REVIEW ARTICLE

A Survey on Herbal Medicines for Hypoglycemia in Diabetic Patients

Robab Sheikhpour [1*], Parichehr Yaghmaei [1]

Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

Received: 10 January 2012- **Accepted:** 15 May 2012

ABSTRACT

Diabetes mellitus is one of the major metabolic disorders. It is a global epidemic with an estimated worldwide prevalence of 6% (246 million people) in 2007. Diabetes is recognized for severe complications including diabetic nephropathy, neuropathy, and retinopathy. Currently, available therapy acts by increasing insulin secretion (sulphonylurea and glinides), decreasing insulin resistance (glitazones and metformin) or delaying the absorption of glucose from the intestine (acarbose). Insulin treatment is expensive and induces weight gain. None of these drugs have been shown to stop the progressive decline of beta-cell function. Many traditional plant treatments exist as a hidden wealth of potentially useful natural products for diabetes control. There are approximately 800 to 1200 plants that exhibit hypoglycemic activity. Herbal medicine represents one of the most important fields of traditional medicine all over the world and provides a valuable alternative therapeutic. Herbal medicines are frequently considered to be less toxic and free from side effects rather than synthetic ones. Many plants like Citrullus colocynthis, fenugreek and ginger are useful in diabetes. The hypoglycemic properties of the plants are surveyed in this paper such as Citrullus colocynthis, fenugreek, and ginger.

KEYWORDS: Citrullus colocynthis, Fenugreek, Ginger, Diabetes.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by abnormally high levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test (1,2). More than 200 million people have type 2 diabetes; they continue to rise and have reached an epidemic proportion (3). The total number of people with diabetes is expected to reach 370 million worldwide in 2030. Hyperglycaemia induces glucose oxidation and initiates an non-enzymatic glycation of proteins, which in turn leads to enhanced production of reactive oxygen species (ROS)(4). Currently, available therapy acts by increasing insulin secretion (sulphonylurea and glinides), decreasing insulin resistance (glitazones and metformin) or delaying the absorption of glucose from the intestine (acarbose). None of these drugs have been shown to stop the progressive decline of beta-cell function, and none address the elevated glucagon secretion (3). Oral antidiabetic drugs (OADs) are associated with side effects, such as weight gain, hypoglycaemia, lactate acidosis, and peripheral oedema. After some years, most of the subjects with type 2 diabetes need insulin treatment for control of hyperglycaemia. Insulin treatment is expensive and troublesome for the patients, and also induces weight gain. Given this background, there is a need for new classes of blood-glucose-lowering drugs. Herbal medicines

*__Correspondence:__ Robab Sheikhpour, Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran. **Tel:** (+98) 351-6282884. **Email:** sheikhpour_r@yahoo.com

provide a valuable therapeuthic alternative. Traditional medicine has also been used in the treatment of diabetes in Iran for centuries (3, 4, 5). Many traditional plant treatments exist as a hidden wealth of potentially useful natural products for diabetes control (6). Despite recommendations by the World Health Organization in 1980, few traditional anti-diabetic plants have received scientific or medical scrutiny. Currently, a number of natural products exist that demonstrate hypoglycemic activity. Indeed, depending upon the source that one might use, there are approximately 800 to 1200 plants that exhibit hypoglycemic activity (5, 7). These drugs are frequently considered to be less toxic and free from side effects rather than synthetic ones. The plants Citrullus colocynthis, Fenugreek and Zingiber have hypoglycemic property. These drugs can be consumed by diabetic patients at different doses. The pathophysiological basis of these therapeutics is reviewed from point of various literatures.

1. Citrullus Colocynthis (CCT)

Citrullus colocynthis genus belongs to cucurbitataceas. It is also known as bitter apple, bitter cucumber, egusi. It is a desert plant of the family Cucurbitaceae naturally adapted to arid environments. This plant is mainly found in Mediterranean Europe, Asia, Turkey, Nubia, Trieste, Egypt, Iran, Pakistan, Afghanistan, India, and North Africa.

It has a large, fleshy perennial root, which sends out slender, tough, angular, scabrid vine-like stems. These usually lie on the ground in need of something to climb over, but which, if an opportunity is present, they will climb over shrubs and herbs by means of axiliary branching tendrils. The leaves are angular, lobed and, as already stated, almost the exact duplicate of watermelon leaves. The flowers are yellow, long-peduncled, solitary in the axils of the leaves. They are monecious, the stamens and pistils being borne in different flowers on the same plant. Each has a yellow campanulate, five-lobed corolla and a five-parted calyx. The female flowers are readily distinguished by a globose, hairy, inferior ovary (8).

Each plant produces 15-30 round fruits, about 3-4 inches in diameter, green with undulate yellow stripes, becoming yellow all over when dry. Seeds are small (1-4 inch or less in length). The fruits are widely used medicinally (9). The fruit which is known in commerce as the Turkish colocynth is collected by the native peasants (fellaheens) in July and August, before it is quite ripe (4). The fruit is globular, smooth, with a hard but thin rind, something like a gourd. It is filled with a soft, white pulp, in which are imbedded numerous seed (8).

1.1. The Component of Citrullus Colocynthis

Citrullus colocynthis contains large amounts of phenolics and flavonoids that have antioxidant activities (10). It mainly contains glycosides; cucurbitacins A, B, C, D, and E , cucurbitacines I, J, K, L, and cucurbitacin E-2, citrullol, alkaloids, resin , gums , potassium, phosphorous and iron. (11). Also seeds contain crude fiber, protein and fat.

1.1.1. Fat Content

The composition of the seed fat of Citrullus colocynthis as established by the present investigation is palmitic 10.40%; stearic 6.52%; arachidic 1.70%; oleic 20.92%; linoleic 58.81%; and linolenic 1.65%. This composition agrees largely with the general trend of the family and of the genus Citrullus specifically, being rich in total unsaturation (81.9%) with linoleic acid as the major component (12).

1.1.2. Protein Content

The protein content of seeds of colocynthis is found to be 8.25 % and rich in lysine, leucine and sulfor-amino acid like methionine.

1.2. The Properties of Citrullus Colocynthis

The fruits are traditionally used against poisonous bites of dogs and snake bites. The plant subjected for the current research work had been used traditionally as antidiabetic.

Therefore, it was thought interesting to evaluate the antidiabetic profile of the selected plant part (root), which has not yet been scientifically undertaken (11). It was used as purgative, anthelmentic, antipyritic, carmanative, and curative for tumors, leucoderma, asthma, jaundice, enlargment of spleen, tuberculous glands of the neck (10).

It is a proven antioxidant, anti tumor, antimicrobial, antimalarial, epatoprotective, anti-inflammatory activity. It is also antispermatogenic, carcinogenic and has a hepatonephroprotective effect (because of a number of compounds of this group) (11).

There is some evidence that this drug may induce side effects. The comparative toxicity of the alcoholic extract of CCT has been studied in seven insect species in which the adult honey bee was more effective. Sheep which were fed fresh CCT fruits and leaves (0.2-10 g/kg) showed signs of poisoning. Doses of 10 g/kg of CCT from 1 day to 2 weeks caused death in goats. The other side-effects of this plant are toxic acute colitis, reversible infertility and hepatotoxicity in rats. These damages were sometimes enhanced with higher doses of CCT . The liver is a sensitive organ and many substances including toxins accumulate in this organ and induce liver toxicity (13). Figure 1 shows Citrullus colocynthis. Dallak reported that decreased GSH levels in diabetic rats' liver were observed significantly (GSH acts as an antioxidant and its level is reduced in diabetes mellitus). Decreased GSH levels represent increased utilization due to increased oxidative stress. Increased GSH content in livers of rats treated with C. clocynthis may be one important factor responsible for inhibition of lipid peroxidation, which could explain the decrease in the levels of TBARS (14).

Figure 1- Citrullus Colocynthis

In another study, oral administration of the plant extract reduced the plasma level of AST and LDH significantly. However, the plant extract failed to reduce the increased blood level of GGT and ALP in diabetic rats (13). Zamani reported that the presence of high amounts of saponins in Citrullus colocynthis might contribute to the reduction of cholesterol levels by reducing the absorption of cholesterol, increasing the repel of fecesic estrol, and diarrhea due to increase in peristalsis. Thus, it is reasonable to assume that the effect of Citrullus colocynthis on the blood lipid profile in rabbits might also be owing to the presence of these saponins (15). The effect of saponins, natural or synthetic, in lowering the levels of cholesterols has been demonstrated in a number of studies (16).

Another study showed that fifty days of treatment with Citrullus colocynthis led to a reduction in the activity of ALP enzyme(activity of this enzyme raised in kidney of non treated diabetic rats compared to control group); a result that could support our earlier deduction that this plant extract may have the ability to protect kidney damage. C-glutamyl transpeptidase is a microsomal enzyme that is present in kidney and liver tissues (10).

In another study, Ahmed observed the antimicrobial activity of extract from fruits, leaves, stems and roots against various Gram-positive and Gram-negative bacteria (17).

1.3. Citrullus Colocynthis and Diabetes

Citrullus colocynthis demonstrates multiple beneficial anti-diabetic mechanisms, including modulation of carbohydrate metabolism, restoration of beta-cell integrity, insulin-releasing activity and improvements in glucose uptake/utilisation (11). It decreases gluconeogensis and inhibits release of counter-regulatory hormones. On the other hand, it has been suggested that the mechanism responsible for the serum glucose lowering effect of Citrullus colocynthis were attributed

to an inhibitory effect of glucose absorption ; an increased incorporation of circulating glucose as hepatic glycogen, or an enchanced secretion of insulin. Multiple mechanisms have been proposed as the cause of Citrullus colocynthis's hypoglycemic properties. Components of Citrullus colocynthis extract appear to have structural similarities to animal insulin, as measured by electrophoresis and infrared spectrum analysis (10).

Sebbagh showed that C. colocynthis oil supplementation may have a beneficial effect by partly preserving or restoring pancreatic beta-cell mass in the STZ-induced diabetes rat mode (18).

Zaree showed that oral Citrullus colocynthis fruit extract is useful for prevention/reduction of development of diabetes through the lowering of oxidative stress and glycemia (19).

In a study, oral administration of intervention with Citrullus colocynthis and OHA in 25 patients for 2 months demonstrated significant reduction in both FBG and HbA1c levels, compared with patients taking placebo and OHA. There were no significant changes in secondary outcome measures of lipid levels. However, three patients reported mild diarrhoea at the beginning of the study. The glycosidic extract at an oral dose of 50 mg/kg significantly lowered the fasting glucose levels after 2 and 3 hours and it was highly significant after 6 hours. The saponin extract at the same oral dose significantly lowered the fasting glucose levels after 1 and 2 hours and it was highly significant ($p<0.001$) after 3 and 6 hours (17).

Atef showed Citrullus colocynthis has a beneficial effect on improving the glycemic profile without severe adverse effects in type II diabetic patients (10).

2. Fenugreek

Fenugreek (Trigonella foenum graecum) is a plant from the family Leguminosae cultivated in some countries such as India, Africa, Egypt, Morocco, and occasionally in England. Fenugreek is an aromatic which is 30-60 cm tall. It is an old medicinal plant and has been commonly used as a traditional food and medicine (20, 21). The seeds are hot, with a sharp bitter taste (22). The main chemical constituents of T. Foenum-graecum are fibers, flavonoids, polysaccharides, tannins, saponins, flavonoids, polysaccharides fixed oils, and some identified alkaloids viz., trigonelline and choline. The seeds of fenugreek contain a large quantity of folic acid (84mg/100g). It contents also contain disogenin, gitogenin, neogitogenin, homorientin saponaretin, neogigogenin, and trigogenin (22). A review of the literature on fenugreek reveals no reports of clinically significant harmful adverse effects. Although fenugreek has traditionally been considered safe and well tolerated, some side effects have been associated with its use. Caution in using fenugreek is warranted in patients known to be allergic to it or who are allergic to chickpeas because of possible cross-reactivity. Fenugreek containing curry powder was found to be an allergen in a patient who reported severe bronchospasm, wheezing, and diarrhea. Other reported side effects include transient diarrhea, flatulence, and dizziness (23).

Figure 2 shows Fenugreek.

2.1. The Properties of Fenugreek

In addition, wide range of its medicinal applications were identified and its medical use for the treatment of inflammation, tumors, cardiovascular diseases, renal insufficiency, infections, and metabolic disorders has been clear in several studies. It has been also shown that at the stated dose, it increases the bone marrow cell counts indicating its stimulatory effect on blood cells especially macrophages.

Figure 2- Fenugreek

One of the nutritional profiles of Fenugreek seed is iron and may influence the iron absorption (Fenugreek Trigonella Foenum-Graecum (21).

Another study shows that fenugreek increases the appetite, removes bad taste from the mouth, and is useful in the heart disease, and by having suppurative, aperient, diuretic, emmenagogue effects is useful in dropsy, chronic cough, enlargement of the liver and the spleen. The leaves are useful in external and internal swellings and burns and also prevent the hair falling off (22).

Renuka reported the seeds have restorative and nutritive properties. In addition, wide range of its medicinal applications were identified and its medical use for the treatment of inflammation, tumors, cardiovascular diseases, renal insufficiency, infections, and metabolic disorders has been clear in several studies. Also fenugreek seed may have antioxidant or free radical scavenger properties in preventing these hanges (23).

Another research shows Trigonella foenum graecum (leguminosae) (Eng: fenugreek, Tamil: Vendayam) is a well known spicy agent which prevents ageing, labour pain, impart immunity, and improves mental function. Moreover, it adds vitality to the body and is also used in nervous disorders, dyspepsia, inflammation, tumors, cholesterolemic, and hyperglycemic. Also another study indicates that the pharmacological activities of Trigonella foenum graecum include anti diabetic, antifertility, antifungal, analgesic, anti inflammatory, antipyretic, immunomodulatory and anti-oxidant activities (24).

However, a few studies were available about the effects of Fenugreek and its toxicity on immunomodulatory effects and haematopoietic stem cells of bone marrow. Also the mechanisms of these effects have not been clear (20).

In another study, Extract of fenugreek (Trigonella foenum-graecum) seeds was isolated and evaluated for antioxidant activity using various in vitro assay systems. The seed extract exhibited scavenging of hydroxyl radicals (OH) and inhibition of hydrogen peroxide-induced lipid peroxidation in rat liver mitochondria. The OH scavenging activity of the extract was evaluated by pulse radiolysis and the deoxyribose system. The antimutagenic activity of the extract was recorded by following the inhibition of c-radiation induced strand break formation in plasmid pBR322 DNA. The extract at high concentrations acted as a scavenger of 2, 20 - diphenyl-1- picryl hydrazyl hydrate (DPPH) and 2, 20 - azinobis 3- ethylbenzothiazoline - 6 - sulfonate (ABTS) radicals (22).

Fenugreek seeds also reduce serum triglycerides, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C). These effects may be due to sapogenins, which increases biliary cholesterol excretion, and in turn leads to lowered serum cholesterol levels. The lipid-lowering effect of fenugreek might also be attributed to its estrogenic constituent, indirectly increasing thyroid hormone T4 (23).

2.2. Fenugreek and Diabetes

Fenugreek seeds are known to improve diabetic status. Medicinal properties of fenugreek such as hypocholesterolemic and hypolipdemic have also been studied. In Southeast Asia, the water extract of fenugreek seeds is used in the management of diabetes and is known to improve kidney function during diabetes (25). Renuka reported that Fenugreek (Trigonella foenum-graecum) is commonly used as a condiment and seasoning in food preparations; it is assumed to possess nutritive and restorative properties and has been used in folk medicines for centuries for a wide range of diseases including diabetes, fever, and abdominal colic as a poultice for abscesses, and boils. The hypoglycemic property of fenugreek was observed in diabetic patients (24). Various reports revealed that fenugreek possesses a plethora of benefits under various experimental conditions. The fenugreek seed possesses antidiabetic effect. The present study indicated that the extract of fenugreek seeds notably decreased blood glucose level in diabetic rats. In agreement with the present results, the hypoglycemic effect of fenugreek seeds has been experimentally proved in induced diabetic rats,

dogs, mice and healthy volunteers and type-I and II diabetic patients (24). Another report has demonstrated that Trigonella foenum-graecum (fenugreek) seeds can reduce blood glucose and cholesterol in type 1 and type 2 diabetics and experimental diabetic animals (26).

Fenugreek has primarily been described as an antihyperglycemic herb in humans as well as in laboratory animals (22). Also the soluble dietary fibre (SDF) fraction of Trigonella foenum-graecum (Tfsdf) has shown to reduce postprandial elevation in blood glucose level of Type 2 model diabetic rats by delaying the digestion of sucrose (22).

Neeraja and Rajyalakshmi presented a poorly designed, complex case series including six men with type 2 diabetes and six without diabetes. The cases suggest fenugreek reduced postprandial hyperglycemia primarily in subjects with diabetes, but less so in subjects without diabetes. This effect might be more pronounced if raw seeds rather than boiled seeds had been used. Results from several additional case series also suggest fenugreek seeds may improve glycemic control in type 2 diabetes(23).

Studies of Shani et al. Ribes et al., Khosla et al. and Madar et al. showed that fenugreek seeds decreased FBS levels in animals. Madar et al. , Jain et al. , Sharma et al., Al Hoobori et al., and Abdel-Barry et al. showed hypoglycemic effects of fenugreek seeds for type 2 diabetes. Mechanism of its action is not fully understood and has been attributed to a high percentage (50%) of dietary fibre, polyunsaturated fatty acid, alkaloid teigonelline, saponins and pectins present in these seeds. It was also demonstrated in some studies that fenugreek seeds delayed gastric emptying and caused inhibition of glucose transport as the seeds contain 50% pectin that forms a colloid suspension when hydrated. Thus, they can decrease rate of gastric emptying and slow carbohydrate absorption (27).

It may be concluded that fenugreek seed extract possesses anti diabetic activities and the seeds extract can be used as an antidiabetic agent (25).

3. Ginger

Zingiber officinale (ZO) is commonly known as ginger. Ginger is an underground rhizome of plant Zingiber Officinale belonging to the family Zingibeaceae. Currently, it is considered as a common constituent of diet worldwide (28). The Chinese have used ginger for at least 2500 years as a digestive aid and antinausea remedy; they also used it to treat bleeding disorders, rheumatism, baldness, toothache, snakebite, and respiratory conditions. In Traditional Chinese Medicines (TCM), ginger is considered as a pungent, dry, warming, yang herb to be used for ailments triggered by cold, damp weather. Ginger is used extensively in Ayurveda, the traditional medicines of India, to block excessive clotting (i.e. heart disease), reduce cholesterol and fight arthritis. In Malaysia and Indonesia, ginger soup is given to new mothers for 30 days after their delivery to help warm them and sweat out impurities. In Arabian medicines, ginger is considered as an aphrodisiac. Some Africans believe that eating ginger regularly will help repel mosquitoes.

Figure 3- Stem of Ginger Zingiber

Figure 4- Ginger Root

Ginger was migrated westward to Europe in Greek and Roman times. The Greeks wrapped ginger in bread and ate it after meals as a digestive aid. Subsequently, ginger was incorporated directly into bread and confections such as gingerbread. Ginger was so valued by the Spanish that they established ginger plantations in Jamaica in the 1600s (29). Figure 3 and 4 show the stem of ginger zingiber and ginger root.

3.1. The Properties of Ginger

Ginger (zingiber officinale), is a perennial herb with thick tuberous rhizomes. The erect leafy aerial stem grows up to approximately 1 meter in height and has purple flowers. Ginger contains up to 3% of an essential oil that causes the fragrance of the spice. The main constituents are sesquiterpenoids with zingiberene as their main component. Other components include β-esquiphellandrene, bisabolene, and farnesene which are also sesquiterpenoids (β-sesquiphellandrene, cineol and citral). The pungent taste of ginger is due to nonvolatile phenylpropanoid – derived compounds, gingerols , shogaols and paradol. The shogaols are formed from gingerols when ginger is dried or cooked. Zingerone is also produced from gingerols during this process, and it is less pungent and has a sweet aroma (30). Ginger has been traditionally used in the treatment of diabetes mellitus. It prevents or reduces nausea and vomiting in postoperative patients. Ginger reduces vomiting in patients treated with cytotoxic compounds (31).

Ginger extract possesses antioxidative characteristic, since it can scavenge superoxide anion and hydroxyl radicals (33). Both in vitro and animal experiments with ginger, it has been shown that this plant possesses antioxidant action and can have a protective effect against free radical damage. Ginger stimulates appetite (31). Its extract possesses anti tumor effects in vitro on certain cells infected with the Epstein-Barr virus, as well as antioxidant effects that could have applications against certain types of cancer.

Ginger's active principles protect nerve cells and may have potential in the treatment of Alzheimer's disease. Ginger promotes the release of bile from the gall bladder (31). It has a sialagogue action, which stimulates the production of saliva (30).

A crude extract of ginger (Zo.Cr) induced a dose-dependent (0.3-3 mg/kg) fall in the arterial blood pressure of anesthetized rats. The researchers concluded that ginger could be regarded as an effective prospective treatment for hypertension in humans. Ginger may be useful for the treatment of heart diseases and lung diseases (28). It stimulates the production of saliva and acts as a hypolipidaemic agent in cholesterol-fed rabbits. Akhani et al. reported that ginger treatment significantly decreased both serum cholesterol and triglycerides (32). Ginger compounds (6-gingerol and 6-paradol) had inhibitory effects on the viability and DNA synthesis of human promyelocytic leukemia cells. Ginger's essential oil significantly suppressed formation of DNA adducts by aflatoxin B1 in a microsomal enzyme-mediated reaction (29). Ginger extracts possess antibacterial activity. These results may suggest that the n-hexane, ethyl acetate and soxhlet extracts of the ginger roots could be used for treating bacterial infections, drypepsia and colic (30). Bhandari found that the ethanolic extract of ginger significantly reduced total cholesterol and triglycerides of serum and increased the HDL-cholesterol levels; also, the extract can protect tissues from lipid peroxidation and exhibits a significant lipid lowering activity in diabetic rats (32). The study of Gujaral revealed that serum and liver cholesterol decreased when ginger was administered to hypercholesterolemic rats (31). Bhandari have reported that an ethanolic extract of ginger prevent hypercholesterolemia and development of atherosclerosis in cholesterol fed rabbits. Bhandari found that, the ethanolic extract of ginger significantly reduced total cholesterol and triglycerides of serum and increased the HDL-cholesterol levels; also, the extract can protect tissues from lipid peroxidation and exhibits a significant lipid lowering activity in diabetic rats (28).

3.2. Ginger and diabetes

Ginger has been traditionally used in the treatment of diabetes mellitus. Several studies have reported the hypoglycaemic properties of ginger in animal models.

The fresh and dried rhizome of ginger is widely used in traditional medicines. Scientist have studied the effect of the juice of Z. officinale (4 mL/kg, p.o. daily) for 6 weeks on streptozotocin (STZ)-induced type I diabetic rats with particular reference to the involvement of serotonin (5-hydroxytryptamine; 5-HT) receptors in glycaemic control. In normoglycaemic rats, 5-HT (1mg/kg, i.p.) produced hyperglycaemia and hypoinsulinaemia, which was significantly prevented by the juice of Z. officinale. STZ-diabetes produced a significant increase in fasting glucose levels that was associated with a significant decrease in serum insulin levels. Treatment with Z. officinale produced a significant increase in insulin levels and a decrease in fasting glucose levels in diabetic rats. In an oral glucose tolerance test, treatment with Z. officinale was found to decrease significantly the area under the curve of glucose and to increase the area under the curve of insulin in STZ-diabetic rats. Treatment with Z. officinale also caused a decrease in serum cholesterol, serum triglyceride and blood pressure in diabetic rats. Our data suggest a potential antidiabetic activity of the juice of Z. officinale in type I diabetic rats, possibly involving 5-HT receptors (33).

In the present study, the hypoglycaemic potentials of ginger (Zingiber officinale) were studied in rats. An aqueous extract of raw ginger was administered daily (500 mg/kg, intraperitoneally) for a period of 7 weeks to streptozotocin (STZ) induced diabetic rats. Fasting blood serum was analyzed for blood glucose, cholesterol and triacylglycerol levels. The STZ-injected rats exhibited hyperglycaemia accompanied with weight loss, indicating their diabetic condition. At a dose of 500 mg/kg, raw ginger was significantly effective in lowering serum glucose, cholesterol and triacylglycerol levels in the ginger-treated diabetic rats compared with the control diabetic rats. The ginger treatment also resulted in a significant reduction in urine protein levels. In addition, the ginger-treated diabetic rats sustained their initial weights during the treatment period. Moreover, ginger decreased both water intake and urine output in the STZ-induced diabetic rats. The present results indicate that raw ginger possesses hypoglycaemic, hypocholesterolaemic and hypolipidaemic potential. Additionally, raw ginger is effective in reversing the diabetic proteinuria observed in the diabetic rats. Thus, ginger may be of great value in managing the effects of diabetic complications in human subjects (34).

The present study evaluated the antihyperglycaemic effect of its aqueous extract administered orally (daily) in three different doses (100, 300, 500 mg/kg body weight) for a period of 30 d to streptozotocin (STZ)-induced diabetic rats. A dose-dependent antihyperglycaemic effect revealed a decrease of plasma glucose levels by 38 and 68 % on the 15th and 30th day, respectively, after the rats were given 500 mg/kg. The 500 mg/kg ZO significantly ($P < 0{\cdot}05$) decreased kidney weight (% body weight) in ZO-treated diabetic rats v. control rats, though the decrease in liver weight (% body weight) was not statistically significant. Kidney glycogen content increased significantly ($P < 0{\cdot}05$) while liver and skeletal muscle glycogen content decreased significantly ($P < 0{\cdot}05$) in diabetic controls vs. normal controls. ZO (500 mg/kg) also significantly decreased kidney glycogen ($P < 0{\cdot}05$) and increased liver and skeletal muscle glycogen in STZ-diabetic rats when compared to diabetic controls. Activities of glucokinase, phosphofructokinase and pyruvate kinase in diabetic controls were decreased by 94, 53 and 61 % respectively, when compared to normal controls and ZO significantly increased ($P < 0{\cdot}05$) those enzymes' activities in STZ-diabetic rats. Therefore, the present study showed that ginger is a potential phytomedicines for the treatment of diabetes through its effects on the activities of glycolytic enzymes (36). Ginger is

usually regarded as safe in small amounts, or approximately 2-4 grams per day (35,36).

CONCLUSION

Diabetes mellitus is a group of metabolic diseases caused by a combination of insulin resistance and impaired insulin secretion by pancreatic B cell. The number of antidiabetic agents is increasing as our understanding of the pathophysiology of T2DM develops. Currently available therapy acts by increasing insulin secretion (sulphonylurea and glinides), decreasing insulin resistance (glitazones and metformin) or delaying the absorption of glucose from the intestine (acarbose), but most of synthetic drugs have different side effects and none of these drugs have been shown to stop the progressive decline of beta-cell function. Therefore the use of the herbal medicines is more important than before. It provides a valuable therapeuthic alternative. Also Herbal medicines are frequently considered to be less toxic and free from side effects than synthetic ones. Citrullus colocynthis, Fenugreek and Zingiber are herbal medicines which have antidiabetic effect. The effect of different doses and the long-term durability are required for this class of compounds.

REFERENCES

1. Sheikhpour R. Evaluation of lipid profile in diabetic patient. Clinical Biochemistry. 2011; 44(13): s160.
2. Sheikhpour R, Jalali B, Yaghmaei P, fkhami-Ardekani M, Rashidi M.Comprison of two supplementary zinc does on lipid peroxidation in diabetic patient.Iranian .Iranian Journal of Diabetes and Obesity. 2010; 2(2):17-22.
3. Sheikhpour R. Characteristics of type2 diabetic patient with a long time of diabetes. Clinical Biochemistry.2011; 44(13):s 54.
4. Yaghmaei P, Parivar K, Esmaeili M.The effect of Matricaria recutita extract injected into the nucleus paragigantocellularis on the brain, symptoms of morphine withdrawal in mice, rats. Medical Scince Journal of Islamic Azad University.2006;16(3): 147-153.
5. Yaghmaei P. Oryan Sh. Effects of ethanolic extract of fruit, Vitex agnus-castus on anxiety in male wistar rats. Medical Scince Journal of Isfahan University. 2007;27:45-53
6. Rafati A, Morady S, Jalali B,Yaghmaei P. The comparison of Anethum graveolens dhi and lovestathin in lipid and lipoprotein in rat . Medical Science Journal of Shahid sadouqi University .2006;12(4): 49-55.
7. Yaghmaei P, Parivar K, Karkhane L. The effect of Kombucha extract on obesity and the rate of fat accumulation in visceral mass of male Wistar Rat. Medical Scince Journal of Islamic Azad University. 2009;4(4):61-68.
8. Urilloyd J,Citrulus colocynthis. Reprinted from the western druggist.Chicago.1898.june.
9. Jayaramani R, ARihara Shivakumar T, Joshi Vd, Palei Nn. Antidiabetic effect of petroleum ether extract of citrulus colocynthis frute against streptozocin induced hyperglycemic rats .J Biol-plant boil. 2009; 54 (2):127-134.
10. Atef E, Abd EB, Hatem KA. Effect of citrulus colocynthis ameliorate the oxidative stress and nepharopathy in diabetic experimental. International Journal of Pharmaceutical Studies and Research. 2011;2(2):1-10.
11. Agarwal V, Sharma Ak, Upadhyay A, Singh G, Gupta R. Hypoglycemic effects of citrullus colocynthis roots .Acta poloniae pharmaceutica drug research. 2012;69(1):75-79.
12. Sen Gupta A, Chakrabarty MM. The component fatty acids of Citrullus colocynthis seed fat. Journal of the Science of Food and Agriculture.1964;15(2):69-132.
13. Dehgani F, Panjehshahin MR. The Toxic Effect of Alcoholic Extract of Citrullus colocynthis on Rat Liver. Iranian of pharmacology and therapeutic. 2006;5(2):117-119.
14. Dallak M. In vivo, hypolipidemic and antioxidant effects of Citrullus colocynthis pulp extract in alloxan-induced diabetic rats. African Journal of Biotechnology. 2011; 10(48): 9898-903.
15. Zamani M, Rahimi AO, Mahdavi R, Nikbakhsh M, Jabbari MV, Rezazadeh H, et al. Assessment of anti-hyperlipidemic effect of Citrullus colocynthis. Revista Brasileira de Farmacognosia.2007;17(4):492-6.
16. Morehouse LA, Bangerter FW, DeNinno MP, Inskeep PB, McCarthy PA, Pettini JL, et al. Comparison of synthetic saponin cholesterol absorption inhibitors in rabbits: evidence for a non-stoichiometric, intestinal mechanism of action. Journal of lipid research.1999; 40(3): 464-74.
17. Memon U, Hakeem A. Antibacterial of Citrullus colocynthis. Pakistan Journal of Pharmaceutical Sciences.2003; 16(1):1-6.
18. Sebbagh N, Cruciani-Guglielmacci C, Ouali F, Berthault MF, Rouch C, Sari DC, et al. Comparative effects of Citrullus colocynthis,

sunflower and olive oil-enriched diet in streptozotocin-induced diabetes in rats. Diabetes & Metabolism. 2009;35(3):178-84.
19. Zaree AB , Fallahhossini H, Sharifabady R, Norooz zadeh A, Emani H ,Ghoshooni H. The Effect of Citrullus Colocynthis Extract on Preventing/ Reducing Streptozotocin- Induced Diabetes in Rat. Kowsar Medical Journal. 2007; 12(1): 13-20.
20. Dallak M, Bin-Jaliah I. Antioxidant activity of citrulus colocynthis pulp extract in RBCof allixan induced diabetic. Pak J Physiol. 2010; 6(1):112-22.
21. Araee M, Norouzi M, Habibi G, Sheikhvatan M. Toxicity of trigonella foenum graecum in bone marrow cell proliferation in rat. Pak. J. Pharm. Sci. 2009;22(2):126-130.
22. Fedelic Ashish T, Rachina A, Pathak AK. Pharmacological actions and potential uses of trigonella foenum graecum. Asian Journal of Pharmaceutical and Clinical Research. 2009;2(4);28-38.
23. Basch E, Ulbricht C, Kuo G, Szapary Ph, Smith M. Therapeutic Applications of Fenugreek**.** Alternative Medicine Review .2003; 8(1), 20-28.
24. Renuka C, Ramesh N, Saravanan K. Evaluation of the antidiabetic effect of Trigonella foenum-graecum seed powder on alloxaninduced diabetic albino rats.International Journal of PharmTech Research.2009;1(4): 1580-4.
25. Kumar GS, Shetty AK, Sambaiah K, Salimath PV. Antidiabetic property of fenugreek seed mucilage and spent turmeric in streptozotocin-induced diabetic rats. Nutrition Research 2005;25(11): 1021–8.
26. Xue WL, Li XS, Zhang J, Liu YH, Wang ZL, Zhang RJ. Effect of Trigonella foenum-graecum (fenugreek) extract on blood glucose, blood lipid and hemorheological properties in streptozotocin-induced diabetic rats. Asia Pac J Clin Nutr .2007;16 (1):422-6.
27. Mitra A, Bhattacharya D. Dose-dependent effects of Fenugreek composite in Diabetes with dislipidaemia. Internet Journal of Food Safety. 2006;8 : 49-55.
28. Saeid JM, Mohamed AB, Al-Baddy MA. Effect of Aqueous Extract of Ginger (Zingiber officinale) on Blood Biochemistry Parameters of Broiler. International Journal of Poultry Science. 2010;9 (10): 944-7.
29. Kemper KJ. Ginger (Zingiber officinale). Longwood Herbal Task Force.1999;3:1-18.
30. Malu SP,Obochi EN, Antidiabetic of ginger .Global Journal of pure and applied science. 2009;15(3):365-69.
31. Armando Gonzalez Stuart. Ginger.2005.
32. Elshater AE, Salman MA, Moussa MA. Effect of Ginger Extract Consumption on levels of blood Glucose, Lipid Profile and Kidney Functions in Alloxan Induced-Diabetic Rats. Egyptian Academic Journal of Biological Sciences. 2009;2(1):153-62.
33. Abd Elraheem A,Elsaater M.Effect of ginger extract consumption on level of blood glucose,lipid profile and kidney functions in Alloxan induced diabetic rat. Egypt. Acad. J. biolog. Sci. 2009;2 (1): 153-62.
34. Akhani SP, Vishwakarma SL, Goyal RK. Anti-diabetic activity of Zingiber officinal in streptozotocin-induced type I diabetic rats. J Pharm Pharmacol. 2004;56(1):101-5.
35. Al-Amin ZM, Thomson M, Al-Qattan KK, Peltonen-Shalaby R, Ali M. Anti-diabetic and hypolipidaemic properties of ginger (Zingiber officinale) in streptozotocin-induced diabetic rats.Br J Nutr. 2006;96(4): 660-6.
36. Wadkar KA, Magdum CS, Patil SS, Naikwade NS. Anti diabetic potential and Indian medicinal plant. Journal of Herbal Medicines and Toxicology. 2008;2 (1): 45-50.