Natural insulin sensitizers for the management of diabetes mellitus: a review of possible molecular mechanisms

Running Title: Natural Insulin Sensitizer Agents

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Abstract

Diabetes mellitus is a growing health challenge globally which is increasing in epidemic proportion. Naturally occurring pharmacological agents are more likely to provide beneficial therapeutic effects without undesirable side-effects compared to the synthetic agents. There is growing evidence that some naturally occurring pharmacological agents derived from plants have potential anti-hyperglycemic effects. In this study, we have reviewed the molecular mechanism behind potential hypoglycemic properties of four well-known herbal-based agents namely ginger, curcumin, garlic and cinnamon. Also, we present the related clinical data confirming experimental results aiming to develop novel therapeutic strategies based on these herbal agents potentially for the management of patients with diabetes.

Keywords: Diabetes Mellitus, Ginger, Curcumin, Garlic, Cinnamon, Oxidative Stress, Glut-4, Pharmaceutical, Herbal Medicine.

Introduction

The incidence of diabetes mellitus (DM) is rising exponentially [1]. This chronic disorder has a negative effect on most the metabolic pathways [2, 3]. DM is a potent upstream event for the development of various complications such as diabetic nephropathy, retinopathy, neuropathy and cardiovascular diseases [2]. Uncontrolled DM can trigger other pathophysiologic pathways such as oxidative stress, inflammation, fibrotic process and apoptotic events and thereby impose deleterious impacts on most tissues contributing to tissue dysfunctions [2, 3]. Many antidiabetic drugs with different therapeutic potentials have been developed to normalize glycemia and to reduce the risk of diabetic complications [4-6]. Since these agents are associated with some unfavorable side effects [7, 8], the use of naturally derived compounds in the management of patients with diabetes is growing [9-11]. These natural-based agents can potentially increase insulin sensitivity and improve insulin resistance thereby could be potentially used as therapeutic agents for the management of diabetes [9-11]. In the current study, we review the possible antidiabetic effects of some well-known natural-based agents.

The two common subtypes of DM are type 1 diabetes (T1DM) and type 2 diabetes (T2DM) [12]. About 90-95% of patients with DM have T2DM and is mainly contributed by insulin resistance in peripheral tissues [12-14].

Insulin Signal Transduction and Insulin Sensitivity

Insulin signal transduction (IST) is a complex molecular pathway with sequential steps involving different enzymes and mediators resulting in glucose entering into the cells facilitated by GLUT-4 (glucose transporter-4) transporters [15, 16]. GLUT-4 is a protein mainly localized in adipocytes, muscles and myocardial cells and is responsible for glucose uptake into these cells in response to circulating insulin [17]. The IST is initiated by binding of insulin to its specific receptors known as insulin receptors (IRs) [17]. This binding process induces downstream events such as recruitment of different adaptor proteins including insulin

receptor substrates (IRSs), Shc (SHC-transforming) protein and APS protein (an adapter protein) [18, 19]. These events provide a binding site for the IRS-1 (insulin receptor substrate type 1) [19]. IRS-1 is also sensitive to other types of kinases such as ERK1/2 (extracellular signal-regulated kinase 1/2), atypical PKC (protein kinase C), S6K1 (ribosomal protein S6 kinase beta-1), SIK2 (serine/threonine-protein kinase 2), Akt (protein kinase B), mTOR (mammalian target of rapamycin), ROCK1 (Rho-associated protein kinase 1), AMPK (AMP-activated protein kinase) and GSK3 (glycogen synthase kinase 3) which are activated after phosphorylation [19, 20]. Activated IRS-1 binds to PI3K (phosphoinositide 3-kinase) and activate it which in turn catalyzes the conversion of PIP_2 (Phosphatidylinositol 4,5-bisphosphate) to PIP_3 (Phosphatidylinositol 3,4,5-trisphosphate) [21]. PIP_3 is itself a potent activator for Akt, which induces GLUT-4 localization and thereby facilitates glucose entering into the insulin-dependent cells [21, 22]. Any disturbance in these sequential delicate steps can potentially impair normal IST and thereby, induces varying degrees of insulin resistance and DM [16]. Hence, any factors which could potentially promote these sequential steps can induce insulin sensitivity and thereby improve insulin resistance [15, 23-25].

Natural Insulin Sensitizers

In addition to synthetic medications, some plants and/or their extract can be considered as natural pharmaceuticals which have hypoglycemic effects through different molecular pathways [9-11, 26]. Emerging in vitro and in vivo evidence suggest that the five main naturally occurring agents that have potential antihyperglycemic effects are saffron, ginger, curcumin, cinnamon and garlic [9, 27-30]. We have previously reviewed the antihyperglycemic potentials of saffron and its active ingredients [9]. In the following sections, we have discussed the four main naturally derived plants with antihyperglycemic properties viz ginger, curcumin, garlic and cinnamon and their potential molecular mechanisms.

1. Curcumin

Curcumin is an active diarylheptanoid compound from the curcuminoid family which is mainly found in turmeric species and is responsible for the yellow color of this plant [31, 32]. Besides as a dietary supplement, this phytochemical has various pharmacological actions [33-39] as well as insulin-sensitizing and hypoglycemic effects [36, 40-45]. It can exert its antidiabetic effects in T2DM through various molecular pathways [27]. Curcumin has strong anti-inflammatory potentials which enable it to lower inflammation-induced insulin resistance in DM [46]. It can attenuate the inflammatory events in the beta cells by suppressing the activity of T lymphocytes and reducing the expression of inflammatory cytokines in the diabetic milieu [46]. Evidence suggests that curcumin is a potent antioxidant which neutralizes the oxidative stress involved in promoting insulin resistance [47]. It can induce Nrf2 activity and up-regulate elements of the antioxidant defense system [48, 49]. It has also been shown that curcumin might improve mitochondrial function and reduces the free radical generation leading to lower oxidative damages in the beta cells [50, 51]. Moreover, Curcumin may provide an insulin sensitizer effect by stimulating the GLUT-4 expression in the diabetic milieu [52]. Curcumin could also promote beta cell function and thereby improve insulin sensitivity [40, 52]. Improvement in lipid metabolism can be considered as another possible molecular pathway by which curcumin increases insulin sensitivity [53-55].

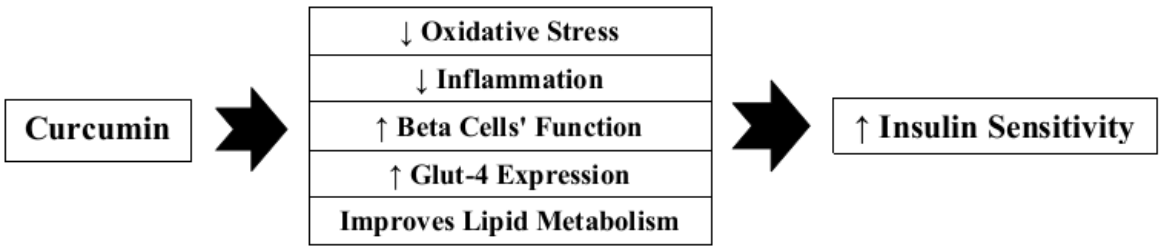

Figure 1; Curcumin induces insulin sensitivity via at least five molecular mechanisms

There is also clinical evidence suggesting the potential role of curcumin as an antihyperglycemic agent [27, 56, 57] (table 1). Na et al in 2013 demonstrated that it can reduce

the HbA_{1c} (hemoglobin A_{1c}) and improve insulin resistance via lowering the FFAs (free fatty acids) in patients with diabetes [27]. Chuengsamarn et al after a randomized controlled trial of 6 months reported that curcumin reduced the fasting blood glucose and HbA1c via improvement in insulin sensitivity and glucose homeostasis in patients with T2DM [56]. Jiménez-Osorio et al have shown that curcumin markedly reduced fasting plasma glucose in patients with T2DM [58]. Moreover, Hodaie and coworkers have shown that curcumin markedly reduced fasting hyperglycemia and HbA1c in patients with T2DM [57]. These clinical trials have confirmed the experimental data suggesting that curcumin has antihyperglycemic effects by improving insulin sensitivity in a diabetic milieu [27, 56, 57].

2. Ginger

Ginger is a flavoring plant belonging to Zingiberaceae family which has pharmacological effects beyond its use as a food additive [59]. Evidence demonstrated that the rhizomes of the ginger roots widely used in ancient medicine have significant hypoglycemic effects [59-61]. Ginger can induce insulin sensitivity via different molecular pathways such as antioxidative, anti-inflammatory, lipid modulatory and by preventing lipid peroxidation [62-64]. It can also modulate the molecular mechanisms of IST as PI3K activity, Akt activation, IRS-1 phosphorylation and GLUT-4 localization in 3T3-L1 adipocytes [29].

Clinical evidence has confirmed these findings [62]. Khandouzi and coworkers in 2015 surveyed the antidiabetic effects of ginger and found that it reduces hyperglycemia, fasting blood glucose, HbA1c and MDA (malondialdehyde) in patients with T2DM potentially mediated by its antioxidative properties [62]. Mozaffari and colleagues in 2014 conducted a clinical trial demonstrating that ginger powder reduces fasting blood glucose, HbA1c and induces insulin sensitivity in patients with T2DM [65]. Moreover, Bahramian et al in 2018 demonstrated that daily administration of ginger in women with gestational diabetes has no significant effects on fasting hyperglycemia and HbA1c, but increased the glucose tolerance in

these patients [66]. Similarly, Haas and coworkers in 2015 reported that daily usage of ginger supplements reduced fasting hyperglycemia and HbA1c as well as increased insulin sensitivity in patients with T2DM [67]. This evidence suggests that ginger species has potential insulin sensitizer effects that could be of potential benefit in patients with T2DM.

3. Garlic

Garlic (Allium sativum) plant is an ancient species possessing a wide range of pharmacological effects including antimicrobial, anti-cancer, anti-inflammatory, immunomodulatory, neuroprotective, antioxidative as well as anti-diabetic properties [68-71]. Evidence demonstrated that garlic extract can modulate some molecular mechanisms involved in IST [72-76]. It can induce AMP-activated protein kinase and increase insulin sensitivity in adipocytes [30]. Also, garlic extract can reduce the oxidative stress leading to an improvement in insulin sensitivity [76], which was confirmed by other studies [77].

There are also clinical data demonstrating the antihyperglycemic properties of garlic [78]. Ashraf et al in 2011 has shown that aged garlic extract can exert obvious hypoglycemic effects by lowering the fasting blood glucose (FBG) and HbA1c in patients with T2DM [78]. Kumar and coworkers in 2013 reported that garlic extract induces insulin sensitivity by reducing the inflammatory response and deaminase levels as well as resulted in an improvement in lipid profile in patients with T2DM [79]. Faroughi et al in 2017 provided data in gestational diabetes demonstrating garlic pill significantly increased insulin sensitivity in women with gestational diabetes [80]. Although more clinical trials are needed, the available evidence suggests potential antihyperglycemic effects of garlic and its extracts.

4. Cinnamon

Cinnamon is a spice of the genus Cinnamomum. It has been primarily recognized as a food additive, but has potent medicinal effects and thereby used for thousands of years in ancient medicine [81]. There is evidence suggesting that cinnamon and/or its active flavoring

ingredient, cinnamaldehyde, can improve glucose homeostasis and induce insulin sensitivity in adipocytes and muscle tissues via several molecular pathways (fig 2) [82, 83]. It can increase glucose transport across the cell membrane by promoting GLUT-4 expression/localization [84]. Also, cinnamon can promote different steps of IST such as IRS-1 phosphorylation and PI3K activity thereby inducing insulin sensitivity [84]. Modulatory effects on the pathophysiologic pathways involved in insulin resistance such as AGE-RAGE interaction, oxidative damages and inflammatory responses are the other possible ways by which cinnamon induces insulin sensitivity in adipose and muscle tissues [84]. Treatment with cinnamon extract decreases the mRNA expression of the inflammatory mediators such as IL (interleukin)-1β, IL6, and TNF-α (tumor necrosis factor-alpha) and modulates the mRNA expression of IR, IRS-1 and 2, PI3K, and Akt [84, 85]. It can also improve insulin sensitivity via PPAR (peroxisome proliferator-activated receptors) activation in 3T3-L1 adipocyte [28]. These effects are accompanied by improved insulin signaling in brain tissues that confirming the effect of cinnamon on the IST [86].

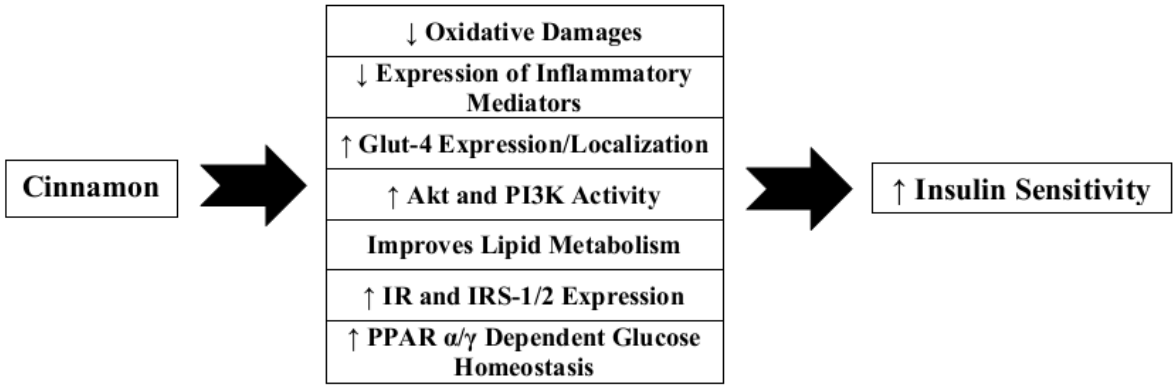

Fig 2; Main molecular pathways by which cinnamon induces insulin signal transduction

There are also clinical studies demonstrating the effect of cinnamon on insulin sensitivity [87]. Stoecker et al in 2010 showed that cinnamon therapy in T2DM patients reduced FBG, HbA1c and HOMA-IR [87]. It also modified glucose homeostasis by promoting postprandial GLP-1

(glucagon-like peptide-1) secretion [88, 89]. Mang et al in 2006 demonstrated that cinnamon increases insulin sensitivity by improving the lipid metabolism in patients with T2DM [90]. Wang et al in 2007 provided further evidence in patients with diabetes and polycystic ovary syndrome demonstrating the insulin-sensitizing effects of cinnamon [91]. More clinical evidence is presented in table 1. We also have some reports indicating no significant effects on cinnamon extract on insulin sensitivity [92, 93].

Natural Agent	Population of Study (without placebo groups)	Dosage/Duration	Clinical Effects	Ref.
Curcumin	50 Patients with T2DM	300 mg/day/6 months	Decreased FBS, HbA1c, HOMA-IR and insulin sensitivity	[27]
	113 Patients with T2DM	250 mg/day/6 months	Reduced FBS, HbA1c and LDL	[56]
	105 Patients with diabetic or non-diabetic CKD	320 mg/day/8 weeks	Declined FBS	[58]
	53 Patients with T2DM	1500 mg/day/10 weeks	Reduced FBS and body weight	[57]
Ginger	22 Patients with T2DM	2 g/day/12 weeks	Reduced FBS, HbA1c and Apo lipoproteins	[62]
	88 Patients with T2DM	3 g/day/8 weeks	Decreased FBS, HbA1c and insulin resistance	[65]
	76 women with gestational diabetes	500 mg/day/8 weeks	No significant effects on FBS and HbA1c, but improved the glucose tolerance	[66]
	33 Patients with T2DM	1600 mg/day/12 weeks	Markedly reduced FBS, HbA1c, and insulin sensitivity	[67]
Garlic	210 Patients with T2DM	300, 600, 900, 1200, and 1500 mg/day/ 24 weeks	Reduced the FBS and HbA1c	[78]
	60 Patients with T2DM	250 mg/day/12 weeks	Induced insulin sensitivity via attenuating inflammatory events and improving lipid profile	[79]
	26 women with gestational diabetes	400 mg/day/8 weeks	Reduces FBS and HbA1c	[80]
Cinnamon	137 Patients with T2DM	500 mg/day/2 months	Declined FBS, HbA1c and HOMA-IR	[87]
	79 Patients with T2DM	3 g/day/4 months	Reduced FBS, LDL, HDL, and HbA1c	[90]
	40 diabetic women with PCOS	1 g/day/8 weeks	Increases insulin sensitivity and declines HOMA-IR	[91]

	137 patients with hyperglycemia	500 mg/day/2 months	Reduced LDL, HDL, FBS, and increases insulin sensitivity	[94]
	66 women with PCOS	1.5 g/day/12 weeks	Declined FBS and HbA1c	[95]

Table 1: Clinical evidences about insulin sensitizing effects of ginger, curcumin, garlic and cinnamon (CKD=chronic kidney disease, FBS= fasting blood glucose, HOMA-IR=homeostatic index of insulin resistance, LDL= low density lipoprotein, HDL= high density lipoprotein, HbA1c= glycosylated hemoglobin, PCOS= polycystic ovary syndrome)

Conclusion

Herbal-based therapeutic approaches for patients with diabetes have been tried for thousands of years and has received more attention recently. There is a growing evidence that ginger, curcumin, garlic and cinnamon have potent antihyperglycemic effects and thereby their extracts can be potentially useful in the management of patients with T2DM. Although some clinical trials have confirmed the experimental evidence, there is a need for more clinical trial evidence especially, for garlic and cinnamon. This suggests that herbal-based agents could be the next generation of therapeutic intervention for the management of diabetes. However more clinical trials are needed for identifying the ideal dosage, duration of therapy, and formulation is still required.

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Conflict of Interests

The authors clearly declare that they have no conflict of interest in this study.

References

1. Mayer-Davis, E.J., et al., *Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012.* New England Journal of Medicine, 2017. **376**(15): p. 1419-1429.
2. Forbes, J.M. and M.E. Cooper, *Mechanisms of diabetic complications.* Physiological reviews, 2013. **93**(1): p. 137-188.
3. Volpe, C.M.O., et al., *Cellular death, reactive oxygen species (ROS) and diabetic complications.* Cell death & disease, 2018. **9**(2): p. 119.
4. Yaribeygi, H., et al., *Antioxidative potential of antidiabetic agents: A possible protective mechanism against vascular complications in diabetic patients.* Journal of cellular physiology, 2019. **234**(3): p. 2436-2446.
5. Yaribeygi, H., et al., *A review of the anti-inflammatory properties of antidiabetic agents providing protective effects against vascular complications in diabetes.* Journal of cellular physiology, 2019. **234**(6): p. 8286-8294.
6. Yaribeygi, H., et al., *Effects of novel antidiabetes agents on apoptotic processes in diabetes and malignancy: Implications for lowering tissue damage.* Life sciences, 2019.
7. Chaudhury, A., et al., *Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management.* Frontiers in endocrinology, 2017. **8**: p. 6.
8. Bennett, W.L., et al., *Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations.* Annals of internal medicine, 2011. **154**(9): p. 602-613.
9. Yaribeygi, H., et al., *Antidiabetic potential of saffron and its active constituents.* Journal of cellular physiology, 2019. **234**(6): p. 8610-8617.
10. Yaribeygi, H., et al., *Molecular mechanisms by which aerobic exercise induces insulin sensitivity.* Journal of cellular physiology, 2019. **234**(8): p. 12385-12392.
11. Yaribeygi, H., et al., *Molecular mechanisms of trehalose in modulating glucose homeostasis in diabetes.* Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2019.
12. Association, A.D., *Diagnosis and classification of diabetes mellitus.* Diabetes care, 2014. **37**(Supplement 1): p. S81-S90.
13. de Faria Maraschin, J., *Classification of diabetes*, in *Diabetes*. 2013, Springer. p. 12-19.
14. O'Neal, K.S., J.L. Johnson, and R.L. Panak, *Recognizing and appropriately treating latent autoimmune diabetes in adults.* Diabetes Spectrum, 2016. **29**(4): p. 249-252.
15. Yaribeygi, H., et al., *Insulin resistance: Review of the underlying molecular mechanisms.* Journal of cellular physiology, 2019. **234**(6): p. 8152-8161.
16. Samuel, V.T. and G.I. Shulman, *The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux.* The Journal of clinical investigation, 2016. **126**(1): p. 12-22.
17. Færch, K., et al., *Insulin resistance is accompanied by increased fasting glucagon and delayed glucagon suppression in individuals with normal and impaired glucose regulation.* Diabetes, 2016: p. db160240.
18. Hall, J.E., *Guyton and Hall textbook of medical physiology e-Book*. 2015: Elsevier Health Sciences.
19. Kiselyov, V.V., et al., *Harmonic oscillator model of the insulin and IGF1 receptors' allosteric binding and activation.* Molecular systems biology, 2009. **5**(1): p. 243.
20. Copps, K. and M. White, *Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2.* Diabetologia, 2012. **55**(10): p. 2565-2582.
21. Ho, C.K., G. Sriram, and K.M. Dipple, *Insulin sensitivity predictions in individuals with obesity and type II diabetes mellitus using mathematical model of the insulin signal transduction pathway.* Molecular genetics and metabolism, 2016. **119**(3): p. 288-292.
22. Koeppen, B.M. and B.A. Stanton, *Berne and levy physiology e-book*. 2017: Elsevier Health Sciences.

23. Berry, C., M. Lal, and B. Binukumar, *Crosstalk between the unfolded protein response, MicroRNAs, and insulin signaling pathways: in search of biomarkers for the diagnosis and treatment of type 2 diabetes.* Frontiers in endocrinology, 2018. **9**: p. 210.
24. Yaribeygi, H., et al., *PPAR-α agonist fenofibrate potentiates antioxidative elements and improves oxidative stress of hepatic cells in streptozotocin-induced diabetic animals.* Comparative Clinical Pathology, 2019. **28**(1): p. 203-209.
25. Yaribeygi, H., S.L. Atkin, and A. Sahebkar, *Wingless-type inducible signaling pathway protein-1 (WISP1) adipokine and glucose homeostasis.* Journal of cellular physiology, 2019.
26. Yaribeygi, H., S.L. Atkin, and A. Sahebkar, *Natural compounds with DPP-4 inhibitory effects: Implications for the treatment of diabetes.* Journal of cellular biochemistry, 2019. **120**(7): p. 10909-10913.
27. Na, L.X., et al., *Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial.* Molecular nutrition & food research, 2013. **57**(9): p. 1569-1577.
28. Sheng, X., et al., *Improved insulin resistance and lipid metabolism by cinnamon extract through activation of peroxisome proliferator-activated receptors.* PPAR research, 2008. **2008**.
29. Chen, J., et al., *Gingerenone A Sensitizes the Insulin Receptor and Increases Glucose Uptake by Inhibiting the Activity of p70 S6 Kinase.* Molecular nutrition & food research, 2018. **62**(23): p. 1800709.
30. Miki, S., et al., *Aged garlic extract suppresses the increase of plasma glycated albumin level and enhances the AMP-activated protein kinase in adipose tissue in TSOD mice.* Molecular nutrition & food research, 2017. **61**(5): p. 1600797.
31. Mirzaei, H., et al., *Curcumin: A new candidate for melanoma therapy?* International journal of cancer, 2016. **139**(8): p. 1683-1695.
32. Sahebkar, A., *Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome?* Biofactors, 2013. **39**(2): p. 197-208.
33. Abdollahi, E., et al., *Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades?* Journal of Cellular Physiology, 2018. **233**(2): p. 830-848.
34. Ahangari, N., et al., *Curcumin in tissue engineering: A traditional remedy for modern medicine.* BioFactors, 2019. **45**(2): p. 135-151.
35. Karimian, M.S., et al., *Curcumin as a natural regulator of monocyte chemoattractant protein-1.* Cytokine and Growth Factor Reviews, 2017. **33**: p. 55-63.
36. Mirzaei, H., et al., *MicroRNA: A novel target of curcumin in cancer therapy.* Journal of Cellular Physiology, 2017. **233**(4): p. 3004-3015.
37. Panahi, Y., et al., *Efficacy and Safety of Phytosomal Curcumin in Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial.* Drug Research, 2017. **67**(4): p. 244-251.
38. Rezaee, R., et al., *Curcumin: A potentially powerful tool to reverse cisplatin-induced toxicity.* Pharmacological Research, 2017. **117**: p. 218-227.
39. Tabeshpour, J., et al., *Effects of curcumin on ion channels and pumps: A review.* IUBMB Life, 2019. **71**(7): p. 812-820.
40. Chuengsamarn, S., et al., *Curcumin extract for prevention of type 2 diabetes.* Diabetes care, 2012. **35**(11): p. 2121-2127.
41. Zhang, D.-w., et al., *Curcumin and diabetes: a systematic review.* Evidence-Based Complementary and Alternative Medicine, 2013. **2013**.
42. Hajavi, J., et al., *Curcumin: A Naturally Occurring Modulator of Adipokines in Diabetes.* Journal of Cellular Biochemistry, 2017. **118**(12): p. 4170-4182.
43. Panahi, Y., et al., *Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial.* Inflammopharmacology, 2017. **25**(1): p. 25-31.

44. Panahi, Y., et al., *Effects of Curcuminoids Plus Piperine on Glycemic, Hepatic and Inflammatory Biomarkers in Patients with Type 2 Diabetes Mellitus: A Randomized Double-Blind Placebo-Controlled Trial.* Drug Research, 2018. **68**(7): p. 403-409.
45. Parsamanesh, N., et al., *Therapeutic potential of curcumin in diabetic complications.* Pharmacological Research, 2018. **136**: p. 181-193.
46. Castro, C.N., et al., *Curcumin ameliorates autoimmune diabetes. Evidence in accelerated murine models of type 1 diabetes.* Clinical & Experimental Immunology, 2014. **177**(1): p. 149-160.
47. Meng, B., J. Li, and H. Cao, *Antioxidant and antiinflammatory activities of curcumin on diabetes mellitus and its complications.* Current pharmaceutical design, 2013. **19**(11): p. 2101-2113.
48. He, H.-J., et al., *Curcumin attenuates Nrf2 signaling defect, oxidative stress in muscle and glucose intolerance in high fat diet-fed mice.* World journal of diabetes, 2012. **3**(5): p. 94.
49. Yang, H., et al., *Curcumin attenuates urinary excretion of albumin in type II diabetic patients with enhancing nuclear factor erythroid-derived 2-like 2 (Nrf2) system and repressing inflammatory signaling efficacies.* Experimental and Clinical Endocrinology & Diabetes, 2015. **123**(06): p. 360-367.
50. Soto-Urquieta, M.G., et al., *Curcumin restores mitochondrial functions and decreases lipid peroxidation in liver and kidneys of diabetic db/db mice.* Biological research, 2014. **47**(1): p. 74.
51. Rashid, K. and P.C. Sil, *Curcumin ameliorates testicular damage in diabetic rats by suppressing cellular stress-mediated mitochondria and endoplasmic reticulum-dependent apoptotic death.* Biochimica et biophysica acta (BBA)-molecular basis of disease, 2015. **1852**(1): p. 70-82.
52. Moradi, A., et al., *The effect of curcumin on GLUT4 gene expression as a diabetic resistance marker in C2C12 Myoblast Cells.* Iranian Journal of Diabetes and Obesity, 2014. **6**(2): p. 98-105.
53. Kim, B.H., et al., *Protective effects of curcumin on renal oxidative stress and lipid metabolism in a rat model of type 2 diabetic nephropathy.* Yonsei medical journal, 2016. **57**(3): p. 664-673.
54. Soetikno, V., et al., *Curcumin decreases renal triglyceride accumulation through AMPK–SREBP signaling pathway in streptozotocin-induced type 1 diabetic rats.* The Journal of nutritional biochemistry, 2013. **24**(5): p. 796-802.
55. Panahi, Y., et al., *Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: a randomized controlled trial.* Journal of cardiovascular pharmacology, 2016. **68**(3): p. 223-229.
56. Chuengsamarn, S., et al., *Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial.* The Journal of nutritional biochemistry, 2014. **25**(2): p. 144-150.
57. Hodaie, H., et al., *The effects of curcumin supplementation on control glycemic and anthropometric indices in overweight patients with type 2 diabetes.* Iranian Journal of Endocrinology and Metabolism, 2017. **19**(1): p. 1-9.
58. Jiménez-Osorio, A.S., et al., *The effect of dietary supplementation with curcumin on redox status and Nrf2 activation in patients with nondiabetic or diabetic proteinuric chronic kidney disease: a pilot study.* Journal of Renal Nutrition, 2016. **26**(4): p. 237-244.
59. White, B., *Ginger: an overview.* Am Fam Physician, 2007. **75**(11): p. 1689-91.
60. Fritsche, A., et al., *Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes–results of the GINGER study.* Diabetes, Obesity and Metabolism, 2010. **12**(2): p. 115-123.
61. Sharifi-Rad, M., et al., *Plants of the genus Zingiber as a source of bioactive phytochemicals: From tradition to pharmacy.* Molecules, 2017. **22**(12): p. 2145.
62. Khandouzi, N., et al., *The effects of ginger on fasting blood sugar, hemoglobin a1c, apolipoprotein B, apolipoprotein aI and malondialdehyde in type 2 diabetic patients.* Iranian journal of pharmaceutical research: IJPR, 2015. **14**(1): p. 131.

63. Bekkouch, O., et al., *In Vitro Antioxidant and In Vivo Lipid-Lowering Properties of Zingiber officinale Crude Aqueous Extract and Methanolic Fraction: A Follow-Up Study.* Evidence-Based Complementary and Alternative Medicine, 2019. **2019**.
64. Alshathly, M.R., *Efficacy of Ginger (Zingiber officinale) in ameliorating streptozotocin-induced diabetic liver injury in rats: Histological and biochemical studies.* Journal of Microscopy and Ultrastructure, 2019. **7**(2): p. 91.
65. Mozaffari-Khosravi, H., et al., *The effect of ginger powder supplementation on insulin resistance and glycemic indices in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial.* Complementary therapies in medicine, 2014. **22**(1): p. 9-16.
66. Bahramian, Z., et al., *The Effect of Ginger Capsules on the Control of Blood Sugar in Gestational Diabetes: A Triple-Blind Randomized Controlled Clinical Trial.* Crescent Journal of Medical and Biological Sciences, 2018. **5**(4): p. 358-365.
67. Haas, W., *The role of ginger in type 2 diabetes mellitus.* Integrative Medicine Alert, 2015. **18**(8): p. 85-87.
68. Agarwal, K.C., *Therapeutic actions of garlic constituents.* Medicinal research reviews, 1996. **16**(1): p. 111-124.
69. Farooqui, T. and A.A. Farooqui, *Neuroprotective Effects of Garlic in Model Systems of Neurodegenerative Diseases*, in *Role of the Mediterranean Diet in the Brain and Neurodegenerative Diseases*. 2018, Elsevier. p. 253-269.
70. Varshney, R. and M.J. Budoff, *Garlic and heart disease.* The Journal of nutrition, 2016. **146**(2): p. 416S-421S.
71. Arreola, R., et al., *Immunomodulation and anti-inflammatory effects of garlic compounds.* Journal of immunology research, 2015. **2015**.
72. Sultana, M.R., et al., *Garlic activates SIRT-3 to prevent cardiac oxidative stress and mitochondrial dysfunction in diabetes.* Life sciences, 2016. **164**: p. 42-51.
73. Al-Qattan, K.K., et al., *Garlic decreases liver and kidney receptor for advanced glycation end products expression in experimental diabetes.* Pathophysiology, 2016. **23**(2): p. 135-145.
74. Seo, Y.-J., et al., *Effect of garlic and aged black garlic on hyperglycemia and dyslipidemia in animal model of type 2 diabetes mellitus.* J Food Sci Nutr, 2009. **14**(1): p. 1-7.
75. Maeda, T., et al., *Aged garlic extract ameliorates fatty liver and insulin resistance and improves the gut microbiota profile in a mouse model of insulin resistance.* Experimental and Therapeutic Medicine, 2019. **18**(1): p. 857-866.
76. Padiya, R., et al., *Garlic improves insulin sensitivity and associated metabolic syndromes in fructose fed rats.* Nutrition & metabolism, 2011. **8**(1): p. 53.
77. Jalal, R., et al., *Hypoglycemic effect of aqueous shallot and garlic extracts in rats with fructose-induced insulin resistance.* Journal of Clinical Biochemistry and Nutrition, 2007. **41**(3): p. 218-223.
78. Ashraf, R., R.A. Khan, and I. Ashraf, *Garlic (Allium sativum) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients.* Pak J Pharm Sci, 2011. **24**(4): p. 565-570.
79. Kumar, R., et al., *Antihyperglycemic, antihyperlipidemic, anti-inflammatory and adenosine deaminase–lowering effects of garlic in patients with type 2 diabetes mellitus with obesity.* Diabetes, metabolic syndrome and obesity: targets and therapy, 2013. **6**: p. 49.
80. Faroughi, F., *The Effect of Garlic Pill on Blood Glucose Levels in Borderline Gestational Diabetes Mellitus: a Randomized Controlled Trial*. 2017, Tabriz University of Medical Sciences, School of Nursing and Midwifery.
81. Gruenwald, J., J. Freder, and N. Armbruester, *Cinnamon and health.* Critical reviews in food science and nutrition, 2010. **50**(9): p. 822-834.
82. Khan, A., et al., *Cinnamon improves glucose and lipids of people with type 2 diabetes.* Diabetes care, 2003. **26**(12): p. 3215-3218.

83. Kim, S.H., S.H. Hyun, and S.Y. Choung, *Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice.* Journal of ethnopharmacology, 2006. **104**(1-2): p. 119-123.
84. Qin, B., K.S. Panickar, and R.A. Anderson, *Cinnamon: potential role in the prevention of insulin resistance, metabolic syndrome, and type 2 diabetes.* Journal of diabetes science and technology, 2010. **4**(3): p. 685-693.
85. Qin, B., et al., *Tumor necrosis factor-α induces intestinal insulin resistance and stimulates the overproduction of intestinal apolipoprotein B48-containing lipoproteins.* Diabetes, 2007. **56**(2): p. 450-461.
86. Sartorius, T., et al., *Cinnamon extract improves insulin sensitivity in the brain and lowers liver fat in mouse models of obesity.* PloS one, 2014. **9**(3): p. e92358.
87. Stoecker, B.J., et al., *Cinnamon extract lowers blood glucose in hyperglycemic subjects*. 2010, Federation of American Societies for Experimental Biology.
88. Hlebowicz, J., et al., *Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and ghrelin concentrations in healthy subjects.* The American journal of clinical nutrition, 2009. **89**(3): p. 815-821.
89. Hlebowicz, J., et al., *Effect of cinnamon on postprandial blood glucose, gastric emptying, and satiety in healthy subjects.* The American journal of clinical nutrition, 2007. **85**(6): p. 1552-1556.
90. Mang, B., et al., *Effects of a cinnamon extract on plasma glucose, HbA1c, and serum lipids in diabetes mellitus type 2.* European journal of clinical investigation, 2006. **36**(5): p. 340-344.
91. Wang, J.G., et al., *The effect of cinnamon extract on insulin resistance parameters in polycystic ovary syndrome: a pilot study.* Fertility and sterility, 2007. **88**(1): p. 240-243.
92. Blevins, S.M., et al., *Effect of cinnamon on glucose and lipid levels in Non–insulin-dependent type 2 diabetes.* Diabetes care, 2007. **30**(9): p. 2236-2237.
93. Talaei, B., et al., *Effects of cinnamon consumption on glycemic indicators, advanced glycation end products, and antioxidant status in type 2 diabetic patients.* Nutrients, 2017. **9**(9): p. 991.
94. Anderson, R.A., et al., *Cinnamon extract lowers glucose, insulin and cholesterol in people with elevated serum glucose.* Journal of traditional and complementary medicine, 2016. **6**(4): p. 332-336.
95. Hajimonfarednejad, M., et al., *Insulin resistance improvement by cinnamon powder in polycystic ovary syndrome: A randomized double-blind placebo controlled clinical trial.* Phytotherapy research, 2018. **32**(2): p. 276-283.