Available online on 15.06.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Recent updates on natural compounds in treatment of diabetes mellitus: A comprehensive Approach

Nidhi Bais [1]*, G.P. Choudhary [2]

School of Pharmacy, DAVV, Indore, M.P., India

ABSTRACT

Diabetes is one of the major public health concerns over the world Persistent hyperglycemia or uncontrolled diabetes has the potential to cause serious complications such as kidney disease, vision loss, cardiovascular disease, and lower-limb amputations which contributed towards morbidity and mortality Herbal medicine, phytomedicine or botanical medicine are synonymous, utilizes plants intended for medicinal purposes. Medicinal use of herbal medicine in the treatment and prevention of diseases including diabetes has a long history compared to conventional medicine Several medicinal plants and their preparations have been demonstrated to act at key points of glucidic metabolism. The most common mechanisms of action found include the inhibition of α-glucosidase and of AGE formation, the increase of GLUT-4 and PPARs expression and antioxidant activity. However, the selection of herbs might depends on several factors, which include the stage of progression of diabetes, types of comorbidities that the patients are having, availability, affordability as well as the safety profile of the herbs. This review focuses on the herbal and natural remedies that play the role in the treatment or prevention of this morbid disorder e diabetes, including their underlying mechanisms for the blood glucose-lowering property and the herbal products already been marketed for the remedial action of diabetes

Keywords: Diabetes, kidney disease, vision loss, α-glucosidase

Article Info: Received 04 May 2019; Review Completed 09 June 2019; Accepted 11 June 2019; Available online 15 June 2019

Cite this article as:

Bais N, Choudhary GP, Recent updates on natural compounds in treatment of diabetes mellitus: A comprehensive Approach, Journal of Drug Delivery and Therapeutics. 2019; 9(3-s):1019-1024 **http://dx.doi.org/10.22270/jddt.v9i3-s.2934**

***Address for Correspondence:**

Nidhi Bais, School of Pharmacy, DAVV, Indore, M.P., India

Introduction

Herbal medicine is one of the subgroups of complementary and alternative medicinal (CAM) therapies. Many patients consider CAM over conventional therapies due to dissatisfied outcomes from the conventional therapies, higher treatment costs and increased side effects of modern medicines. Therefore, the active ingredients of the medicinal plants are directing towards its particular use in diseased condition, may be applied in complex formulation of one or more plants. The use of traditional herbal medicines is more associated with patient conception and less paternalistic compared to allopathic medicine in general.(1-3) Moreover, traditional herbal medicines may be used in combination with or as alternative to the conventional allopathic medicines. Thus, there are thousands of medicinal plants for the treatment of a range of diseases. There are several complications which are targeted to treat with herbal medications, including cancer, memory impaired condition, liver disorder, peptic ulcer and other gastrointestinal disorder, inflammatory disorder, hypertension and other cardiovascular disease, diabetes mellitus, hyperlipidemia, tuberculosis, dermatological infections, along with undefined muscular pains and other diseases related to urinary tract, respiratory tract and central nervous system.(4-12) The worldwide utilization of herbal medicines are summarized in Fig. 1. In this article, we aim to focus the potential herbal medications as an effective and sustainable alternative for the treatment of diabetes. In due course of the study, we have done extensive literature search to provide a summarized database on available herbal treatments in the control and treatment of diabetic condition.

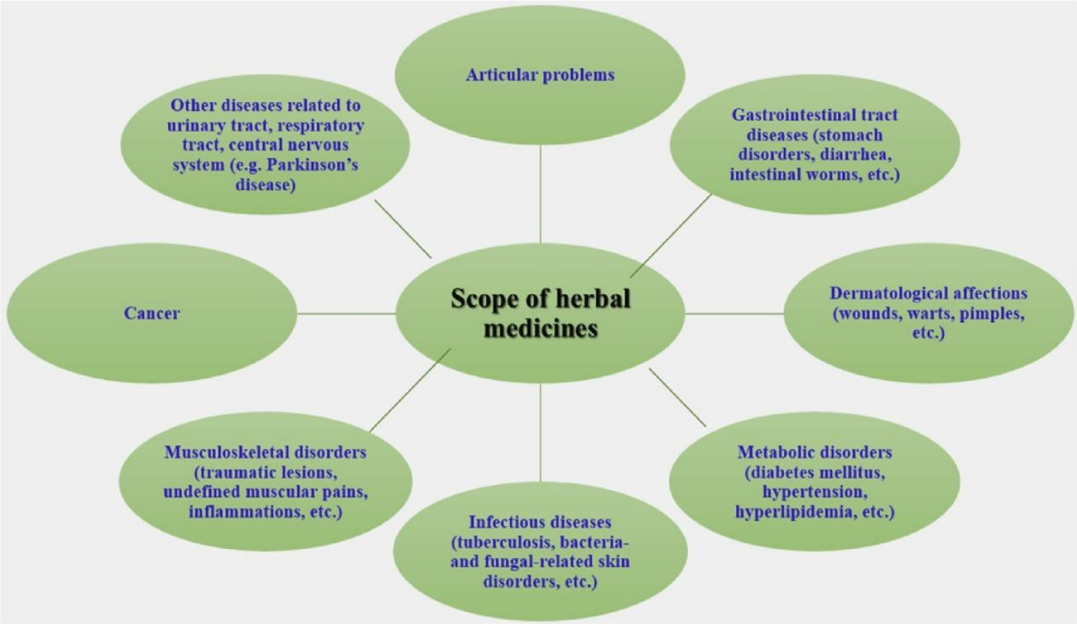

Fig. 1. The traditional utilization of herbal medicines in different field of medical field.

The selection of herbs for diabetes

Several medicinal plant have shown to be effective in different stages of diabetes, such as curcumin is proposed to be used as one of interventions in pre-diabetes therapy to prevent the progression of T2DM due to its proven benefits and safety profile,(13) whereas, cinnamon can be a better option for diabetic patients who are having co-existing hypertension,(14) and on the other hand, the extract of *Aloe vera* leaf gel with doses of 300 mg/kg demonstrated increased levels of insulin from regenerated pancreatic beta-cells.(15) Therefore it is important to know the history of the patient and therapeutic benefits of the medicinal plant for proper treatment of the patient. The following sections of this article will institute different activities of medicinal plants to replace the existing therapies of diabetes.

Herbs that regulate insulin secretion

Defects in insulin secretion are the one of the main causes that leads to Diabetes Mellitus. Recently, numerous botanical herbs have demonstrated antidiabetic potential through regulation of insulin secretion (Table 1). As the long-term use of conventional secretagogues such as glibenclamide in diabetes patients tend to cause damage of b-cells due to overstimulation of pancreatic islet, treatment can be switched to the use of Cuminum cyminum in long-term diabetes treatment since it can help in lowering the blood glucose level and at the same time it carries benefit of beta-cells protection.

Table 1: Herbals in the management of plasma glucose level, acting through secretogogues mechanism or by improvement of insulin sensitivity to the cells.

S.N.	Botanical name	Part used	Type of extract	Animal model	Outcome (effects
1	Afzelia africana diabetes	Stem bark	Aqueous extract	STZ-induced	The blood glucose level was significantly reduced in a dose dependent manner with the best result obtained at 200 mg kg_1 body weight per day,
2	Urtica dioica	Leaf	Hydroalcoholic extract	Fructose-induced insulin resistance	The blood glucose and FIRI in hyperglycemic rats were reduced in a dose-dependent manner with the best result obtained at 200 mg kg_1 body weight/day. The plasma insulin level was also found to be reduced in
3	Chloroxylon swietenia	Bark	Methanolic and aqueous extract	STZ-induced diabetes Male albino	Wistar rats Diabetic rats in treatment group showed moderate reduction in blood glucose and glycosylated haemoglobin levels, in addition, plasma insulin were elevated. The outcomes of methanolic extract were comparable to glibenclamide
4	Anacardium occidentale	Leaf	Ethanol extract	STZ-induced diabetes	The same time, glycosylated haemoglobin level, FIRI and serum insulin level weredecreased in treatment group
5	Forsythia suspense extract	Fruit	Ethyl acetate fraction of methanol	STZ-induced diabetes Male	Significantly decreased; insulin secretion and glucose tolerance were significantly increased Kunming mice Blood glucose was

Herbs have impact on glucose absorption

The utilization of a-glucosidase inhibitor is one of the remedies for diabetes as it suppresses carbohydrate digestion, thus decelerating the process of glucose assimilation and resulting in significant reduction of postprandial plasma glucose and insulin level with a significant decrease of HbA1c postprandially. There is a wide use of a-glucosidase inhibitor in the control of T2DM, for e.g., acarbose, voglibose, miglitol, etc. (16)

Table 2:List of medicinal herbs affecting the absorption of carbohydrates from the gastrointestinal environment by inhibiting a-glucosidase and a-amylase.

S. No.	Herb	Botanical name	Part used	Type of extract	Chemical constituen	Animal model	Outcome (effects
1	Leafflower	Phyllanthus urinaria	Leaves	50% aqueous methanolic extract	Corilagin, gallic acid and macatannin		macatannin B demonstrated low inhibitory activity against amylase (21%, 23% and 33% respectively in 1 mmol.L_1 concentration
2	Cinnamon	Cinnamomum zeylanicum	Bark Metha	Methanol extract	Tannins, flavonoids, glycosides, terpenoids, coumarins and anthraquinones	STZ-induced diabetic rats In vitro:	Inhibition of yeast and mammalian a-glucosidase (IC50 ¼ 5.83 mg ml1 & 670 mg ml1 respectively) In vivo: Decreased postprandial hyperglycemia by 78.2% and 52.0% compared to normal rats
3	Black seed treatment	Nigella sativa	Seeds	Aqueous extract	Flavonoids, unsaturated fatty acids, nigellone, thymoquinone (TQ), p-cymene and carvone	In vitro: Inhibition of sodiumdependent glucose transport In vivo: Chronic	improved glucose tolerance and reduced body weight similarly as metformi
4	China aster	Callistephus chinensis	Flower	70 % ethanol extract	Apigenin, apigenin-7-O-b-Dglucoside, hyperin, kaempferol, kaempferol-7-O-b-Dglucoside, luteolin		In vitro: Inhibition of sodiumdependent glucose transport In vivo: Chronic treatment improved glucose tolerance and reduced body weight similarly as metformin

Herbs regulate multiple actions on glucose regulation

Apart from the described herbs, several herbs investigated to have multiple mechanisms in the control of diabetic condition. Few of the medicinal herbs has been described in this section those have multiple mode of action, including regeneration of pancreatic B cells, increases insulin sensitivity, enhance glucose utilization and antioxidant property. Long term elevated blood glucose level in diabetic patients could develop variety of vascular complications due to excessive production of reactive oxygen species (ROS) and the reduction of activities of endogenous antioxidants, such as superoxide dismutase (SOD) and catalase (CAT); hence, by correcting the impaired antioxidant status in diabetic patients will be a benefit in treating diabetes mellitus and also its vascular complications.

Table 3: Multimodal activities of listed herbs in the effective control of diabetic symptoms.

S. No.	Herb	Botanical name	Part used	Type of extract	Cases	Outcome effects
1	Garlic	Allium sativum L	Garlic	Ethanol	Streptokinin induced diabetic rats	pancreatic B cells, sparing insulin effect, increasing glucose utilization, hydroxy methyl glutaryl CoA reductase inhibitor, antioxidant, anti-inflammatory
2	Ginseng	Panax Ginseng	Berry	Methanol	Streptokinin induced diabetic rats	Enhancement of insulin sensitivity, stimulate insulin signaling, increase translocation of GLUT4, antioxidant
3	Aloe vera	Aloe Barbadensis Miller	Leaves	Methanol	Streptokinin induced diabetic rats	ncrease secretion of insulin from pancreatic beta cells., antioxidant, anti-inflammatory, inhibiting pancreatic a-amylase activity,increase insulin sensitivity
4	Bitter Melon	Momordica charantia	Fruit	Aqueous extract	Alloxan-induced diabetic mice	Stimulate glucose utilization, protection of B cell, downregulate MAPKs and NF-kB, upregulate PPAR, modulation of PTP1B, enhance glucose uptake, stimulate insulin secretion

Other Species with Promising Data for the Management of Diabetes

Several other species have been used in the ethnobotanical traditions of many countries around the world to treat diabetes (17–19), Gymnema sylvestre (Retz.) R.Br. ex Sm., commonly known as gurmar, has been used since ancient times, particularly in Ayurvedic medicine, and its anti-obesity and anti-diabetic efficacy has been clinically demonstrated [20] and confirmed in animal models [21]. The anti-diabetic activity of gurmar has been attributed mainly to gymnemic acids, gymnemasaponins and gurmarin contained in the leaves [22]. A dihydroxygymnemic acetate (20 mg/kg), isolated from G. sylvestre leaves, has been administered in streptozocin-induced diabetic rats for 45 days,

G. sylvestre leaves extract (500 mg/day for 3 months) was similarly able to reduce fasting and post prandial blood glucose and glycated hemoglobin, causing a favourable shift in lipid profile, in type 2 diabetic patieints [23].

Morus alba L. leaves demonstrated to possess a wide range of pharmacological activities in both in vitro and in vivo tests, including antidiabetic activity [24]

Linum usitatissimum L. seed oil, also referred to as flaxseed oil, is contains over than 50% ω-3 fatty acids, mainly represented by α-linolenic acid [25]. A recent randomized controlled interventional trial demonstrated the ability of L. usitatissimum seed oil (25 mg/day) to ameliorate some symptoms of metabolic syndrome, including blood pressure and lipid peroxidation [26]

Zingiber officinale Roscoe has demonstrated beneficial effects on hyperglicemia in several experimental studies, by increasing insulin sensitivity and synthesis, and glucose uptake by tissues, and by reducing oxidative stress, whilst protecting pancreatic β-cells [27]. In a double-blind placebo-controlled randomized clinical trial, the administration of Z. officinale powder (3 g/day for months), containing not quantified gingerols, in type 2 diabetic patients reduced serum glucose and glycated hemoglobin levels, decreased insulin resistance and increase total antioxidant capacity [28].

Cinnamon Botanical preparation of cinnamon may results from the dried inner bark of the shoots grown on cut stock of Cinnamomum verum J. Presl. as well as from the trunk bark, freed or cork of Cinnamomum cassia (L.) J. Presl., both species belonging to the family Lauraceae [19]. The parts of the plant used are the dried bark, free from the outer cork, which contains mainly cinnamaldehyde, eugenol and coumarin in concentrations that can vary abundantly between the two species [29]. Indeed, C. verum essential oil contains about 50–63% cinnamaldehyde and only traces of coumarins; C. cassia essential oil, instead, contains up to 95% cinnamaldehyde and up to 1% coumarins, toget

Advanced herbs in clinical trial for the treatment of diabetes

Different active principles of herbal medications possess their individual pharmacological actions to the biological system and are in use since many centuries. Due to their positive role in medicinal field, they have an extensive and worldwide recognition along with their application as herbal medicines. However, lack of safety and efficacy profile of the herbs imposed to insufficient pharmacological, pharmacokinetic and clinical status on the majority of herbal medicinal products. This widespread gap in gathering the regulatory necessities in research on herbal medications further adds to the dilemma of regulation of herbal drugs.30

Marketed herbal medications for diabetic treatment

Enormous research of herbal products for the remedy of diabetes has developed several antidiabetic products in the market worldwide. Few of them include, Diabecon®, Glyoherb, Diabeta Plus, etc.

Table 4: Composition of marketed polyherbal formulations used in the treatment of diabetes.

S. No.	Polyherbal Formulations	Ingredients
1	Diabecon31	Sphaeranthus indicus, Tribulus terrestris, Tinospora cordifolia, Triphala, Curcuma longa, Rumex maritimus, Aloe vera, Swertia chirata, Ocimum sanctum, Gymnema sylvestre, Sphaeranthus indicus, Glycyrrhiza glabra, Commiphora wightii, Phyllanthus amarus, Boerhavia diffusa, Piper nigrum, Tribulus terrestris, Pterocarpus marsupium, Syzygium cumini, Tinospora cordifolia, Berberis aristata, Gmelina arborea, Asparagus racemosus, Abutilon indicum, Casearia esculenta, Berberis aristata, Gossypium herbaceum.
2	Glyoherb32	Gudmar (Gymnema sylvestre), Mahamejva, Katuki (Picrorhiza kurrooa), Chirayata (Swertia chirata), Karela (Momordica charantia), Indrajav (Holarrhena pubescens), Amala (Phyllanthus emblica), Gokshur (Tribulus terretris), Haritaki (Terminalia chebula), Jambu bij (Eugenia Jambolana), Methi (Trigonella foenum-graecum), Neem, Chandraprabha, Arogyavardhini, Haridra (Curcuma longa), Bang Bhasma, Devdar, Daruhaldi (Berberis aristata), Nagarmotha (Cyperus scariosus), Shuddha Shilajit, Galo
3	Diabeta Plus33	Vijayasar (Pterocarpus marsupium), Gurmar (Gymnema sylves), Jamun (Syzygium cumini), Karela (Momordica charantia), Shilajit (Asphaltum), Madagascar periwinkle (Catharanthus roseus)

Conclusion

The use of plants is one of the ancient traditions, being imposed to current society in the urge to evaluate the mechanism of their underlying pharmacological action and their associated benefits and adverse effects. Thus, use of herbal medicines is still continued in modern society for the prevention, wellbeing and treatment of diabetes.The comprehensive overview of the dataset suggests that dietary natural products and phytotherapy have today an interesting role in controlling the normal to border-line glucidic levels and as an integrative therapy

References

1. Kesavadev J, Saboo B, Sadikot S, et al. Unproven therapies for diabetes and their implications. Adv Ther. 2017;34(1):60e77. https://doi.org/10.1007/ s12325-016-0439-x.

2. Vasant More S, Kim I-S, Choi D-K. Recent update on the role of Chinese material medica and formulations in diabetic retinopathy. Molecules. 2017;22(1): 76. https://doi.org/10.3390/molecules22010076. 8. Bing P, Jing G, Linhua Z, et al. Retrospective study of Traditional Chinese Medicine treatment of type 2 diabetes mellitus. J Tradit Chin Med. 2016;36(3): 307e313. https://doi.org/10.1016/S0254-6272(16)30042-5.

3. Kumar S, Dobos GJ, Rampp T. The significance of ayurvedic medicinal plants. J Evid Based Complement Altern Med. 2016:1e8. https://doi.org/10.1177/ 2156587216671392.

4. Afolayan AJ, Grierson DS, Mbeng WO. Ethnobotanical survey of medicinal plants used in the management of skin disorders among the Xhosa communities of the Amathole District, Eastern Cape, South Africa. J Ethnopharmacol. 2014;153(1):220e232. https://doi.org/10.1016/j.jep.2014.02.023.

5. Famewo EB, Clarke AM, Afolayan AJ. Identification of bacterial contaminants in polyherbal medicines used for the treatment of tuberculosis in Amatole District of the Eastern Cape Province, South Africa, using rapid 16S rRNA technique. J Heal Popul Nutr. 2016;0(0):1e9. https://doi.org/10.1186/s41043- 016-0064-y.

6. Menendez-Baceta G, Aceituno-Mata L, Molina M, Reyes-Garc AV, Tard OJ, Pardo-De-Santayana M. Medicinal plants traditionally used in the northwest of the basque country (biscay and Alava), Iberian peninsula. J Ethnopharmacol. 2014;152(1):113e134. https://doi.org/10.1016/j.jep.2013.12.038.

7. Cavero RY, Akerreta S, Calvo MI. Medicinal plants used for dermatological affections in Navarra and their pharmacological validation. J Ethnopharmacol. 2013;149(2):533e542. https://doi.org/10.1016/j.jep.2013.07.012.

8. De Rus Jacquet A, Subedi R, Ghimire SK, Rochet JC. Nepalese traditional medicine and symptoms related to Parkinsons disease and other disorders: patterns of the usage of plant resources along the Himalayan altitudinal range. J Ethnopharmacol. 2014;

153(1):178e189. https://doi.org/10.1016/ j.jep.2014.02.016. 15. Ye L, Jia Y, Ji K, et al. Traditional Chinese medicine in the prevention and treatment of cancer and cancer metastasis (Review). Oncol Lett. 2015;10(3): 1240e1250. https://doi.org/10.3892/ol.2015.3459.

9. Menale B, Muoio R. Use of medicinal plants in the south-eastern area of the partenio regional park (Campania, southern Italy). J Ethnopharmacol. 2014;153(1):297e307. https://doi.org/10.1016/j.jep.2014.02.039.

10. Mani Senthil Kumar KT, Gorain B, Roy DK, et al. Anti-inflammatory activity of Acanthus ilicifolius. J Ethnopharmacol. 2008;120(1). https://doi.org/10.1016/ j.jep.2008.07.024.

11. Senthil Kumar KTM, Puia Z, Samanta SK, et al. The gastroprotective role of Acanthus ilicifolius - a study to Unravel the underlying mechanism of antiulcer activity. Sci Pharm. 2012;80(3). https://doi.org/10.3797/scipharm.1108- 11.

12. Tuttolomondo T, Licata M, Leto C, et al. Ethnobotanical investigation on wild medicinal plants in the monti sicani regional park (sicily, Italy). J Ethnopharmacol. 2014;153(3):568e586. https://doi.org/10.1016/ j.jep.2014.02.032.

13. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care. 2012;35:2121e2127. https://doi.org/10.2337/dc12-0116. November.

14. Howard ME, White ND. Potential Benefi Ts of Cinnamon in Type 2 Diabetes. 2013;7(1):2013e2016. https://doi.org/10.1177/1559827612462960.

15. Pothuraju R, Sharma RK, Onteru SK, Singh S, Hussain SA. Hypoglycemic and Hypolipidemic Effects Of Aloe vera extract

preparations: a review. Phyther Res. 2016;30(2):200e207. https://doi.org/10.1002/ptr.5532.

16.van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. a-glucosidase inhibitors for patients with type 2 diabetes. *Diabetes Care*. 2004;28(1). http://care.diabetesjournals.org/content/28/1/154.short (Accessed 24 May 2017).

17. Sathasivampillai, S.V.; Rajamanoharan, P.R.S.; Munday, M.; Heinrich, M. Plants used to treat diabetes in Sri Lankan Siddha Medicine—An ethnopharmacological review of historical and modern sources. J. Ethnopharmacol. 2017, 198, 531–599. [CrossRef] [PubMed]

18. Afifi-Yazar, F.U.; Kasabri, V.; Abu-Dahab, R. Medicinal plants from Jordan in the treatment of diabetes: Traditional uses vs. in vitro and in vivo evaluations—Part 2. Planta Med. 2011, 77, 1210–1220. [CrossRef] [PubMed]

19. Ezuruike, U.F.; Prieto, J.M. The use of plants in the traditional management of diabetes in Nigeria: Pharmacological and toxicological considerations. J. Ethnopharmacol. 2014, 155, 857–924. [CrossRef] [PubMed]

20. NIH ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT02370121 (accessed on 22 November 2017).

21. Pothuraju, R.; Sharma, R.K.; Chagalamarri, J.; Jangra, S.; Kumar Kavadi, P. A systematic review of Gymnema sylvestre in obesity and diabetes management. J. Sci. Food Agric. 2014, 94, 834–840. [CrossRef] [PubMed]

22. Tiwari, P.; Mishra, B.N.; Sangwan, N.S. Phytochemical and Pharmacological Properties of Gymnema sylvestre: An Important Medicinal Plant. Biomed. Res. Int. 2014, 2014, 830285. [CrossRef] [PubMed]

23. Kumar, S.N.; Mani, U.V.; Mani, I. An open label study on the supplementation of Gymnema sylvestre in type 2 diabetics. J. Diet. Suppl. 2010, 7, 273–282. [CrossRef] [PubMed]

24. Gryn-Rynko, A.; Bazylak, G.; Olszewska-Slonina, D. New potential phytotherapeutics obtained from white mulberry (Morus alba L.) leaves. Biomed. Pharmacother. 2016, 84, 628–636. [CrossRef] [PubMed]

25. Singh, K.K.; Mridula, D.; Rehal, J.; Barnwal, P. Flaxseed: A potential source of food, feed and fiber. Crit. Rev. Food Sci. Nutr. 2011, 51, 210–222. [CrossRef] [PubMed]

26. Akrami, A.; Nikaein, F.; Babajafari, S.; Faghih, S.; Yarmohammadi, H. Comparison of the effects of flaxseed oil and sunflower seed oil consumption on serum glucose, lipid profile, blood pressure, and lipid peroxidation in patients with metabolic syndrome. J. Clin. Lipidol. 2017, in press. [CrossRef] [PubMed]

27. Akash, M.S.H.; Rehman, K.; Tariq, M.; Chen, S. Zingiber officinale and Type 2 Diabetes Mellitus: Evidence from Experimental Studies. Crit. Rev. Eukaryot. Gene Expr. 2015, 25, 91–112. [CrossRef] [PubMed] Molecules 2018, 23, 105 21 of 22

28. Shidfar, F.; Rajab, A.; Rahideh, T.; Khandouzi, N.; Hosseini, S.; Shidfar, S. The effect of ginger (Zingiber officinale) on glycemic markers in patients with type 2 diabetes. J. Complement. Integr. Med. 2015, 12, 165–170. [CrossRef] [PubMed]

29. Archer, A.W. Determination of cinnamaldehyde, coumarin and cinnamyl alcohol in cinnamon and cassia by high-performance liquid chromatography. J. Chromatogr. A 1988, 447, 272–276. [CrossRef]

30. Parveen A, Parveen B, Parveen R, Ahmad S. Challenges and guidelines for clinical trial of herbal drugs. J Pharm Bioallied Sci. 2015;7(4):329e333. https://doi.org/10.4103/0975-7406.168035.

31. Maninder Kaur VV. Diabetes and antidiabetic herbal formulations: an alternative to Allopathy. Int J Pharmacogn. 2014;1(10):614e626. https://doi.org/

10.13040/IJPSR.0975-8232.IJP.1(10).614-26. 32. Modak M, Dixit P, Londhe J, Ghaskadbi S, Paul T, Devasagayam A. Serial review

indian herbs and herbal drugs used for the treatment of diabetes. J Clin Biochem Nutr. 2007;40:163e173.

33. Diabeta Plus e Maintain Good Blood Sugar Level e Natural Herbal Supplements j AyurvedicCure.com.