Review **Open Access**

Functional foods in the treatment of type 2 diabetes: olive leaf extract, turmeric and fenugreek, a qualitative review

Mona Boaz,[1,4] Eyal Leibovitz,[2] Yosefa Bar Dayan,[3] and Julio Wainstein[3]

[1]Epidemiology and Research Unit; [2]Internal Medicine Department A; [3]Diabetes Unit, E. Wolfson Medical Center, Holon, Israel, 58100; [4]Department of Nutrition, School of Health Sciences, Ariel University Center, Ariel, Israel 40700

Corresponding Author: Dr. Mona Boaz, Epidemiology and Research Unit, E. Wolfson Medical Center, Holon, Israel, 58100, Tel/Fax: (972)-3-502-8384

Submission date: October 12, 2011; Acceptance date: November 29, 2011; Publication date: November 30, 2011

Abstract

Almost 30% of US residents ages 65 and older have diabetes. The cost of diabetes care was estimated at $174 billion in 2007, including $116 billion in additional medical costs, and $58 billion in reduced productivity. Globally, the estimated cost of diabetes care was $376 billion in 2010, representing 12% of health expenditures. Many individuals with diabetes make use of functional foods, nutritional supplements, and/or herbal remedies to manage their disease. The functional foods olive leaf extract, turmeric, and fenugreek are commonly used in traditional medicine systems to manage diabetes. All three of these functional foods have antioxidant and anti-inflammatory properties as well as specific insulin sensitizing qualities. In vitro studies offer proof of mechanism, and animal studies consistently show treatment efficacy for all three foods. The few human studies that have been conducted, however, use surrogate rather than clinical endpoints. The establishment of these and other functional foods as evidence based interventions for diabetes requires well designed, adequately powered, and randomized controlled pivotal trials with clinical endpoints.

Keywords: type 2 diabetes, olive leaf extract, turmeric, and fenugreek

Background

More than one third of all American adults are obese, reflecting an upward prevalence trend over the past two decades [1]. This obesity epidemic is associated with an increased risk of obesity-associated morbidity, including heart disease, stroke, certain cancers, and, most importantly, diabetes [2]. Approximately 26.9% of all US residents aged 65 years and older had diabetes in 2010, and an additional 1.9 million individuals aged 20 years and older were newly diagnosed with the disease [3].

Diabetes is no longer a disease of developed nations. It has been estimated that 6.4% of the global adult population, or 285 million individuals, had diabetes in 2010, and that this number is expected to increase to 7.7% or 439 million adults worldwide by 2030 [4]. These

estimates represent a 46.3% increase over earlier prevalence estimates for the period ending in 2025 [5]. Thus, it is clear that diabetes is a major global public health crisis.

The cost of diabetes care is staggering, estimated at $174 billion for the year 2007, including $116 billion in additional medical costs and $58 billion in reduced productivity costs [3]. Globally, the estimated cost of diabetes care was $376 billion in 2010, representing 12% of health care expenditures, and is expected to rise to $490 billion in 2030 [6].

In addition to medication, many individuals with diabetes use functional foods and/or take nutritional supplements and/or herbal remedies to manage their disease [7, 8]. Some functional foods have been extensively studied, including olive leaf extract, turmeric and fenugreek. All three of these functional foods have been used in traditional medicine systems to manage diabetes [9, 10].

The present qualitative review is undertaken to examine the pre-clinical and clinical evidence regarding the efficacy of each of these functional foods in treating diabetes in humans.

OLIVE LEAF EXTRACT

Bioactive properties

Olive leaves, particularly Olea europaea L., are rich in phenolic compounds including flavones, flavonols, catechin, and substituted phenols [11]. The most abundant polyphenol in olive leaves is oleuropein, which accounts for approximately 20% of phenolic compounds in the olive leaf, which has been shown to suppress improved insulin secretion in H_2O_2-exposed cells [12]. Olive leaf phenolic compounds have been shown to have both antioxidant and anti-inflammatory properties [13, 14].

Used in traditional medicine to treat hyperglycemia and diabetes [15], olive leaf extract has been shown to improve beta cell viability and protect against cell death after cytokine exposure through suppression of caspase 3/7 activity, protecting insulin secretion, and reducing reactive oxygen species production post exposure [16]. It has been proposed that olive leaf extract potentiates glucose-induced insulin release and increases peripheral glucose uptake.

Animal Studies

Olive leaf extract has been shown to reduce hyperglycemia and hyperinsulinemia in sand rats fed a high cholesterol [17] or hypercaloric [18] diet. The oral administration of olive leaf extract significantly decreased serum glucose while simultaneously increasing serum insulin in streptozotocin-induced diabetic rats, but not controls, an effect described by the investigators as more effective than the antidiabetic effect of glibenclamide [19].

In an alloxan-induced diabetic rabbit model, oleurpein, the most abundant active phenolic compound in olive leaf extract, was shown to reduce both blood glucose and plasma malondialdehyde [MDA] as well as other markers of oxidative stress [20]. Similarly, in alloxan-induced Wistar rats, oleurpein and hydroxytyrosol, derived from olive leaf extract, reduced blood glucose and cholesterol, and normalized the markers of oxidative stress [21]. Male Wistar rats fed a high carbohydrate, high fat diet with olive leaf extract did not develop the same cardiovascular, hepatic, and diabetes-like metabolic abnormalities

observed in rats fed identical diets without olive leaf extract [22]. Investigators attributed these observations to the anti-inflammatory and antioxidant properties of olive leaf extract polyphenols, especially oleuropein and hydroxytyrosol.

Human Studies

Olive leaf extract efficacy has not been widely studied in humans. In an in vitro study, Jurkat cells in culture were exposed to continuously generated hydrogen peroxide. Extracts, including olive oil and olive mill waste water, were evaluated for their ability to decrease the hydrogen peroxide-induced formation of single strand breaks in the nuclear DNA, and the toxic effects were estimated from the increase of DNA damage when the extracts or isolated compounds were incubated directly with the cells. Significant protection was observed in extracts from olive oil and olive mill wastewater. However, when olive oil extracts had a concentration above 100-mcg/ml, the extracts exerted DNA damaging effects by themselves in the absence of any H2O2. Although extracts from olive leaves and olive fruits were protective, they were also able to induce DNA damage by themselves [23]. The efficacy of olive leaf extract on metabolic, hemodynamic and anthropometric measures was studied in a clinical trial in borderline hypertensive monozygotic twins. A significant reduction in both systolic and diastolic blood pressure was observed, however, differences in glucose were not detected [24].

In a randomized, double blind clinical trial, 79 adults with type 2 diabetes [T2DM] were randomized to treatment with 500 mg of olive leaf extract tablets, taken orally once daily or matching the placebo. Subjects treated with olive leaf extract exhibited significantly lower HbA1c, and fasting plasma insulin levels; however, post prandial plasma insulin levels did not differ significantly by treatment group [25].

TURMERIC

Bioactive properties

Curcumin, a dietary polyphenol in turmeric, has been shown to exert an anti-adipogenic function in both human and murine preadipocytes, particularly in the early stages of adipocyte differentiation [26]. A dose-dependent decrease in leptin and lipopolysaccharide-induced IL-6 secretion was observed in adipocytes incubated with curcumin [27]. Downregulation of other inflammatory cytokines such as resistin and upregulation of adiponectin have also been observed [28]. Through its interaction with several signal transduction pathways, curcumin can reverse insulin resistance, hyperglycemia, and other inflammatory symptoms associated with obesity and metabolic diseases. Curcumin has been shown to inhibit fatty acid synthase, repressing lipid accumulation, down-regulating mRNA levels of peroxisome proliferators-activated receptor [PPAR] γ, inhibiting lipid accumulation [29].

MCP-1 upregulates amylin, the most abundant pancreatic islet amyloid component, through ERK1/2/JNK-AP1 and NF-κB related signaling pathways, contributing to the plasma amylin elevation in obesity and insulin resistance [30]. Curcumin has been shown to activate the volume-regulated anion channel in murine pancreatic beta cells, enhancing insulin release [31]. Additionally, by inducing phase 2 enzyme HO-1 expression, curcumin has been shown to have a cytoprotective effect on mouse pancreatic beta cells [32].

In addition to curcumin, turmeric contains the water soluble pepetide tumerin, which has been shown to have antioxidant capacity and to inhibit α-amylase and α-glucosidase activity, suggesting possible anti-diabetic treatment potential [33].

Animal Studies

The hypoglycemic effect of turmeric and its constituent curcumin has been reported in a variety of animal models in association with antioxidant action, and has been attributed to a decrease in sorbitol dehydrogenase [34]. Curcumin lowered blood glucose, glycosylated hemoglobin, free fatty acids, total cholesterol, triglyceride and lipid peroxidation levels while increasing plasma insulin and hepatic glycokinase activity levels in C57BL/Ks-db/db diabetic mice, a model for human T2DM. Hamsters fed a high fat, high cholesterol diet treated with curcumin exhibited a normalization of lipoprotein profile together with a reduction in leptin levels and attenuated insulin resistance [35].

In male Sprague Dawley rats with T2DM induced by a high fat diet, curcumin reduced hyperglycemia, and improved insulin sensitivity while concomitantly reducing TNF-α levels, implying an anti-inflammatory effect [36]. Similarly, dietary curcumin improved glucose tolerance, reduced insulin resistance, increased adipose tissue adiponectin production, and decreased pro-inflammatory cytokines including TNF-α, IL-1β, and limited white adipose tissue macrophage infiltration in obese, leptin-deficient ob/ob C57 BL/6J mice [37].

In addition to ameliorating diabetes, turmeric and curcumin have been shown to reduce diabetes complications including ophthalmologic, nephrologic and cardiovascular complications. In rats with streptozotocin [STZ] -induced diabetes, turmeric and curcumin delayed cataract maturation [38] and reduced renal lesions [39]. In atherosclerotic rabbits fed a high fat diet, curcumin reduced plasma lipid peroxides, increased antioxidant α-tocopherol and coenzyme Q levels, and reversed atherosclerotic damage to the thoracic and abdominal aorta [40].

Human Studies

Few clinical trials of turmeric, curcumin or others of its bioactive components have been conducted. In a study in healthy subjects, the intake of 6g/day turmeric increased postprandial serum insulin levels, while reducing plasma glucose levels [41]. Adults with type 2 DM treated for eight-weeks with NCB-02, a standardized preparation of curcuminoids, exhibited improved endothelial dysfunction associated with reductions in inflammatory cytokines and markers of oxidative stress [42]. In adults with type 2 diabetes and diabetic nephropathy, short-term turmeric supplementation attenuated proteinuria, TGF-β and IL-8 [43].

FENUGREEK

Bioactive properties

Trigonella foenum-graecum (fenugreek) has long been used in traditional medicine systems for its hypoglycemic properties [44], widely attributed to the amino acid 4-hydroxyisoleucine, which has been isolated from fenugreek seeds and shown to have insulinotropic activity in isolated pancreatic beta cells [45]. In addition to insulin

sensitizing effects, fenugreek contains steroid saponin compounds including diasgenin, alkaloids and trigonelline, which have been shown to inhibit in vitro sodium-dependent intestinal glucose uptake and have anti-inflammatory properties [46, 47]. Fenugreek has also been shown to exhibit dose-dependent antioxidant properties, preventing lipid peroxidation and other oxidative damage in several in vitro models [48-50]. Finally soluble dietary fiber extracted from funugreek seeds has been shown to blunt serum glucose increase following an oral glucose load associated with decreased intestinal disaccharidase activity and glucose absorption together with increased gastrointestinal motility [51].

Animal Studies

In alloxan-induced diabetic rats, fenugreek was shown to have a dose-dependent hypoglycemic action following a glucose load, associated with increased glucose transport rates [52], which may reflect increased induction of glucose transporter Glut-4 translocation, enhancing muscle, liver, and adipose cell glucose uptake [53].

Fenugreek has also been associated with alterations in enzymes associated with carbohydrate metabolism. In diabetic rat models, hepatic enzymes associated with glycolysis including lactate dehydrogenase, pyruvate kinase, phosphofructokinase and hexokinas isozymes Type I, II and IV, are all increased by fenugreek, while hepatic enzymes associated with gluconeogenesis are decreased including glucose-6-phosphatase, phosphoenolpyruvate carboxykinase and fructose-1,6-bisphosphatase [54-57].

Human Studies

Clinical trials of fenugreek for diabetes endpoints have been conducted in humans. In a study of fenugreek treatment efficacy, 60 adults with type 2 diabetes were treated with 25 g fenugreek seed powder for 24 weeks, leading to improved measures of glucose homeostasis, including reduced urinary gluxose, glycosylated hemoglobin, and area under the curve for both glucose and insulin [58]. However, the lack of a parallel control group or placebo intervention restricted the generalization of results or determination of causality.

A total of 24 adults with type 2 diabetes were treated for eight weeks with 10 g powdered fenugreek seeds mixed in yoghurt or soaked in hot water. In an analysis of the 18 individuals who completed the study, significant reductions in fasting blood sugar were observed in subjects treated with fenugreek seeds soaked in hot water, but not among subjects treated with fenugreek seeds mixed with yoghurt [59]. Because the intention-to-treat analysis was not reported, both internal and external validity are compromised.

In a double blind, placebo-controlled, cross-over clinical trial, a wheat bread incorporating fenugreek was tested for metabolic effects and taste acceptability in eight individuals with lifestyle-controlled type 2 diabetes. Subjects were randomized to receive 56 g bread with 5% fenugreek or regular wheat bread baked at the same bakery. Post-prandial blood glucose and insulin were measured periodically over a 4-hour period after consumption. Blood insulin area under the curve was significantly reduced following consumption of fenugreek-containing bread, and this bread was indistinguishable from the whole-wheat control in terms of flavor and appearance [60]. These findings suggest that fenugreek may represent an effective food-based means of reducing plasma insulin among individuals with type 2 diabetes.

Fenugreek seed extract has been shown to reduce spontaneous fat consumption,

leading to a marginal reduction of total energy consumption, in healthy male volunteers [61]. Similarly, in healthy overweight individuals, fenugreek seed extract significantly reduced dietary fat intake and decreased the insulin/glucose ratio [62], however, changes in body weight and appetite/satiety scores were not observed.

In a meta-analysis of the efficacy of herbal supplements on glucose homeostasis in adults with type 2 diabetes, fenugreek was identified as a food associated with significant HbA1c reduction: -1.13% [95% CI -0.11%--2.14%, p=0.03]. The analysis identified a significant heterogeneity of results, indicating the need for well-designed, randomized, placebo-controlled and pivotal clinical trials.

CONCLUSIONS

In vitro studies have consistently identifyed mechanisms through which olive leaf extract, turmeric and fenugreek might exert treatment benefit for individuals with type 2 diabetes. All three foods poses antioxidant qualities which can reduce free radical associated tissue injury and the formation of advanced glycation end products [AGE], which promote vascular endothelial cell proliferation, migration, damage, and death [63]. Additionally, all three foods have anti-inflammatory properties, which may be of benefit in treating both obesity and type 2 diabetes [64].

Animal studies further demonstrate the potential treatment benefits of these foods. Improved glucose homeostasis as well as a normalized lipid profile has been demonstrated in a number of animal models.

Well designed, randomized, placebo-controlled clinical trials aimed at testing the efficacy of these foods in treating type 2 diabetes in humans are scarce. Such studies, adequately powered to detect clinical, rather than only surrogate endpoints, would greatly assist in establishing a solid evidence base for the use of these foods in treating type 2 diabetes.

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and Trends in Obesity Among US Adults, 1999-2008. JAMA 2010; 303:235-241.
2. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Practical Guide Identification, Evaluation, and Treatment of overweight and Obesity in Adults NIH Publication Number 00-4084, 2000.
3. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
4. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010 ; 87:4-14.
5. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998 Sep; 21:1414-31.
6. Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, Nichols G. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87:293-301.

7. Shane-McWhorter L. American Diabetes Association Guide to Herbs and Nutritional Supplements. American Diabetes Association, 2009.
8. Ben-Arye E, Schiff E, Karkabi K, Keshet Y, Lev E. Exploring association of spiritual perspectives with complementary medicine use among patients with Type 2 diabetes in Israel. Ethn Health 2011; 16:1-10.
9. Otoom SA, Al-Safi SA, Kerem ZK, Alkofahi A. The use of medicinal herbs by diabetic Jordanian patients. J Herb Pharmacother 2006; 6:31-41.
10. Hussain Z, Waheed A, Qureshi RA, Burdi DK, Verspohl EJ, Khan N, Hasan M. The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells. Phytother Res 2004; 18:73-7.
11. Japon-Lujan R, Luque-Rodriguez JM, Luque de Castro MD. Dynamic ultrasound-assisted extraction of oleuropein and related polyphenols from olive leaves. J Chromatogr A 2006; 1108: 76-82.
12. Cumaoğlu A, Rackova L, Stefek M, Kartal M, Maechler P, Karasu C. Effects of olive leaf polyphenols against H_2O_2 toxicity in insulin secreting β-cells. Acta Biochim Pol 2011; 58:45-50.
13. Benavente-Garcia J, Castillo J, Lorente A, Ortuno A, Del Rio JA. Antioxidant activity of phenolics extrated from Olea europaea L. leaves. Food Chem 2000; 68: 457-62.
14. Visioli F, Poli A, Galli C. Antioxidant and other biological activities of phenols from olives and olive oil. Med Res Rev 2002; 22: 65-75.
15. Pereia JA, Pereira APG, Ferreira ICFR, Valentau P, Andrede PB, Seabra RM, Estevinho LM, Bento A. Table olives from Portugal: phenolics compounds, antioxidant potential and antimicrobial activity of table olives from Portugal. J Agric Food Chem 2006; 54: 8425-31.
16. Cumaoğlu A, Ari N, Kartal M, Karasu Ç. Polyphenolic extracts from Olea europea L. protect against cytokine-induced β-cell damage through maintenance of redox homeostasis. Rejuvenation Res 2011; 14:325-34.
17. Bennani-Kabchi N, Fdhil H, Cherrah Y, Kehel L, el Bouayadi F, Amarti A, Saïdi M, Marquié G. Effects of Olea europea var. oleaster leaves in hypercholesterolemic insulin-resistant sand rats. Therapie 1999; 54:717-23.
18. Bennani-Kabchi N, Fdhil H, Cherrah Y, El Bouayadi F, Kehel L, Marquie G. Therapeutic effect of Olea europea var. oleaster leaves on carbohydrate and lipid metabolism in obese and prediabetic sand rats (Psammomys obesus). Ann Pharm Fr 2000; 58:271-7.
19. Eidi A, Eidi M, Darzi R. Antidiabetic effect of Olea europaea L. in normal and diabetic rats. Phytother Res 2009; 23:347-50.
20. Al-Azzawie HF, Alhamdani MS. Hypoglycemic and antioxidant effect of oleuropein in alloxan-diabetic rabbits. Life Sci 2006; 78:1371-7.
21. Jemai H, El Feki A, Sayadi S. Antidiabetic and antioxidant effects of hydroxytyrosol and oleuropein from olive leaves in alloxan-diabetic rats. J Agric Food Chem 2009; 57:8798-804.
22. Poudyal H, Campbell F, Brown L. Olive leaf extract attenuates cardiac, hepatic, and metabolic changes in high carbohydrate-, high fat-fed rats. J Nutr 2010; 140:946-53.

23. Nousis L, Doulias PT, Aligiannis N, Bazios D, Agalias A, Galaris D, Mitakou S. DNA protecting and genotoxic effects of olive oil related components in cells exposed to hydrogen peroxide. Free Radic Res 2005; 39:787-95.
24. Perrinjaquet-Moccetti T, Busjahn A, Schmidlin C, Schmidt A, Bradl B, Aydogan C. Food supplementation with an olive (Olea europaea L.) leaf extract reduces blood pressure in borderline hypertensive monozygotic twins. Phytother Res 2008; 22:1239-42.
25. Wainstein J, Ganz T, Boaz M, Bar Dayan Y, Dolev E, Kerem Z, Madar Z. Effect of Olive Leaves and Olive leaf polyphenol concentrate [OLPC] as Hypoglycemic Agents in both diabetic subjects and in Rats. Clinical trial registration number: NCT01427998 [unpublished data].
26. Kim CY, Le TT, Chen C, Cheng JX, Kim KH. Curcumin inhibits adipocyte differentiation through modulation of mitotic clonal expansion. J Nutr Biochem 2011; 22:910-20**.**
27. Ciardi C, Jenny M, Tschoner A, Ueberall F, Patsch J, Pedrini M, Ebenbichler C, Fuchs D. Food additives such as sodium sulphite, sodium benzoate and curcumin inhibit leptin release in lipopolysaccharide-treated murine adipocytes in vitro. Br J Nutr 2011; 1:1-8.
28. Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annu Rev Nutr 2010; 30:173-99.
29. Zhao J, Sun XB, Ye F, Tian WX. Suppression of fatty acid synthase, differentiation and lipid accumulation in adipocytes by curcumin. Mol Cell Biochem. 2011; 351:19-28.
30. Cai K, Qi D, Hou X, Wang O, Chen J, Deng B, Qian L, Liu X, Le Y. MCP-1 upregulates amylin expression in murine pancreatic β cells through ERK/JNK-AP1 and NF-κB related signaling pathways independent of CCR2. PLoS One. 2011; 6:e19559.
31. Best L, Elliott AC, Brown PD. Curcumin induces electrical activity in rat pancreatic beta cells by activating the volume-regulated anion channel. Biochem Pharmacol 2007; 73: 1768-75.
32. Pugazhenthi S, Ackov L, Selvaraj G, Wang M, Alam J. Regulation of heme oxygenase-1 expression by demethoxy curcuminoids through Nrf2 by PI3-kinase/Akt-mediated pathway in mouse beta cells. Am J Physiol Endocrinol Metab 2007; 293: E645-655.
33. Lekshmi PC, Arimboor R, Raghu KG, Menon AN. Turmerin, the antioxidant protein from turmeric [Curcuma longa] exhibits antihyperglycaemic effects. Nat Prod Res. 2011 Oct 6. [Epub ahead of print].
34. Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant Foods Hum Nutr 2002; 57: 41-52.
35. Jang EM, Choi MS, Jung UJ, Kim MJ, Kim HJ, Jeon SM, Shin SK, Seong CN, Lee MK. Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat-fed hamsters. Metabolism. 2008 Nov; 57:1576-83.
36. El-Moselhy MA, Taye A, Sharkawi SS, El-Sisi SF, Ahmed AF. The antihyperglycemic effect of curcumin in high fat diet fed rats. Role of TNF-α and free fatty acids. Food Chem Toxicol. 2011; 49:1129-40.

37. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112: 1796-1808.
38. Suryanarayana P, Saraswat M, Mrudula T, Krishna TP, Krishnaswamy K, Reddy GB. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. Invest Ophthalmol Vis Sci 2005; 46: 2092-99.
39. Suresh Babu P, Srinivasan K. Amelioration of renal lesions associated with diabetes by dietary curcumin in streptozotocin diabetic rats. Mol Cell Bioshem 1998; 181: 87-96.
40. Quiles JL, Mesa MD, Ramírez-Tortosa CL, Aguilera CM, Battino M, Gil A, Ramírez-Tortosa MC. Curcuma longa extract supplementation reduces oxidative stress and attenuates aortic fatty streak development in rabbits. Arterioscler Thromb Vasc Biol 2002; 22:1225-31.
41. Wickenberg J, Ingemansson SL, Hlebowicz J. Effects of Curcuma longa (turmeric)on postprandial plasma glucose and insulin in healthy subjects. Nutr J 2010; 9:43-8.
42. Usharani P, Mateen AA, Naidu MU, Raju YS, Chandra N. Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study. Drugs R D 2008; 9:243-50.
43. Khajehdehi P, Pakfetrat M, Javidnia K, Azad F, Malekmakan L, Nasab MH, Dehghanzadeh G. Oral supplementation of turmeric attenuates proteinuria,transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: A randomized, double-blind and placebo-controlled study. Scand J Urol Nephrol 2011 May 31. (Epub ahead of print)
44. Nahas R, Moher M. Complementary and alsternative medicine for the treatment of type 2 diabetes. Can Fam Physician 2009; 55: 591-6.
45. Broca C, Manteghetti M, Gross R, Baissac Y, Jacob M, Petit P, Sauvaire Y, Ribes G. 4-Hydroxyisoleucine: effects of synthetic and natural analogues on insulin secretion. Euro J Pharmacol 2000; 390: 339-45.
46. Al Habori M, Raman A, Lawrence MJ, Skett P. In vitro effect of fenugreek extracts on intestinal sodium-dependent glucose uptake and hepatic glycogen phosphorylase A. Int J Exp Diabetes Res 2001; 2: 91-9.
47. Kawabata T, Cui MY, Hasegawa T, Takano F, Ohta T. Anti-inflammatory and anti-melanogenic steroidal saponin glycosides from Fenugreek (Trigonella foenum-graecum L.) seeds. Planta Med. 2011; 77:705-10.
48. Dixit P, Ghaskadbi S, Mohan H, Devasagayam TPA. Antioxidant properties of germinated fenugreek seeds. Phytother Res 2005; 19: 977-83
49. Kaviarasan S, Naik GH, Gangabhagirathi R, Anuradha CV, Pryadarsini KI. In vitro studies on antiradical and antioxidant activities of fenugreek (Trigonella foenum graecum) seeds. Food Chem 2007; 103: 31-7.
50. Madar Z, Stark AH. New legume sources as therapeutic agents. Br J Nutr. 2002 Dec;88 Suppl 3:S287-92.
51. Hannan JM, Ali L, Rokeya B, Khaleque J, Akhter M, Flatt PR, Abdel-Wahab YH. Soluble dietary fibre fraction of Trigonella foenum-graecum (fenugreek) seed improves glucose homeostasis in animal models of type 1 and type 2 diabetes by

delaying carbohydrate digestion and absorption, and enhancing insulin action. Br J Nutr 2007; 97:514-21.

52. Vijayakumar MV, Singh S, Chhipa RR, Bhat MK. The hypoglycemic activity of fenugreek seed extract is mediated through the stimulation of an insulin signalling pathway. Fr J Pharmacol 2005; 146: 41-8.
53. Mohammad S, Taha A, Akhtar K, Bamezai RN, Baquer NZ. In vivo effect of Trigonella foenum graecum on the expression of yruvate kinase, phosphoenolpyruvate carboxykinase and distribution of glucose transporter [GLUT4] in alloxan diabetic rats. Can J Physio Pharm 2006; 84: 647-54.
54. Mohammad S, Taha A, Bamezai RNK, Basir SF, Baquer NA. Lower doses of vanadium in comibination with Trigonella restore altered carbohydrate metabolism and antioxidant status in alloxan diabetic rats. Clinica Chimica acta 2004; 342: 105-14.
55. Yadav UCS, Moorthy K, Baquer NZ. Effects of sodium orthovanadate and Trigonella foenum graecum seeds on hepatic and renal lipogenic enzymes and lipid profile during alloxan diabetes. J Biosci 2004; 29: 81-91.
56. Raju J, Gupta D, Rao AR, Yadava PK, Baquer NZ. TSP foenum graecum [fenugreek] seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reversing the altered glycolytic, gluconeogenic and lipogenic enzymes. Mol Cell Biochem 2001; 224: 45-51.
57. Preet A, Siddiqui MR, Taha A, Badal J, Hussain ME, Yadava PK, Baquer NZ. Long term effect of Trigonella foenum graecum and its combination with sodium orthovanadate in preventing histopathological and biochemical abnormalities in diabetic rat ocular tissues. Mol Cell Biochem 2006; 289: 137-47.
58. Sharma RD, Sarkar A, Hazara DK, Pishra B, Singh JB, Sharma SK, Maheshwari BB, Maheshwari PK. Use of fenugreek seed powder in the management of non-insulin dependent diabetes mellitus. Nutr Res 1996; 16: 1331-39.
59. Kassaian N, Azadbakht L, Forghani B, Amini M. Effect of fenugreek seeds on blood glucose and lipid profiles in type 2 diabetic patients. Int J Vitam Nutr Res 2009; 79:34-9.
60. Losso JN, Holliday DL, Finley JW, Martin RJ, Rood JC, Yu Y, Greenway FL. Fenugreek bread: a treatment for diabetes mellitus. J Med Food 2009; 12:1046-9.
61. Chevassus H, Molinier N, Costa F, Galtier F, Renard E, Petit P. A fenugreek seed extract selectively reduces spontaneous fat consumption in healthy volunteers. Eur J Clin Pharmacol 2009; 65:1175-8.
62. Chevassus H, Gaillard JB, Farret A, Costa F, Gabillaud I, Mas E, Dupuy AM, Michel F, Cantié C, Renard E, Galtier F, Petit P. A fenugreek seed extract selectively reduces spontaneous fat intake in overweight subjects. Eur J Clin Pharmacol 2010; 66:449-55.
63. Xie Y, You SJ, Zhang YL, Han Q, Cao YJ, Xu XS, Yang YP, Li J, Liu CF. Protective role of autophagy in AGE-induced early injury of human vascular endothelial cells. Mol Med Report 2011; 4:459-64.
64. Luo P, Wang MH. Eicosanoids, β-cell function, and diabetes. Prostaglandins Other Lipid Mediat 2011; 95:1-10.