

Nutraceutical in the Management of Diabetes Mellitus: A Review

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Abstract

Objective: Diabetes mellitus (DM) is recognized as one of the most critical health issues and leading causes of death worldwide. This disease is associated with macro-vascular and micro-vascular complications. The prevention of DM and its complications is always essential. In recent years, due to the known biological properties of some foods, the tendency to consume these foods has increased. This narrative review showed the effect of cinnamon, ginseng, thyme, sesame oil, fenugreek, saffron, aloe vera, garlic, ginger, turmeric, and green tea on improving insulin sensitivity, reducing blood sugar, blood lipid, and blood pressure, and regulating metabolism. Therefore, it is suggested that these nutraceuticals could be considered in the special food formulation of diabetic patients. It seems that the anti-diabetic properties of nutraceutical interest of diabetic persons specify their potential role in improving insulin sensitivity, lowering blood sugar, blood lipid, and blood pressure, and regulating metabolism.


Keywords: Nutraceutical, Diabetes mellitus, Blood sugar, Blood lipids, Blood pressure, Insulin sensitivity

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Introduction

Diabetes mellitus (DM), as one of the most important health issues, has become a worldwide concern. The 10th edition of the International Diabetes Federation (IDF) Atlas estimated that 1 in 10 people aged 20-79 have diabetes, equivalent to 537 million people in the world (1). It was estimated that the number of diabetic patients will globally increase to 640 million by 2040 (2). This metabolic disorder has been noted due to its complications including increased blood sugar, blood lipid and blood pressure (3). The prevalence of micro-vascular complications of diabetes, including neuropathy, nephropathy and retinopathy, are reported higher than its macro-vascular complications such as cardiovascular disease, stroke and peripheral arterial disease (4).

Unhealthy diet and lifestyle, obesity and genetic factors are risk factors of type 2 diabetes (5). Hence, in these years, attempts have been made to reduce the spread of the disease and its complications with medicinal plants (6). The potential anti-diabetic activity of alkaloids, glycosides, terpenoids, phenolic compounds and flavonoids has been shown in various experiments (7). Studies have indicated that about 800 plants may have anti-diabetic potential and beneficial effects in treating or preventing the complications of diabetes (8). Therefore, using new strategies, including functional foods such as whole or fortified and enriched foods will increase the effectiveness of diabetes management. The word "Nutraceuticals" includes "nutrients" and "medicines". They have a medicinal effect on human health (9).

Cinnamon

Cinnamon is a bushy evergreen tree of the Lauraceous family (10) and is known as an antioxidant, anti-fungal, and anti-inflammatory agent. The start of its utilization as a medicine goes back to about 2800 BC (11). Cinnamon effectively treats diabetes, heart disease, hyperlipidemia, and hypertension (12). C.

Zeylanicum is an effective species to reducing cholesterol and glucose levels (13). Polyphenols in cinnamon can increase insulin sensitivity, that associated with lower blood pressure (12). On the other hand, these molecules have various properties, such as antioxidant and anti-obesity (14). The hypoglycemic activity of this substance may be mediated by several mechanisms, including the stimulation of insulin secretion and insulin receptor signal, activation and regulation of enzymes involved in carbohydrate metabolism, glycolysis and gluconeogenesis, stimulation of cellular glucose uptake and glycogen content, and increased expression of Glucose transporter type 4 (GLUT-4) and peroxisome proliferator-activated receptors (PPARs) (15).

Anderson et al. showed that supplementation of 500 mg of cinnamon water extract for two months was associated with decreased blood glucose, fasting insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and increased insulin sensitivity in people with high blood glucose (16). Qin et al. have shown that cinnamon can significantly reduce blood glucose and lipid levels, and prevent obesity, especially abdominal obesity (17). Another clinical trial showed that intervention with cinnamon (120 and 360 mg/day) and gliclazide for three months could significantly reduce fasting blood glucose (FBG) and HbA_{1c} levels (18).

Inconsistent results were also reported in some clinical trials. Cinnamon has not appeared to improve FBG, HbA_{1c} or lipid parameters in diabetic patients in a meta-analysis of randomized controlled trials (19). Therefore, further investigations seem to be necessary to evaluate the therapeutic potential of cinnamon (20).

Ginseng

Ginseng is traditional herbal medicine in East Asian countries (21). This low-growing perennial plant has fleshy roots from the

family Araliaceae and is usually related to the *Panax* species. The main active ingredients of ginseng are ginsenoside panaxadiol, protopanaxadiol and compound K and been classified as a functional food (22).

Ginseng has many medicinal properties, including antioxidant, glycemic lowering, lipid lowering, antimicrobial, anti-inflammatory, anti-stress, and anti-cancer activities, and protecting the nervous system, heart, and liver (22,23). Ginseng anti-glycemic mechanisms can effectively inhibit protein-tyrosine phosphatase 1B (PTP1B) via PPAR and insulin signaling pathways (IRS-AMPK, PI3K/Akt, GSK-3 β). These mechanisms are associated with increased glucose uptake, glycogen synthesis, inhibition of gluconeogenesis, and impaired intestinal glucose uptake (3).

Consuming Korean red ginseng (5g /12 weeks) reduces FBG, oral glucose tolerance test (OGTT), serum insulin, and C-peptide levels in type 2 diabetic patients (23). Systemic analysis and meta-analysis showed that ginseng supplementation (0.96-13.6 g/daily for 4-20 weeks) improved FBG, postprandial insulin, Cholesterol, Triglyceride (TG), and LDL- cholesterol significantly (24). American ginseng extract supplementation (3g/day, for eight weeks) significantly has reduced FBG, systolic blood pressure SBP, HbA_{1c}, and LDL-cholesterol compared with placebo in patients with type 2 diabetes (25). However, some studies on this plant still remain obscure due to conflicting results (26).

Thymes persicus

Iranian thyme, with the scientific name of *Thymus persicus*, is one of the native plants of Iran and belongs to the Mint family. The anti-diabetic, antioxidant, anti-fungal, anti-viral, anti-bacterial, anti-Alzheimer and anti-tumor properties of this plant have been proven (27). Thyme as a source of triterpenoids, has several properties including hypoglycemic activity, anti-hyperlipidemic activity, anti-inflammatory, liver protective, antimicrobial,

anti-HIV-1, anti-ulcer and gastrointestinal protection (28).

Zamani et al. (2018) have shown a significant reduction in insulin resistance, serum insulin levels, and blood pressure with consumption of 1400 mg/daily of *Zataria multiflora* powder for 12 weeks (29). The beneficial effect of *Zataria multiflora* on insulin resistance in insulin-resistant and high fructose-fed rats was done by three mechanisms, including the direct effect of insulin, an increase of adiponectin and Peroxisome proliferator activated receptor (PPAR γ) protein expression. The intragastric injection of thyme extract (1000 mg/kg) for two weeks leads to a significant reduction in blood sugar, serum triglycerides, and insulin resistance (30).

Sesame oil

Sesame oil comprises lignans, minerals, vitamins, phytosterols, unsaturated fatty acids and tocopherols. Sesame oil has been shown the anti-hyperglycemic, anti-hyperlipidemic, anti-hypertensive, antioxidant, anti-cancer properties and immune-regulating activities (31).

The diabetic rats treated with sesame butter (1.25 g/kg) and sesame oil (0.5 g/kg) for six weeks showed lower glucose and higher high-density lipoprotein than the control diabetic rats. Sesame butter supplementation increased total antioxidant capacity and decreased malondialdehyde concentration in diabetic rats (32). In another study, daily consumption of 35g of sesame oil significantly reduced blood pressure, heart rate and arterial stiffness (33). Consuming sesame oil (35 g/daily) leads to an anti-glycemic effect in diabetic hypertensive patients during 60 days (34).

Fenugreek

Fenugreek is one of the annual herbaceous legumes of Fabaceae plants. It can have many therapeutic measures, including anti-diabetic, anti-hyperlipidemic, anti-inflammatory, anti-cancer and antioxidant (3). Fenugreek may exert its anti-hyperglycemic activity by

improving insulin resistance in fat and liver cells, increasing glucose uptake, increasing the activity of liver enzymes such as glucokinase and hexokinase, increasing serum insulin levels and increasing insulin sensitivity (31). The hypoglycemic activity of fenugreek is mainly determined by active compounds such as galactomannan, saponin and 4-hydroxyleucine (35).

The fasting consumption of fenugreek seed extract supplemented with furostanolic saponins (500 mg/day for 90 days) significantly reduced postprandial blood glucose and HbA_{1c} compared with placebo in patients with type 2 diabetes (36). Orally consumption of 25g of fenugreek seed solution (two times/daily for one month) has been shown a significant decrease in total cholesterol (TC), TG, LDL levels and an increase in high-density lipoprotein (HDL) levels in type 2 diabetic patients compared to the control group (37).

Saffron

Saffron, the dried stigma of *Crocus sativus* L, is mainly used as a food coloring and flavoring. The three main secondary metabolites are crocin, picrocrocin and safranal (38). Saffron may attribute to the reduction of oxidative stress and improve diabetes control (39).

The known mechanisms of effects of saffron are stimulating glucose uptake, inhibiting intestinal glucose absorption, and inhibiting the uptake of insulinase activity in the liver and kidneys, inhibiting glucose production, inhibiting the uptake of renal glucose or correction of insulin resistance and stimulation of β -cells (40). The results show that saffron could be a new therapeutic approach in diabetes (39).

Milajerdi et al. reviewed a three-blind randomized study involving 54 patients with type 2 diabetes who accidentally received saffron (15mg saffron hydroalcoholic extracts) two times daily for eight weeks. The results showed that the serum level of fasting blood sugar (FBS) in the saffron group decreased

significantly compared to the placebo (41). Saffron powder supplementation (100 mg/daily) significantly reduced FBG and serum TNF- α levels at eight weeks compared with placebo by reducing the expression level of some inflammatory mediators (39).

Aloe vera

Aloe vera is a plant from the Asphodelaceae/Xanthorrhoeaceae family (3). Aloe vera extract contains polysaccharides, anthraquinones and lectins with anti-diabetic activities (42). Gel derived from the flesh of leaf pulp consumed may cause hypoglycemic effects by stimulating β -cells (8,43). A. Vera has been shown to have many beneficial actions, including antioxidants, hypoglycemic, anti-hyperlipidemic, anti-inflammatory and immune system regulators (44). Possible mechanisms involved in improving blood sugar include positive regulation of insulin signaling pathways, inhibition of glucose uptake (α -glucosidase), delayed gastric emptying and ultimately improving glycemic control (45).

The oral administration of aloe led to blood sugar decrease in diabetic patients (46). The oral administration of aloe vera gel extract (300 mg/kg body weight) significantly reduced fasting blood sugar and improved plasma insulin levels in diabetic rats during 21 days (47).

Garlic (*Allium sativum*)

Garlic is an aromatic onion product belonging to the Amaryllidaceae Alliaceae / Liliaceae family. Its sulfur compounds are responsible for nutritional and medicinal functions (48). Garlic has therapeutic actions, including anti-hyperglycemic, antioxidant, hyperlipidemic, anti-inflammatory, anti-obesity, anti-atherosclerotic and anticoagulant activities (3). The anti-diabetic effect of garlic acts as both an insulin secretor and as an insulin sensitizer. It also increases glucose utilization by over-regulation of enzymes involved in glycolysis and glycogenesis (49).

A systematic study and meta-analysis (2019) concluded that garlic could lower blood pressure in hypertensive patients, just like standard blood pressure medications (48). The garlic supplement (1500 mg/day) significantly suppressed FBG and HbA_{1c} levels relative to metformin in T2DM in 24 weeks (50). The meta-analysis concluded that consuming garlic extract (allicin) significantly reduces blood sugar and lipids over 12 to 24 weeks (51). Therefore, garlic supplementation seems to improve blood sugar in patients with type 2 diabetes and is recommended as an adjunct therapy with conventional anti-glycemic drugs. Few clinical studies showed inconsistent results for the anti-diabetic effects of garlic (52).

Ginger (*Zingiber officinale*)

Zingiber officinale is a flowering plant of the Zingiberaceae family (53). Zingerone, Shogaol, and Gingerol are essential oils and the main elements of this plant that respond to various biological activities (54,55). Some ginger compounds have been reported to have potent antioxidant, anti-inflammatory properties and free radical scavenging effects (12). It can regulate insulin signaling pathways (AMPK, Akt) related to insulin sensitivity and increase glucose uptake in Gluc4 transport, glucose transport and protection of β -cells (55), insulin release/ insulinotropic activity, inhibition of α -amylase and α -glucosidase synthesis, and inhibition of enzymes related to gluconeogenesis and glycogenolysis (56). It protects against diabetic complications such as retinopathy, neuropathy, nephropathy and liver damage (3).

Shidfar et al. reported that consumption of ginger (3g /three months) was associated with decreased serum glucose, HbA_{1c}, and insulin resistance in patients with type 2 diabetes (57). A systemic analysis and meta-analysis have reported that ginger supplementation significantly reduces blood glucose and lipid levels in type 2 diabetic and hyperlipidemic individuals (56).

Turmeric (*Curcuma longa*)

Curcuma longa or turmeric has medicinal properties such as anti-stress, anti-depressant, antimicrobial and skin protection (58). The primary active components of turmeric are curcuminoids, including curcumin, desmethoxycurcumin, demethoxycurcumin and bisdemethoxycurcumin, which are responsible for therapeutic properties like anti-diabetic, anti-hyperlipidemic, antioxidant, anti-inflammatory, anti-apoptotic, anti-obesity, anti-atherosclerotic and anti-cancer (3). Turmeric is used to treat diabetic wounds, arthritis, joint pain, anorexia, cough, gastrointestinal disorders and heart disease (12). The anti-diabetic activity of turmeric induces insulin secretion by affecting insulin secretion/ insulinotropic activity and regulating different insulin signaling pathways (AMPK, Akt) (59). Turmeric destroys insulin resistance and inhibits the reabsorption of glucose, α -glucosidase and α -amylase (60).

Administration of curcumin in the form of nano-micelles (80 mg/day for three months) showed a significant decrease in the mean concentrations of FBG, HbA_{1c} and TG in type 2 diabetic patients (61). The systemic study and meta-analysis concluded that curcumin or combined curcuminoids could significantly reduce FBG levels and HbA_{1c} in diabetic patients (62). It seems that turmeric and its plant elements can be effective against type 2 diabetes and its complications.

Green tea (*Camellia sinensis*)

In hypertensive patients, three months of supplementation of green tea extract (379 mg/daily) significantly reduced systolic and diastolic blood pressure compared to the placebo group (63). Clinical evidence suggests that drinking green, black tea and coffee have direct and indirect protective effects for type 2 diabetes and cardiovascular disease (64). The consumption of green tea extract (500 mg, three times daily, for 16 weeks) significantly improves insulin resistance and increases glucagon-like production of peptide-1 (GLP-1) in type 2 diabetes (65). Although contradictory

results have been reported in studies (66). Table 1 reviews some research.

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References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th ed. Brussels, Belgium: 2021. Available at: <https://www.diabetesatlas.org>.
2. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of diabetes 2017. *Journal of diabetes research*. 2018;2018.
3. Venkatakrisnan K, Chiu HF, Wang CK. Popular functional foods and herbs for the management of type-2-diabetes mellitus: a comprehensive review with special reference to clinical trials and its proposed mechanism. *Journal of Functional Foods*. 2019;57:425-38.
4. Tuttolomondo A, Maida C, Pinto A. Diabetic foot syndrome as a possible cardiovascular marker in diabetic patients. *Journal of diabetes research*. 2015;2015.
5. Hasanpour M, Iranshahy M, Iranshahi M. The application of metabolomics in investigating anti-diabetic activity of medicinal plants. *Biomedicine & Pharmacotherapy*. 2020 ;128:110263.
6. Ansari P, Hannon-Fletcher MP, Flatt PR, Abdel-Wahab YH. Effects of 22 traditional anti-diabetic medicinal plants on DPP-IV enzyme activity and glucose homeostasis in high-fat fed obese diabetic rats. *Bioscience Reports*. 2021;41(1).
7. Patil SP, Goswami A, Kalia K, Kate AS. Plant-derived bioactive peptides: A treatment to cure diabetes. *International Journal of Peptide Research and Therapeutics*. 2020;26(2):955-68.
8. Matalqah SM, Al-Tawalbeh DM. Medicinal plants potential against diabetes mellitus. *diabetes*. 2025;9(10):11.
9. Egbuna C, Dable-Tupas G. Functional foods and nutraceuticals. Springer Nature Switzerland AG. 2020;1:1-632.
10. Sharma S, Mandal A, Kant R, Jachak S, Jagzape M. Is cinnamon efficacious for glycaemic control in type-2 diabetes mellitus?. *diabetes*. 2020;30:32.
11. Kawatra P, Rajagopalan R. Cinnamon: Mystic powers of a minute ingredient. *Pharmacognosy research*. 2015;7(Suppl 1):S1.
12. Ghaffari S, Roshanravan N. The role of nutraceuticals in prevention and treatment of hypertension: An updated review of the literature. *Food Research International*. 2020;128:108749.
13. Tulini FL, Souza VB, Echalar-Barrientos MA, Thomazini M, Pallone EM, Favaro-Trindade CS. Development of solid lipid microparticles loaded with a proanthocyanidin-rich cinnamon extract (*Cinnamomum zeylanicum*): Potential for increasing antioxidant content in functional foods for diabetic population. *Food Research International*. 2016;85:10-8.
14. Zare R, Nadjarzadeh A, Zarshenas MM, Shams M, Heydari M. Efficacy of cinnamon in patients with type II diabetes mellitus: A randomized controlled clinical trial. *Clinical nutrition*. 2019;38(2):549-56.
15. Governa P, Bains G, Borgonetti V, Cettolin G, Giachetti D, Magnano AR, et al. Phytotherapy in the management of diabetes: a review. *Molecules*. 2018;23(1):105.
16. Anderson RA, Zhan Z, Luo R, Guo X, Guo Q, Zhou J, et al. Cinnamon extract lowers glucose, insulin and cholesterol in people with elevated serum glucose. *Journal of traditional and complementary medicine*. 2016;6(4):332-6.
17. Qin B, Panickar KS, Anderson RA. Cinnamon: potential role in the prevention of insulin resistance, metabolic syndrome, and type 2 diabetes. *Journal of diabetes science and technology*. 2010;4(3):685-93.
18. Lu T, Sheng H, Wu J, Cheng Y, Zhu J, Chen Y. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. *Nutrition Research*. 2012; 32(6):408-12.
19. Baker WL, Gutierrez-Williams G, White CM, Kluger J, Coleman CI. Effect of cinnamon on glucose control and lipid parameters. *Diabetes care*. 2008;31(1):41-3.
20. Bandara T, Uluwaduge I, Jansz ER. Bioactivity of cinnamon with special emphasis on diabetes mellitus: a review. *International journal of food sciences and nutrition*. 2012 ;63(3):380-6.
21. Cho EG, Choi SY, Kim H, Choi EJ, Lee EJ, Park PJ, et al. Panax ginseng-derived extracellular vesicles facilitate anti-senescence effects in human skin cells: an eco-friendly and sustainable way to use ginseng substances. *Cells*. 2021;10(3):486.
22. Nuri TH, Yee JC, Gupta M, Khan MA, Ming LC. A review of Panax ginseng as an herbal medicine. *Archives of Pharmacy Practice*. 2016;7(5):61-5.
23. Bang H, Kwak JH, Ahn HY, Shin DY, Lee JH. Korean red ginseng improves glucose control in subjects with impaired fasting glucose, impaired

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

- glucose tolerance, or newly diagnosed type 2 diabetes mellitus. *Journal of medicinal food*. 2014;17(1):128-34.
24. Gui QF, Xu ZR, Xu KY, Yang YM. The efficacy of ginseng-related therapies in type 2 diabetes mellitus: an updated systematic review and meta-analysis. *Medicine*. 2016;95(6).
 25. Vuksan V, Xu ZZ, Jovanovski E, Jenkins AL, Beljan-Zdravkovic U, Sievenpiper JL, et al. Efficacy and safety of American ginseng (*Panax quinquefolius* L.) extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes: a double-blind, randomized, cross-over clinical trial. *European journal of nutrition*. 2019;58(3):1237-45.
 26. Li KK, Gong XJ. A review on the medicinal potential of *Panax ginseng* saponins in diabetes mellitus. *Rsc Advances*. 2015;5(59):47353-66.
 27. Asghari B, Habibzadeh F, Ghorbani Nohooji M. Persian Thyme (*Thymus persicus*): a plant containing active metabolites with antioxidant, anti-diabetic and anti-Alzheimer effects. *Journal of Medicinal Plants*. 2019;18(70):97-109.(in Persian)
 28. Leal F, Taghouti M, Nunes F, Silva A, Coelho AC, Matos M. *Thymus* Plants: A review—Micropropagation, molecular and antifungal activity. *Active ingredients from aromatic and medicinal plants*. 2017:107-26.
 29. Zamani N, Shams M, Nimrouzi M, Zarshenas MM, Foroughi AA, Abarghoeei EF, et al. The effects of *Zataria multiflora* Boiss.(Shirazi thyme) on nonalcoholic fatty liver disease and insulin resistance: A randomized double-blind placebo-controlled clinical trial. *Complementary therapies in medicine*. 2018;41:118-23.
 30. Mohammadi A, Gholamhoseinian A, Fallah H. *Zataria multiflora* increases insulin sensitivity and PPAR γ gene expression in high fructose fed insulin resistant rats. *Iranian journal of basic medical sciences*. 2014;17(4):263.
 31. Maideen NM, Balasubramaniam R. Pharmacologically relevant drug interactions of sulfonylurea antidiabetics with common herbs. *Journal of Herbmed Pharmacology*. 2018;7(3).
 32. Haidari F, Mohammadshahi M, Zarei M, Gorji Z. Effects of sesame butter (Ardeh) versus sesame oil on metabolic and oxidative stress markers in streptozotocin-induced diabetic rats. *Iranian journal of medical sciences*. 2016;41(2):102.
 33. Houston MC. Treatment of hypertension with nutrition and nutraceutical supplements: Part 2. *Alternative and Complementary Therapies*. 2019;25(1):23-36.
 34. Sankar D, Ali A, Sambandam G, Rao R. Sesame oil exhibits synergistic effect with anti-diabetic medication in patients with type 2 diabetes mellitus. *Clinical Nutrition*. 2011;30(3):351-8.
 35. Goyal S, Gupta N, Chatterjee S. Investigating therapeutic potential of *Trigonella foenum-graecum* L. as our defense mechanism against several human diseases. *Journal of toxicology*. 2016;2016.
 36. Verma N, Usman K, Patel N, Jain A, Dhakre S, Swaroop A, et al. A multicenter clinical study to determine the efficacy of a novel fenugreek seed (*Trigonella foenum-graecum*) extract (Fenfuro™) in patients with type 2 diabetes. *Food & Nutrition Research*. 2016;60(1):32382.
 37. Geberemeskel GA, Debebe YG, Nguse NA. Antidiabetic effect of fenugreek seed powder solution (*Trigonella foenum-graecum* L.) on hyperlipidemia in diabetic patients. *Journal of diabetes research*. 2019;2019.
 38. Khorasanchi Z, Shafiee M, Kermanshahi F, Khazaei M, Ryzhikov M, Parizadeh MR, et al. *Crocus sativus* a natural food coloring and flavoring has potent anti-tumor properties. *Phytomedicine*. 2018;43:21-7.
 39. Mobasser M, Ostadrahimi A, Tajaddini A, Asghari S, Barati M, Akbarzadeh M, et al. Effects of saffron supplementation on glycemia and inflammation in patients with type 2 diabetes mellitus: A randomized double-blind, placebo-controlled clinical trial study. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(4):527-34.
 40. Tahereh F, Saeed S. The effect of saffron (*Crocus sativus* L.) and its ingredients on the management of diabetes mellitus and dislipidemia. *African Journal of Pharmacy and Pharmacology*. 2014;8(20):541-9.
 41. Milajerdi A, Jazayeri S, Hashemzadeh N, Shirzadi E, Derakhshan Z, Djazayeri A, et al. The effect of saffron (*Crocus sativus* L.) hydroalcoholic extract on metabolic control in type 2 diabetes mellitus: A triple-blinded randomized clinical trial. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2018;23.
 42. Sharma R, Amin H, Prajapati PK. Plant kingdom Nutraceuticals for diabetes. *Journal of Ayurvedic and Herbal Medicine*. 2016;2(6):224-8.
 43. Bunyapraphatsara N, Yongchaiyudha S, Rungpitarangsi V, Chokeychajaroenporn O. Antidiabetic activity of Aloe vera L. juice II. Clinical trial in diabetes mellitus patients in combination with glibenclamide. *Phytomedicine*. 1996;3(3):245-8.
 44. Kaur N, Fernandez R, Sim J. Effect of Aloe vera on glycemic outcomes in patients with diabetes mellitus: a systematic review protocol. *JB I Evidence Synthesis*. 2017;15(9):2300-6.
 45. Alinejad-Mofrad S, Foadoddini M, Saadatjoo SA, Shayesteh M. Improvement of glucose and lipid profile status with Aloe vera in pre-diabetic subjects: a randomized controlled-trial. *Journal of diabetes & metabolic disorders*. 2015;14(1):1-7.

46. Gupta R, Bajpai KG, Johri S, Saxena AM. An overview of Indian novel traditional medicinal plants with anti-diabetic potentials. *African Journal of Traditional, Complementary and Alternative Medicines*. 2008;5(1):1-7.
47. Rajasekaran S, Ravi K, Sivagnanam K, Subramanian S. Beneficial effects of Aloe vera leaf gel extract on lipid profile status in rats with streptozotocin diabetes. *Clinical and experimental pharmacology and physiology*. 2006;33(3):232-7.
48. Alves QL, Camargo SB, Silva DF. Role of nutraceuticals in the prevention and treatment of hypertension and cardiovascular diseases. *Journal of Hypertension and Management*. 2019;5(1):1-10.
49. Choudhury H, Pandey M, Hua CK, Mun CS, Jing JK, Kong L, et al. An update on natural compounds in the remedy of diabetes mellitus: A systematic review. *Journal of traditional and complementary medicine*. 2018;8(3):361-76.
50. Rizwan AM, Rafeeq AK, Imran A. Effects of garlic on blood glucose levels and HbA1c in patients with type 2 diabetes mellitus. *Journal of Medicinal Plants Research*. 2011;5(13):2922-8.
51. Wang J, Zhang X, Lan H, Wang W. Effect of garlic supplement in the management of type 2 diabetes mellitus (T2DM): a meta-analysis of randomized controlled trials. *Food & nutrition research*. 2017;61(1):1377571.
52. Ballali S, Lanciai F. Functional food and diabetes: a natural way in diabetes prevention?. *International journal of food sciences and nutrition*. 2012;63(sup1):51-61.
53. Haniadka R, Saldanha E, Sunita V, Palatty PL, Fayad R, Baliga MS. A review of the gastroprotective effects of ginger (*Zingiber officinale* Roscoe). *Food & function*. 2013;4(6):845-55.
54. Wang J, Ke W, Bao R, Hu X, Chen F. Beneficial effects of ginger *Zingiber officinale* Roscoe on obesity and metabolic syndrome: a review. *Annals of the New York academy of sciences*. 2017;1398(1):83-98.
55. Lindstedt I. Ginger and diabetes: A mini-review. *Archives of General Internal Medicine*. 2018;2(2):29-33.
56. Jafarnejad S, Keshavarz SA, Mahbubi S, Saremi S, Arab A, Abbasi S, et al. Effect of ginger (*Zingiber officinale*) on blood glucose and lipid concentrations in diabetic and hyperlipidemic subjects: A meta-analysis of randomized controlled trials. *Journal of functional foods*. 2017;29:127-34.
57. 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. *Journal of complementary and integrative medicine*. 2015;12(2):165-70.
58. Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives—A review. *Journal of traditional and complementary medicine*. 2017;7(2):205-33.
59. Ghorbani Z, Hekmatdoost A, Mirmiran P. Anti-hyperglycemic and insulin sensitizer effects of turmeric and its principle constituent curcumin. *International journal of endocrinology and metabolism*. 2014;12(4).
60. Lekshmi PC, Arimboor R, Indulekha PS, Nirmala Menon A. Turmeric (*Curcuma longa* L.) volatile oil inhibits key enzymes linked to type 2 diabetes. *International journal of food sciences and nutrition*. 2012;63(7):832-4.
61. Rahimi HR, Mohammadpour AH, Dastani M, Jaafari MR, Abnous K, Mobarhan MG, et al. The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. *Avicenna journal of phytomedicine*. 2016;6(5):567.
62. De Melo IS, Dos Santos AF, Bueno NB. Curcumin or combined curcuminoids are effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia: systematic review and meta-analysis of randomized controlled trials. *Pharmacological research*. 2018 ;128:137-44.
63. Bogdanski P, Suliburska J, Szulinska M, Stepień M, Pupek-Musialik D, Jablecka A. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. *Nutrition research*. 2012;32(6):421-7.
64. Alkhatib A, Tsang C, Tiss A, Baharun T, Arefanian H, Barake R, et al. Functional foods and lifestyle approaches for diabetes prevention and management. *Nutrients*. 2017;9(12):1310.
65. Liu CY, Huang CJ, Huang LH, Chen IJ, Chiu JP, Hsu CH. Effects of green tea extract on insulin resistance and glucagon-like peptide 1 in patients with type 2 diabetes and lipid abnormalities: a randomized, double-blinded, and placebo-controlled trial. *PLoS One*. 2014 ;9(3):e91163.
66. Fu QY, Li QS, Lin XM, Qiao RY, Yang R, Li XM, et al. Antidiabetic effects of tea. *Molecules*. 2017;22(5):849.