinical test for diabetes. They saw that flies and ants were pulled in to the sweet tasting pee of individuals distressed with specific maladies. Indian doctors around a similar time recognized the sickness and characterized it as 'madhumeha' or nectar pee as they saw that the pee would draw in ants. [3]

The worldwide utilization of another (or) elective pharmaceutical (CAM) for the administration of maladies, for example, diabetes has quickly expanded in the course of the most recent decade. It is accounted for that up to 72.8% of individuals with diabetes utilized natural drug, dietary supplements and other CAM treatments. [4]

As well customary home grown home cures are fast monetary development since they are seen to be free of reactions and for the most part perceived as sheltered because of their regular root. Because of high costs and potential symptoms of manufactured medications, individuals relying upon additional on home grown medications and this pattern are developing, in creating nations as well as in created nations as well. A huge number of individuals today utilize herbs either as sustenance or as pharmaceutical alongside remedy and non physician recommended drugs. This expansion in the utilization of herbs is a worldwide marvel. WHO `estimates, interest for therapeutic plants continuously 2050 would be ~US $5 trillion. Albeit thought about characteristic and protected, a significant number of these herbs can connect with different drugs, causing either possibly risky symptoms and additionally lessened advantages from the solution.[5] The

likelihood of herb– still joint efforts can be higher than drug– quiet relationship, as most home created healing thing (even single-herb things) 1contains blends of pharmacologically intense constituents.[6] The utilization of medical treatment is generally not administered by professionals bringing about expanded mischief to patients, particularly on the off chance that they are utilizing home grown and solution 2 drugs that have inactive co-operations.[7] The practical medicine for diabetes mellitus are insulin implantation and hypoglycemic administrators, anyway these blends have a couple of unpleasant effects and have no results for diabetes complexities in whole deal. Concerning human extended finding out about this disorder and its complexities, it is vital to find ground-breaking blends with cut down side effects in treating diabetes(Show in Table 1).[8] Compounds with lower side effects in treating diabetes. Medicinal plants are good sources as alternative or enhance treatments for this and other diseases. [9,10] A considerable amount of restorative plants are accepted to have Antidiabetic properties and also used to oversee diabetes.[11,12] An extending number of helpful plants are being used to treat diabetes and its related conditions. The current NAPRALERT database records in excess of 1300 sorts of plants addressing more than 750 genera inside 190 families, covering lower plants, for instance, green development and parasites to an extensive variety of higher plants. A noteworthy number of these plants have been used ethno-pharmacologically in standard pharmaceutical as antidiabetics, particularly for T2DM.[13,14] Albeit a large number of these plants have been considered tentatively to approve their physiological action, the substance and pharmacological properties supporting the Antidiabetic movement is slow all around contemplated. In any case, a substantial number of conceivably bio-dynamic atoms have been disengaged and distinguished, several other things which incorporate system of different things starches, alkaloids, glycopeptides, terpenoids, peptides, amines, steroids, flavonoids, lipids, coumarins, sulfur mixes and inorganic particles.[13] Precedents of regular herbs and dietary supplements that have been utilized to treat diabetes incorporate *Momordica charantia, Trigonella foenum-graceum, Gymnema-sylvestre*, *Azadira chtaindica*, l-carnitine, vanadium, chromium and vitamin E. Proposed systems' of activity fundamental the antidiabetic impacts of these mixes incorporate direct consequences for insulin emission, enactment of glycogenesis and hepatic glycolysis, adrenomimeticism, pancreatic beta cell potassium channel blocker action, cAMP initiation, and tweak of glucose assimilation from the digestive system.[15,16]

Table 1: Occurrence of macro vascular complications in type 2 diabetes mellitus

Mortality
• Death rate > 2-fold
• Fatal ischaemic heart disease 2–4-fold
• Fatal stroke 2–3-fold
Morbidity
• Ischaemic heart disease 2–3-fold
• Cerebrovascular disease > 2-fold
• Peripheral vascular disease 2–3-fold
• Hypertension 30–50%

Key: = increment occurrence contrasted and non-diabetic populace; a = level of patients at determination, reliant on demonstrative criteria [17]

Table 2: Classification of Antidiabetic drugs

Class	Examples	Main mode of action
Sulphonyl ureas	Glibenclamide, Gliclazide, Chlorpropamide, Glimepiride, Glipizide, Repaglinide, Nateglinide, Gliquidone, Tolbutamide	Stimulate insulin secretion (typically acting 6–24 hour)
Meglitinides[a]	Nateglinide, Repaglinide	Stimulate insulin secretion (rapid-onset, short-acting < 6 hour)
Biguanide Thiazolidinediones[b]	Pioglitazone, Rosiglitazone, Metformin,	Improve insulin action Increase insulin action (PPARγ) agonists
Alpha-glucosidase inhibitor	Acarbose	Slow rate of carbohydrate digestion

Key: [a] = additionally named 'prandial insulin releasers'; [b] = likewise named 'glitazones'[17]

2. Anti Diabetic Drug-Herb Drug Interactions

Presently multi day, similar to medicate tranquilize cooperation and nourishment sedate communications, herb-tranquilize collaborations are ending up staggeringly normal. It is realized that a huge number of patients are taking natural and regular medications simultaneously, frequently without the information of their doctors and lifting the capability of herb-tranquilize collaborations. The matter of herb-medicate associations seems substantial over the act of natural pharmaceutical. Natural treatments are the plants based items that are utilized to regard as herbs, home grown supplements, biomedicines or botanicals. At the point when home grown medications and customary medications are utilized with, they can team up in body, causing changes in the way the herbs and also the drugs work. Such changes are insinuated as herb-sedate correspondences. There are few herb medicate communications revealed up till now however they can't be

in secret as patients who don't know about the antagonistic impacts that can happen because of simultaneous organization of natural and OTC medications would need to confront decimating results. The conceivable herb-medicate connections.[18,19]

Herb tranquilize associations are an intriguing issue of discussion. Utilization of herbs and their arrangements are going under expanding connect for being conceivably perilous to patients who are as of now taking allopathic meds. The worries are increased for those patients at present taking numerous prescriptions regularly recommended by various doctors.[20]

(At least two) drugs when managed together can possibly cause concoction or pharmacological between activities. Such communications may modify the impact of specialist, prompting diminished or expanded viability or seriousness of unfriendly impacts. The results are reliant on numerous compound and pharmacological elements, for example, the physicochemical idea of the medications being used and how they influence each other pharmacokinetically and pharmacodynamically . Despite the fact that, the components of collaborations among herbs and medications are comparative, they are more unpredictable in nature when a few mixes are included. Herb– medicate associations (HDI) may influence clinical wellbeing and adequacy by means of added substance/synergistic or adversarial collaborations among the natural segments and medication particles While negative or hurtful co-operations have a tendency to get more consideration because of security contemplations, added substance/synergistic impacts actuated by HDIs may result in an upgrade of wanted pharmacological impacts. For instance, the blood glucose cutting down effect of antidiabetic drugs has gave off an impression of being extended by agrimony.[21]

3. Herb Drug Interaction

3.1 Pharmacokinetic drug interaction (quantitative)

Result in modifications of the medication's or regular drug's ingestion, circulation, digestion or end. These collaborations influence tranquilize activity by quantitative modifications, either expanding or diminishing the measure of medication accessible to have an impact. The intruding medicine may go about as an inducer, inhibitor as well as substrate of the cytochrome P450 protein that is accountable for the absorption of the specific solutions. This is the most basic segment for associations between home developed medications and antiretroviral drugs.[22]

a. Drug absorption
b. Drug Distribution
c. Drug metabolism and bioavailability
d. Drug elimination, renal and hepatic clearance

3.2. Pharmacodynamics drug interaction (qualitative)

Pharmacodynamic associations influence a medication's activity subjectively, either through improving impacts (synergistic or added substance activities) or alienating impacts

a. Antagonistic effect
b. Additive effect
c. Synergistic effect

Herb-tranquilize associations can affect on wellbeing and the adequacy of medications. For instance, some natural treatments may

- Increase the side effects of drugs, possibly leading to toxicity
- Decrease the therapeutic effect of drugs, possibly leading to treatment failure.
- Modify the action of drugs, possibly leading to unexpected complications.
- Enhance the therapeutic effect of drugs, possibly leading to over medication [23-25]

Table 3: Example for the interaction between herbal and conventional drugs

Herb	Drug	Interaction
Momordica Charantia (MC)	Rosiglitazone	MC also augmented the Hypoglycaemic activity of Rosiglitazone.[26]
Pongamia pinnata	Hypoglycaemic drugs	Synergistic antihyperglycemic effect.[27]
Guar gum	Metformin, Glibenclamide	Decreases absorption of Metformin and Glibenclamid.[28]
Momordica Charantia	Chlorpropamide	Less glycosuria.[29]
Garlic	Chlorpropamide	Hypoglycaemic response.[30]
Ginseng (*Panax Ginseng*)	Insulin	Synergistic, anti diabetic actions of herb.[31]
St john's wort	Rosiglitazone	Decreases drug effect.[32]

4. Antidiabetic pharmaceutical and herbal interventions

A few gatherings of pharmaceutical specialists are as of now utilized for the treatment of diabetes by means of various instruments, for example, incitement of the arrival of insulin (e.g., sulfonylureas), decrease of hepatic glucose yield and improvement of the fringe take-up of glucose (e.g. biguanidines).[33,34] A portion of the generally utilized enemy of diabetic medications incorporate biguanides, e.g., metformin (through acting specifically to

impact insulin obstruction), peroxi-some proliferator actuated receptor (PPAR) activators, e.g., thiazolidindiones (by means of enhancing insulin opposition), vidagliptin and other related "gliptins" (by means of blocking DPP-4, a chemical that debases the incretin GLP-1) and α-glucosidase inhibitors, e.g. Acarbose and miglitol (by means of postponing the assimilation of complex sugars). Other diabetic specialists target pancreatic beta-cell receptors by official to the sulfonylurea receptor subunit, obstructing the K+-ATP channel to advance insulin discharge.[35,36] Furthermore, mix treatments (e.g. sulfonylureas with biguanides, thiazolidinedione with glucosidase inhibitors) are generally used to expand remedial focuses keeping in mind the end goal to enhance adequacy and to limit reactions.

4.1 Glibenclamide-Aloe Vera

Aloe Vera is local to Africa and is one of the in excess of 400 types of the sort Aloe. The assumed real dynamic parts incorporate sugars (e.g., man-nan, galactose-rich polysaccharides), and galacturonic corrosive.[37] Aloe Vera is local to Africa and is one of the in excess of 400 types of the sort Aloe. The assumed real dynamic parts incorporate sugars (e.g., man-nan, galactose-rich polysaccharides), and galacturonic corrosive.[38] A few investigations report potential cooperation between aloe vera and antidiabetic drugs. of note is its cooperation with glibenclamide, a sulphonylurea which applies its enemy of diabetic potential by restraining ATP delicate potassium directs in pancreatic β cells, bringing about cell layer depolarization and ensuing insulin discharge. The blend of aloe vera and antidiabetics has by and large been appeared to have an added substance impact. For example, aloe has been appeared to create a more prominent enemy of hyperglycaemic impact, when contrasted with the sole treatment with glibenclamide, pioglitazone or repaglinide.[39,40]

4.2 Metformin and *Carica papaya* Linn, *Ginseng-Panax* ginseng

Paw and papaya has a place with the family Cariaceae. It is bounteous in tropical and subtropical nations. Dynamic concentrates incorporate chymopapain and papain. Its leaf remove is taken nearby oral antidiabetic medications and concentrate gotten from unripe natural products have been utilized as a treatment methodology by a few diabetics. Organization of Carica papaya leaf remove with metformin prompted diminish in beginning of activity of metformin and argumentation of the impacts of metformin in alloxan incited diabetic.[41] Panax ginseng is an imperative individual from the ginseng family, have been appeared to have antidiabetic properties influencing insulin ward and insulin free pathways.[42-44]

The consolidated treatment of metformin has been appeared to inspire added substance impacts contrasted with singular parts being utilized alone. Critical changes were seen in plasma glucose and insulin levels, homeostasis display evaluate ment-insulin obstruction (HOMA-IR) and in haematoxylin and eosin-recolored liver tissues.[45-46]

4.3 Glibenclamide or Metformin-Karela

Karela is generally called obnoxious melon as a result of its taste. An extensive number of engineered constituents are found in its juice, including sterols, glucoside mixes and charantin polypeptides.[47] Karela is one of a handful couples of restorative plants are subjected to broad clinical studies in blend with basic antidiabetics. Extended feasibility has been known when used joined with metformin, glymidine and glibenclamide. In one clinical trial primer, 400 mg of chloroform/benzene karela remove was joined with half of the full clinical estimations of either metformin or glibenclamide in NIDDM patients. Results exhibited that the joined mediations propelled a more vital hypoglycemic effect when diverged from that of full measurements of metformin or glibenclamide independently, demonstrating a possible included substance affect.[48] Karela is generally called obnoxious melon as a result of its taste. An extensive number of engineered constituents are found in its juice, including sterols, glucoside mixes and charantin polypeptides.[49-51]

4.4 Metformin-Fenugreek—*Trigonella foenum-graceum*

Fenugreek is routinely utilized as flair in south Asia and is known for its hypoglycaemic and hypocholesterolemic properties.[52] The proximate arrangement of fenugreek (seeds, husk and cotyledons) contains saponin, protein and polyphenols.[53] Communications of fenugreek with known antidiabetics have been assessed in a few artificially prompted diabetic creature models. The mix of fenugreek (150 mg/kg) and metformin (100 mg/kg) created a huge decrease in plasma glucose level (20.7%) in sort 2 diabetes.[54] In a relative report, lipid peroxidation (LPO) affected by ferrous sulfate, hydrogen peroxide and carbon tetrachloride in liver were performed. The mix treatment with fenugreek seed expel and glibenclamide demonstrated a more unmistakable restriction of the hepatic LPO practices and a more important foe of oxidant development stood out from the individual fragments alone, highlighting a potential preferred standpoint of the blend treatment.[54]

4.5 Glipizide and metformin- Prickly pear cactus

Prickly pear desert plant (Nopal) although neighborhood to Mexico is by and by comprehensively used worldwide as sustenance and standard pharmaceutical. Desert plants are apportioned into a couple of genera, including Opuntia (e.g., *Opuntia aciculata*).

Opuntia contains an extent of phytochemicals in factor sums, for instance, polyphenols, dietary minerals and betalains, and distinctive blends along with gallic destructive, vanillic destructive and catechins.[55] Thorny pear seeds have been found to expand muscle and liver glycogen and lessen blood glucose level in STZ-initiated diabetic rats, potentially through an insulin sharpening impact.[56] One examination demonstrated a positive cooperation between the joined impact of thorny pear desert plant cushion and glipizide and metformin in T2DM patients. In this investigation a hypoglycaemic response was watched, in spite of the fact that the creators take note of that clinical examinations are required to help consolidated treatment of this herb and known diabetic medications.[56]

4.6 Pioglitzone-Astragalus (*Radix Astragali*)

Astragalus is a sometimes used regular Chinese pharmaceutical for diabetes. The bioactive constituents of astragalus consolidate polysaccharides, triterpenoids (astragalosides), isoflavones (checking kumatakenin, calycosin and formononetin), glycosides and malonates.[57] In Chinese home grown drug astragalus is regularly utilized as a key herb in antidiabetic definitions. The impact of astragalus on the pharmacokinetics of pioglitazone has been examined in various clinical and preclinical investigations. In solid human subjects, treatment of astragalus extricate essentially lessened the C_{max} and expanded last speed (V/F) of pioglitazone while a contrary impact (i.e. expanded Cmax and lessened V/F) was seen in type2 diabetetes mellitus (T2DM), in spite of the fact that the purposes behind this infection subordinate impact were unclear.[58] In an investigation in rats, co-organization of astragalus decoction and pioglitzone did not seem to change the pharmacokinetic profiles of pioglitzone.[58]

4.7 Garlic (*Allium sativum*) - Metformin

Garlic is known for its scope of therapeutic properties. It is made out of a broad number of sulfur blends, with suspected bioactive blends called allyl thiosulfinates (generally allicin).[59] Garlic has been represented to have antidiabetic properties. A couple of exploratory and clinical examinations have been coordinated to study the correspondence among garlic and antidiabetic meds. In a rat illustrate, the effects of garlic on the pharmacokinetic profiles of metformin were investigated. It was found that garlic extended the apex plasma center (C_{max}) and the zone under the twist (AUC) of metformin, high-lighting the need to alter the metformin estimation when co-made do with garlic.[60] In another examination blend treatment of garlic extricate (50 or 100 mg/kg) and metformin more than 28 days was tried in a rodent model of streptozocin-incited diabetes. Garlic alone, and also in com-bination with metformin, enhanced body weight, while the blend treatment was more successful in diminishing blood glucose levels, featuring that garlic remove potentiates the hypoglycaemic impact of metformin.[61] Potential valuable impacts of garlic squeeze in mix with metformin have been appeared, where the blend constricted tubular poisonous quality prompted by gentamicin.[62,63] In a clinical preliminary, 60 diabetic patients with fasting glucose levels over 126 mg/dl were arbitrarily isolated in two gatherings to get garlic tablets (300 mg thrice day by day) and metformin (500 mg twice day by day), or fake treatment and metformin more than 24 weeks. A basically more conspicuous diminishing in blood glucose level (3– 12%) was found in the social event with co-treatment of garlic and metformin when appeared differently in relation to that of the phony treatment and metformin gathering (0.59%), exhibiting an update affect.[64]

4.8 Gliberclamide-Sesame oil

Sesame oil is gotten from sesame seeds and is comprehensively used in cooking and as a flavor enhancer. It is com-introduced of the going with unsaturated fats: linoleic destructive (41% of total), oleic destructive (39%), palmitic destructive (8%), stearic destructive at least 5% little proportions of other unsaturated fats.[65] Sesame oil has a few customary therapeutic properties and has been accounted for to have antidiabetic properties.[66] In a milestone clinical examination by Sankar *et al*. 62 patients (32 male, 28 female) with T2DM were partitioned in 3 bunches getting sesame oil (~35 g oil/day utilized in cooking or serving of mixed greens readiness) alone, gliberclamide, orsesame oil and gliberclamide blend.[67] In a point of reference clinical examination by Sankar *et al*. 62 patients (32 male, 28 female) with T2DM were divided in 3 packs getting sesame oil (~35 g oil/day used in cooking or serving of blended greens preparation) alone, gliberclamide, orsesame oil and gliberclamide mix.[67]

5. General discussions and conclusion

In light of the outcomes exhibited above, plainly various home grown meds, when taken related to antidiabetic pharmaceutical operators, could conceivably modify their pharmacokinetic or potentially pharmacodynamic properties. These connections are mind boggling given the substantial number of pathophysiological/pharmacological targets related with the malady and the multicomponent properties of natural medication. The group to-bunch variety in concoction arrangement of home grown drug is likewise prone to affect on the idea of the collaborations, making them erratic. In this survey we have discovered that co-operations of hostile to diabetic medications and herbs may result in adversarial

or improvement impacts. The upgrade of glucose bringing down has the likelihood of causing hypoglycaemia, consequently checking of conceivably antagonistic impacts is required and thus it is prescribed that individuals with diabetes intently screen their blood glucose levels when joining the two mixes. In spite of the fact that by far most of accessible confirmation recommends that home grown meds are moderately protected one case report demonstrated that a patient with T2DM who was treated with the mix of Metformin and Repaglinide experienced hypoglycaemia.[68] proposing that patients and clinicians ought to in fact be aware of this plausibility. Additionally inquire about is required to look at the potential for hypoglycaemia in patients who are simultaneously controlled antidiabetic drugs.

Regardless of the potential for unfriendly impacts, the blend of these herbs and antidiabetic meds has been all the more usually appeared to have positive clinical ramifications as it could prompt upgraded antidiabetic impacts, conceivably empowering a decrease in measurements of antidiabetic operators, in this manner limiting their reactions. Interestingly, opposition may prompt hurtful impacts and in this way warrant a preventative cautioning or contraindication for the blend. Despite the fact that not talked about in this audit, hostile to diabetic herbs may likewise connect with other (non-diabetic) drugs when taken simultaneously.[69] These contemplations demonstrate that alert ought to dependably be practiced when home grown prescriptions are joined with pharmaceutical drugs, particularly in elderly patients or patients with constant sicknesses due to their traded off body capacities (e.g. renal and hepatic capacities specifically). Additionally investigate is justified on the components of activity fundamental antidiabetic herb–medicate cooperation. CYP monoxygenase and P-glycoprotein sedate transport pathways are exceptionally compelling given that numerous enemies of diabetic solutions are liable to digestion by these compound frameworks. [70-72]

References

[1]. Lal VK, Gupta PP, Tripathi P, Pandey A. Interaction of aqueous extract of *Trigonella foenum-graecum* seeds with glibenclamide in streptozotocin induced diabetic rats. *Am J Pharm Toxicol.* 2011; 6(4):102-6.

[2]. Frier BM, Fisher M. Diabetes Mellitus. In: Nicki R, Brian R, Stuart H, editors. Davidson's Principle and Practice of Medicine, 21st edition. India: Elsevier; 2010.p.735.

[3]. Dixit S, Asiri F. Pharmacological and Non-pharmacological therapies in the Management of Diabetic Peripheral Neuropathy in Type 2 Diabetes: A Comprehensive Review. *Journal of Cardiovascular Disease Research*. 2014; 5(4):37-48.

[4]. Chang HY, Wallis M, Tiralongo E. Use of complementary and alternative medicine among people living with diabetes: literature review. *J Adv Nurs*. 2007; 58(4):307–19.

[5]. Purohit P, Mishra B. Systematic Review on Interaction Studies of Synthetic Antidiabetic Drugs and Herbal Therapies. *Journal of Pharmaceutical Research*. 2017; 16(2):86-94.

[6]. Miller LG, Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Archives of Internal Medicine*. 1998; 158(20): 2200–2211

[7]. Philp RB, Herbal remedies: the good, the bad, and the ugly. *Journal of Complementary and Integrative Medicine*. 2004; 1:1–11.

[8]. Swanston-Flatt SK, Day C, Bailey CJ, Flatt PR. Evaluation of traditional plant treatments for diabetes: studies in streptozotocin diabetic mice. *Acta Diabetol Lat* 1989; 26(1): 51-55.

[9]. Nasri H, Rafieian-Kopaei M. Herbal medicine and diabetic kidney disease. *J Nephropharmacol* 2013; 2(1): 1-2.

[10]. Jamila F, Mostafa E. Ethnobotanical survey of medicinal plants used by people in Oriental Morocco to manage various ailments. *J Ethnopharmacol* 2014; 154(1): 76-87.

[11]. Qi LW, Liu EH, Chu C, Peng YB, Cai HX, Li P. Anti-diabetic agents from natural products- an update from 2004 to 2009. *Curr Top Med Chem*. 2010; 10(4):434–57.

[12]. Samad A, Shams MS, Ullah Z, Wais M, Nazish I, Sultana Y, Aqil M. Status of herbal medicines in the treatment of diabetes: a review. *Curr Diabetes Rev*. 2009; 5(2):102–11.

[13]. Chang CL, Lin Y, Bartolome AP, Chen YC, Chiu SC, Yang WC. Herbal therapies for type 2 diabetes mellitus: chemistry, biology, and potential application of selected plants and compounds. *Evid Based Complement Altern Med eCAM*. 2013; 2013:378657.

[14]. Mishra R, Mohd Shuaib S, Shiravan S, Mishra PS. A review on herbal antidiabetic drugs. *J App Pharma Sci.* 2011; 01: 235–7.

[15]. Patel DK, Prasad SK, Kumar R, Hemalatha S. An overview on antidiabetic medicinal plants having insulin mimetic property. *Asian Pac J Trop Biomed*. 2012; 2(4): 320–30.

[16]. Hong SH, Heo JI, Kim JH, Kwon SO, Yeo KM, Bakowska-Barczak AM, Kolodziejczyk P, Ryu OH, Choi MK, Kang YH, *et al*. Antidiabetic and Beta cell-protection activities of purple corn anthocyanins. *Biomol Ther* (Seoul). 2013; 21(4):284–9.

[17]. Bailey CJ, Day CA. Antidiabetic drugs. *British journal of cardiology*. 2003; 10:128-36.

[18]. Gohil, K, J. and J.A Patel, Herb-drug interactions; A Review and study based on assessment of clinical case reports in literature. *Indian. J. Pharmacol.,* 2007, 39(3): 129-139.

[19]. Hu, Z., X, Yang, P.C. HO, SY. Chan, P.W. Heng, E.chan, W. Duan, H.L. Koh and S. Zhou, herb-drug interactions; A Literature Review. *Drugs*, 2005, 65(9); 1239-1282.

[20]. Naveen P, Shankar BG, Srikanth V, Laxmaiah C, Prathapani S. A review: herb-drug interactions. *Indo Am J Pharm Res*. 2011; 1(12):364-72.

[21]. Gray AM, Flatt PR. Actions of the traditional anti-diabetic plant, *Agrimony eupatoria* (agrimony): effects on hyperglycemia, cellular glucose metabolism and insulin secretion. *Br J Nutr*. 1998; 80(1):109–14.

[22]. Rogers T. Herb-drug interactions. Canadian AIDS treatment information exchange (CATIE) 2004:01-06. [Last accessed on 2005 Jun 9]. Available from: http://www.catie.ca/pdf/supple-e/herb%20drug%20interactions.pdf.

[23]. Ciddi Veeresam, *et al.* A Insight into Herb- Drug interactions. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 2010; 2 (4).

[24]. Fug – Berman A Herb – drug interactions. *Lancet* 2000: 355: 134-38.

[25]. Ernst E, Littler MH. Herbal medicine. Medical clinics of North America 2002: 86(1): 149-61.

[26]. Susan Nancy Niivitabishekam, Mohammed Assad, V Satya Prasad. Pharmacodynamic interaction of *Momordica charentia* with Rosiglitazone in rats. *Chemico Biological interactions* 2009: 177:247-253.

[27]. Sachin L Badole Subhash L Bodhankar. Concomitant administrations of Petroleum ether extract of the stem bark of *Pongamia pinnata* (L) Pierre with synthetic oral hypoglycaemic drugs in alloxan-induced diabetic mice. *European Journal of Integrative Medicine* 2009: 1: 73-79.

[28]. Adriane Fug – Berman A. Herb – drug interactions. *Lancet* 2000: 355: 134-38.

[29]. Aslam M, Stockley IH. Interaction between Curry ingredient (Karela) and drug Chlorpropamide. *Lancet* 1979: 1; 607.

[30]. Wang, Z Q. *et al*, The effects of St John's wort (*Hypericum Perporatum*) on human Cytochrome P450 activity. *Clin. Pharmacol. Ther*. 2001: 70: 317-326.

[31]. Sotaniemi E A, Haapakshi E, Rautio A. Ginseng therapy in noninsulin-dependent diabetic patients. *Diabetes Care* 1995: 18 (10): 1373-1375.

[32]. Mary L Chavez. Herbal-Drug Interactions. *Int. Chem*. 2005: 9(10): 1-30.

[33]. Turner RC, Cull CA, Frighi V, Holman RR. 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. *JAMA*. 1999; 281(21):2005–12.

[34]. Hermann LS, Lindberg G, Lindblad U, Melander A. Efficacy, effective- ness and safety of sulphonylurea–metformin combination therapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2002; 4(5):296–304.

[35]. Jovanovic L, Hassman DR, Gooch B, Jain R, Greco S, Khutoryan- sky N, Hale PM. Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone. *Diabetes Res Clin Pract*. 2004; 63(2):127–34.

[36]. Del Prato S, Bianchi C, Marchetti P. Beta-cell function and anti-diabetic pharmacotherapy. *Diabetes Metab Res Rev*. 2007; 23(7):518–27.

[37]. Ni Y, Turner D, Yates KM, Tizard I. Isolation and characterization of structural components of *Aloe vera* L. leaf pulp. *Int Immunopharmacol*. 2004; 4(14): 1745–55.

[38]. Yimam M, Zhao J, Corneliusen B, Pantier M, Brownell LA, Jia Q. UP780, a chromone-enriched aloe composition improves insulin sensitivity. *Metab Syndr Relat Disord*. 2013; 11(4): 267–75.

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

[40]. Rheman S, Choi M, Choe K, Yoo H. Interactions between herbs and antidiabetics an overview of the mechanisms, evidence, importance and management. *Arch Pharm Res*. 2015; 38:1281–98.

[41]. Omobhude Fidelis Aluefua, Aminu Chika, Abubakar Amali Muhammad and Aminu Usman. Interactions between Herbs and Antidiabetic Drugs: A Systematic Review. *Res. J. Pharmacol*.2017; 11 (5-6): 6-17.

[42]. Xiong Y, Shen L, Liu KJ, Tso P, Xiong Y, Wang G, Woods SC, Liu M. Antiobesity and antihyperglycemic effects of ginsenoside Rb1 in rats. *Diabetes*. 2010; 59(10):2505–12.

[43]. Cho WC, Chung WS, Lee SK, Leung AW, Cheng CH, Yue KK. Ginsenoside Re of Panax ginseng possesses significant antioxidant and antihy-perlipidemic efficacies in streptozotocin-induced diabetic rats. *Eur J Pharmacol.* 2006; 550(1–3):173–9.

[44]. Lee WK, Kao ST, Liu IM, Cheng JT. Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in Wistar rats. *Clin Exp Pharmacol Physiol*. 2006; 33(1–2):27–32.

[45]. Yoon SH, Han EJ, Sung JH, Chung SH. Anti-diabetic effects of compound K versus metformin versus compound K-metformin combination therapy in diabetic db/db mice. *Biol Pharm Bull*. 2007; 30(11): 2196–200.

[46]. Vuksan V, Sung MK, Sievenpiper JL, Stavro PM, Jenkins AL, Di Buono M, Lee KS, Leiter LA, Nam KY, Arnason JT, *et al*. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-con- trolled study of efficacy and safety. *Nutr Metab Cardiovasc Dis NMCD*. 2008; 18(1):46–56.

[47]. Lotlikar MM, Rajarama Rao MR. Pharmacology of a hypoglycemic principle isolated from the fruit of *Momordica charantia* Linn. *Ind J Pharm*. 1996; 28:129–33.

[48]. Tongia A, Tongia SK, Dave M. Phytochemical determination and extraction of *Momordica charantia* fruit and its hypoglycemic potentiation of oral hypoglycemic drugs in diabetes mellitus (NIDDM). *Indian J Physiol Pharmacol.* 2004; 48(2): 241–4.

[49]. Poonam T, Prakash GP, Kumar LV. Interaction of Momordica charantia with metformin in diabetic rats. *Am J Pharm Toxicol*. 2013; 8:102–6.

[50]. Vijaya K, Sunitha SP, Husssain JA, Sandhya P, Sujatha D, Gopireddy G. Synergistic antihyperglycemic, antihyperlipidemic and antioxidant effects of *Momordica charantia* and metformin in streptozotocin induced diabetic rats. *World J Pharm Res*. 2014; 3:1901–80.

[51]. Anonymous. Fruit extract effect pares (*Momordica charantia*) and metformin against Kadar blood glucose wistar rats induced by alloxan: comparison of treatment single and combination. *Ther Sci Artic*. 2014:1–4.

[52]. Basch E, Ulbricht C, Kuo G, Szapary P, Smith M. Therapeutic applications of fenugreek. *Altern Med Rev*. 2003; 8(1):20–7.

[53]. Naidu MM, Shyamala BN, Naik JP, Sulochanamma G, Srinivas P. Chemical composition and antioxidant activity of the husk and endosperm of fenugreek seeds. *LWT Food Sci Tech*. 2010; 44:451–6.

[54]. Neha S, Anand K, Sunanda P. Administration of fenugreek seed extract produces better effects in the glibenclamide-induced inhibition in hepatic lipid peroxidation: an in vitro study. *Chin J Integr Med*. 2015; 21:1.

[55]. Guzman-Maldonado SH, Morales-Montelongo AL, Mondragon- Jacobo C, Herrera-Hernandez G, Guevara-Lara F, Reynoso-Camacho R. Physicochemical, nutritional, and functional characterization of fruits xoconostle (*Opuntia matudae*) pears from Central-Mexico Region. *J Food Sci.* 2010; 75(6):C485–92.

[56]. Sobieraj DM, Freyer CW. Probable hypoglycemic adverse drug reaction associated with prickly pear cactus, glipizide, and metformin in a patient with type 2 diabetes mellitus. *Ann Pharmacother*. 2010; 44(7–8):1334–7.

[57]. Lin LZ, He XG, Lindenmaier M, Nolan G, Yang J, Cleary M, Qiu SX, Cordell GA. Liquid chromatography-electrospray ionization mass spectrometry study of the flavonoids of the roots of *Astragalus mongholicus* and A. membranaceus. *J Chromatogr A.* 2000; 876(1–2):87–95.

[58]. Shi Z, Gao J, Yuan Y, Zhu S, Yao M. Effect of raw *Radix Rehmanniae* on the pharmacokinetics of pioglitazone in rats. *Pak J Pharm Sci*. 2014; 27(3):537–9.

[59]. Lawson LD, Cardner CD. Composition, stability and bioavailability of garlic products being used in a clinical trial. *J Agric Food Chem*. 2005; 53:6254–61.

[60]. Shikha C, Tamanna N, Kumar SL. Effect of *Allium Sativumon* the pharmacokinetic of Metformin in rat plasma: a herb–drug interaction study. *Der Pharm Chem*. 2011; 3:287–91.

[61]. Poonam T, Prakash GP, Kumar LV. Effect of co-administration of *Allium sativum* extract and Metformin on Blood glucose of Streptozotocin induced diabetic rats. *J Intercult Ethnopharmacol.* 2013; 2:81–4.

[62]. Rafieian-Kopaei M, Baradaran A, Merrikhi A, Nematbakhsh M, Madihi Y, Nasri H. Efficacy of Co-administration of garlic extract and metformin for prevention of gentamicin-renal toxicity in wistar rats: a biochemical study. *Int J Prev Med.* 2013; 4(3): 258–64.

[63]. Tavafi M. Protection of renal tubules against gentamicin induced nephrotoxicity. *J Renal Inj Prev*. 2013; 2(1):5–6.

[64]. Ashraf R, Khan RA, Ashraf I. Garlic (Allium sativum) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. *Pak J Pharm Sci*. 2011; 24(4):565–70.

[65]. Anonymous. Nutrition Facts for sesame oil per 100 g, analysis of fats and fatty acids. In: National nutrient database for standard reference release 28 United States Department of Agriculture (USDA); 2014.

[66]. Sankar D, Rao MR, Sambandam G, Pugalendi KV. A pilot study of open label sesame oil in hypertensive diabetics. *J Med Food*. 2006; 9(3):408–12.

[67]. Sankar D, Ali A, Sambandam G, Rao R. Sesame oil exhibits synergistic effect with anti-diabetic medication in patients with type 2 diabetes mellitus. *Clin Nutr.* 2011; 30(3):351–8.

[68]. Carella A, Marinelli T, Melfitano A, Di Pumpo M, Conte M, Benvenuto A. Hypoglycemia by Ginseng in type 2 Diabetic Patient: case Report. *Heighpubs Obes Diabetes Metab Syndr*. 2017; 1:001–6.

[69]. Rhoades KR. Prescribed medications and OTCs: interactions and thiming issues. *Diabetes Spectrum*. 2002; 15:256–61.

[70]. Bushra R, Aslam B, Khan AY. Food–drug interactions. *Oman Med J.* 2011; 26:77–83.

[71]. Cho HJ, Yoon IS. Pharmacokinetic interactions of herbs with cytochrome p450 and p-glycoprotein. *Evid Based Complement Altern Med eCAM*. 2015:736431.

[72]. Zhou SF, Li ZW, Chen CG, Yu X, Xue Q, Herrington CC. Identification of drugs that interact with herbs in drug development. *Adrian Drug Disc Today*. 2015; 12:664–73.