Sys Rev Pharm 2020;11(11):970-974
A multifaceted review journal in the field of pharmacy

Evaluation of pharmacodynamics of ginger (Zingiber officinale) compared with gliclazide in diabetic rats

TAHA AM[a*], TAYEE EM[b], Abdelkareem E[c] and Taha Azouz[d]

[a,b]Department of Clinical Pharmacology, Faculty of Medicine, Helwan University, Cairo, Egypt
[c]Department of Clinical Pharmacology, Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[d]Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, Egypt
Corresponding author: Dr. Ahmed Mohammed Taha
Department of Pharmacology,Faculty of Medicine, Helwan University, Cairo, Egypt
Tel. No.: (002) 01067991482
Email: ahmed999taha@yahoo.com

Abstract

Background: Diabetes mellitus (DM) is the most common of the endocrine disorders. Despite of the advance in diabetic treatment, many patients seek alternative options due to various reasons.Complementary and alternative medicine (CAM) has gained popularity because of the possibilities it offers to patients. Gliclazide belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Ginger is a potential phytomedicine for the treatment of diabetes through its effects on the activities of glycolytic enzymes.

Aim of the work: To study the pharmacodynamics of Ginger compared with that of gliclazide on diabetic rats.

Materials and methods: This study was carried on 50 Male adult albino rats (200-250g). They were divided into 2 groups. Group 1 included "10 rats" served as "Control group" received single i.v. injection of citrate buffer, in a volume equal to that used as a solvent for streptozotocin (STZ) used to induce diabetes in test groups. Group 2 included diabetic rats "40 rats" which were injected by single intraperitoneal injection of a freshly prepared solution of STZ in a dose of 55 mg/kg body weight.The diabetic rats were divided into 4 subgroups. Group A "Diabetic rats concurrently treated with saline". After STZ injection, rats were received 10% (wt/vol) of glucose in the drinking water for 3 days. After that, rats of this group were treated orally by saline for 6 weeks. Group B "Diabetic rats concurrently treated with gliclazide". After STZ injection, rats were received 10% (wt/vol) of glucose in the drinking water for 3 days. After that, rats of this group were treated orally by 0.3 mg/kg of gliclazide daily for 6 weeks. Group C "Diabetic rats concurrently treated with ginger" After STZ injection, rats were received 10% (wt/vol) of glucose in the drinking water for 3 days. After that, rats of this group were treated orally by (500mg/kg) of ginger daily for 6 weeks. Group D "Diabetic rats concurrently treated with gliclazide and ginger". After STZ injection, rats were received 10% (wt/vol) of glucose in the drinking water for 3 days. After that, rats of this group were treated orally by (0.3 mg/kg) of gliclazide and (1mL/100g.bw) of ginger daily for 6 weeks.Then blood samples were collected and examined for serum glucose, lipid profile, liver and kidney functions. Rats were sacrificed, livers were obtained and prepared for histological examination.

Results: There was statistically significant increase of glucose, triglycerides, low density lipoprotein, total cholesterol, alanine transaminase, aspartate transaminase, urea and creatinine, and significant decrease of high-density lipoprotein in the diabetic group when compared to control group. Administration of either gliclazide or ginger or combination together was associated with improvement of biochemical alterations associated with diabetes with superiority of

Keywords: Antidiabetic; Gliclazide; Ginger; Diabetes mellitus, STZ.

Corresponding author: Dr. Ahmed Mohammed Taha
Department of Pharmacology,Faculty of Medicine, Helwan University, Cairo, Egypt
Tel. No.: (002) 01067991482
Email: ahmed999taha@yahoo.com

gliclazide. Histopathological examination revealed that , normal control had normal structure of the liver, while in diabetic group, the liver tissues showed loss of normal lobular architecture, with liver cell apoptosis (the cells are shrunken, the nuclei were dark stained, fragmented or faint). It was revealed that all diabetic treated groups were able to prevent histopathological abnormalities.

Conclusion: The present study showed that ginger is a potential phytomedicine for the treatment of diabetes through its effects on the activities of glycolytic enzymes. The combination of Ginger with gliclazide represents a valuable combination to improve diabetes and its complications.

INTRODUCTION

Diabetes mellitus (DM) is the most common of the endocrine disorders.The prevalence of diabetes mellitus is expected to reach up to 4.4% in the world by 2030. According to the World Health Organization (WHO), in 2014, 8.5% of adults over the age of 18 suffer from DM, compared to 4.7% in 1980. In 2015, the International Diabetes Federation (IDF) recorded 415 million adults suffering from diabetes and estimated an increase to 642 million by 2040 (Atta et al., 2019).

Currently available treatment options in modern medicine have several adverse effects. Therefore, there is a need to develop safe and effective treatment modalities for diabetes. Medical plants play an important role in the management of diabetes mellitus (Preethi et al., 2013).

Despite of the advance in diabetic treatment, many patients seek alternative options due to various reasons. Complementary and alternative medicine (CAM) has gained popularity because of the possibilities it offers to patients. Complementary medicine refers to the use of products in adjunction to conventional treatments, while alternative medicine is the use of products as a substitute for conventional medicine (Loren et al., 2018).

Ginger has been traditionally used in the treatment of diabetes mellitus. Several studies have reported the hypoglycaemic properties of ginger in animal models. Ginger is a potential phytomedicine for the treatment of diabetes through its effects on the activities of glycolytic enzymes.Ginger rhizomes are widely used in foods for their nutritional and medicinal benefits, especially in Asia as asource of Fe and Ca. More recently, ginger juice was shown to have an antidiabetic effect as it increases the insulin levels in (STZ)-induced diabetic rats (Abdulrazaq et al., 2011).

Ginger is speculated to reduce serum glucose levels through the activities of phenols, polyphenols, and flavonoids, which may inhibit intestinal glucosidase and amylase enzymes (Shanmugam et., al. 2011). The antioxidants within ginger, including paradol and zingerone, can counteract lipid peroxidation (Shanmugam et., al. 2011), (Ghlissi et al., 2013). These antioxidants might also decrease insulin resistance by improving glucose transport through the upregulation of the GLUT-4 transporter and insulin receptors, and enhance the activity of pancreatic beta islet cells secretory function (Kota et al., 2012), (Mahluji 2013).

Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It has been classified differently according to its drug properties in which based on its chemical structure, gliclazide is considered a first-generation sulfonylurea due to the structural presence of a sulfonamide group able to release a proton and the presence of one aromatic group (Ghosh and Collier 2012). On the other hand, based on the pharmacological efficacy, gliclazide is considered a second-generation sulfonylurea which presents a higher potency and a shorter half-life (Scholar 2007). Gliclazide belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Sulfonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors (Ballagi et al., 1990).

MATERIAL AND METHODS

Materials

Drugs and chemicals

- Streptozotocin (STZ) was supplied from Sigma chemical company.
- Citrate buffer Ph 4.5 (citric acid+ sodium citrate) in distilled water 0.1 moles.
- Ginger was supplied from pharmacognsy department, Al Azhar university.
- Heparin. was supplied from Amoun company.
- Gliclazide was supplied from Servier company and was dissolved in distilled water containing 0.9% (wt/vol) sodium chloride for oral administration.

Kits

- Kits for measurement of lipid profile were obtained from Diamond Diagnostic Company, Egypt.
- Kits for measurement of serum glucose were obtained from Biodiagnostic, Giza, Egypt.
- Kits for measurement of liver enzymes (ALT&AST), were obtained from Diamond Diagnostic Company, Egypt.
- Kits for measurement of kidney functions were obtained from Diamond Diagnostic Company, Egypt.

Animals

Experiments were conducted using 50 male adult albino rats weighing (200-250g), bred in the animal house of pharmacology department of AL-Azhar University. The animals were handled according to the guidelines of local ethical committee which comply with the international laws for use and care of laboratory animals. The animals were allowed to acclimatize for 2 weeks before the experiment. The animals were housed four per cage under controlled temperature (23±1°C) in polypropylene cages inside a well-ventilated room, relative humidity 40%- and 12-hour light/dark cycle. They were fed a standard commercial pellet diet and water ad libitum. The diet consists of 71% carbohydrate, 18% protein, 7% fat, 4% salt mixture and adequate minerals and vitamins.

Induction of Diabetes Mellitus

Streptozotocin was dissolved in cold 0.01 M citrate buffer,

pH 4.5and always prepared freshly for immediate use within 5 min. Diabetes was induced in rats by single intraperitoneal injection of a freshly prepared solution of streptozotocin in a dose of 55 mg/kg body weight (Cheng et al., 2002, Arora et al., 2009). After STZ injection, rats were received 10% (wt/vol) of glucose in the drinking water for 3 days to compensate for hypoglycemia which results from insulin release from beta cells of the islets of Langerhans due to their destruction by streptozotocin (Bar-On et al., 1976).The blood glucose concentration was measured 4 days from the day of STZ injection. The rats with blood glucose higher than 250mg/dl were considered diabetics and were used in the experiment.

Experimental design

- This study was carried on 50 Male adult albino rats (200-250g).
- They were divided into 2 groups.
- Group 1 included "10 rats" served as "Control group" received single i.v. injection of citrate buffer, in a volume equal to that used as a solvent for STZ used to induce diabetes in test groups.
- Group 2 included diabetic rats "40 rats" which were injected by single intraperitoneal injection of a freshly prepared solution of streptozotocin in a dose of 55 mg/kg body weight. After STZ injection, rats were received 10% (wt/vol) of glucose in the drinking water for 3 days
- The diabetic rats were divided into 4 subgroups.
- Group A "Diabetic rats concurrently treated with saline for 6 weeks.
- Group B "Diabetic rats concurrently treated orally by 0.3 mg/kg of gliclazide daily for 6 weeks.
- Group C "Diabetic rats concurrently treated orally by (500mg/kg) of ginger daily for 6 weeks.
- Group D "Diabetic rats concurrently treated orally by (0.3 mg/kg) of gliclazide and (1mL/100g.bw) of ginger daily for 6 weeks.
- Then blood samples were collected and examined for serum glucose, lipid profile, liver and kidney functions.
- Rats were sacrificed; livers were obtained and prepared for histological examination.

Collection of blood samples and biochemical analysis

During this study, blood glucose level was measured every 4 days, at the same time. Collection of blood samples were done at the start of the study, after three days after induction with STZ to be sure that hyperglycemia was occurred, and then at the mid (after 3 weeks) and the end of the study (6 weeks) to be statistically analyzed. Blood samples were collected from the retro-orbital venous plexus of rat eye by using heparinized capillary tubes. The collected blood samples were then centrifuged (Cooling centrifuge, sigma 2 k 15) at 300 round/minute for 30 minutes. Then the serum was transferred into clean vials and stored at -18°C for biochemical parameters determination (Schermere, 1967). All biochemical measurements were done in department of biochemistry, faculty of medicine, Cairo University.

Statistical analysis

All values are expressed as mean ± SEM. Data were statistically analyzed using independent samples student (t) test for comparison between two groups. Significance was set at $p \leq 0.05$. Data were computed for statistical analysis by using statistical package for social science (SPSS), version 16 (SPSS Inc, US), running on IBM compatible computer.

RESULTS

In the present study, there was statistically significant increase of glucose, triglycerides, low density lipoprotein, total cholesterol, alanine transaminase, aspartate transaminase, urea and creatinine, in the diabetic group when compared to control group. Otherwise, high density lipoprotein was significantly decreased in diabetic group when compared to control group (Table 1). When comparing diabetic group that received gliclazide alone to control group, results revealed that, there was no significant difference between both groups regarding serum glucose levels, triglycerides, HDL and total cholesterol. On the other side, LDL, ALT, AST, urea and creatinine were significantly increased in gliclazide group when compared to control group (i.e., gliclazide was able to control serum glucose levels and, triglycerides, HDL and total cholesterol; but it was not able to control diabetic effects on the liver and kidney, beside low density lipoprotein) (Table 1).

As regard Ginger, we found that, there was statistically significant decrease of HDL and significant increase of LDL, total cholesterol, ALT, AST, urea and creatinine in ginger group when compared to control group (i.e, ginger could control serum glucose levels and triglycerides only). Otherwise, it could not control LDL, total cholesterol, ALT, AST, urea and creatinine) (Table 1).

When both gliclazide and ginger were combined together, there was no significant difference when compared to control group as regard to serum glucose levels, triglycerides, HDL, LDL, total cholesterol, urea and creatinine, while there was still significant increase of ALT and AST (i.e, this combination can control diabetic changes on serum glucose levels, lipid profile and renal functions) (Table 1).

Comparing effects of gliclazide and ginger, there was no significant difference between both groups regarding serum glucose, triglycerides, HDL, or serum creatinine. On the other side, HDL, total cholesterol, ALT, AST and urea were significantly reduced with gliclazide (Table 2).

Histopathology

In normal (negative) control group, the liver appears normal in structure, with normal hepatic lobule, where cells were arranged radially around the central vein (CV). The cytoplasm was acidophilic, the nuclei is rounded, vesicular and euchromatic with nucleoli. Groups of hepatocytes were intervened by a thin-walled blood sinusoid, with Kupffer cells lining the sinusoids (Figure 1). In diabetic group, the liver tissues showed loss of normal lobular architecture, with liver cell apoptosis (the cells are shrunken, the nuclei were dark stained, fragmented or faint) (Figure 2). Histological sections of the gliclazide, ginger and both showed more or less normal structure of the liver, with no apparent pathological alterations, as shown in negative control group.

Table 1. Biochemical results of studied groups

	Control normal (Group 1)		Diabetic group (group A)		Diabetic group (group B)		Diabetic group (group C)		Diabetic group (group D)		F	p
	Mean	S. D	Mean	S. D	Mean	S. D	Mean	S. D	Mean	S. D		
Glucose	105.30	8.94	219.35*	13.84	103.60	5.42	104.90	3.41	101.60	7.20	311.83	<0.001

TG	183.20	15.10	258.70*	16.11	183.60	14.71	183.90	14.34	185.0	10.37	54.49	<0.001
HDL	29.40	4.64	19.70#	3.33	26.10	11.03	21.40#	3.03	29.30	3.71	5.13	0.002
LDL	28.90	4.18	77.30*	13.27	51.50*	8.36	70.0*	13.01	31.40	4.84	49.24	<0.001
Total cholesterol	94.20	6.71	203.60*	9.52	93.90	5.84	108.30*	6.02	95.40	6.92	434.93	<0.001
ALT	22.60	1.35	60.70*	6.02	32.10*	2.01	36.70*	3.31	27.50*	2.22	194.10	<0.001
AST	19.20	1.32	51.10*	9.63	29.10*	1.84	32.70*	3.97	24.70*	2.53	60.83	<0.001
Urea	21.80	4.68	72.90*	6.61	28.10*	5.16	32.80*	3.60	23.80	4.24	173.41	<0.001
Creatinine	0.65	0.13	2.13*	0.37	1.01*	0.15	0.98*	0.23	0.69	0.11	64.67	<0.001

* Significant increase when compared to control group; # significant decrease when compared to control group.
F: for one analysis of variance
P: the alpha error (statistically) probability

Table 2. Comparison between gliclazide and ginger groups

	Diabetic group (group B)		Diabetic group (group C)		t	p
	Mean	S. D	Mean	S. D		
Glucose	103.60	5.42	104.90	3.41	1.185	0.252
TG	183.60	14.71	183.90	14.34	0.046	0.964
HDL	26.10	11.03	21.40	3.03	1.327	0.201
LDL	51.50	8.36	70.00	13.01	3.845	0.001*
Total cholesterol	93.90	5.84	108.30	6.02	5.430	<0.001*
ALT	32.10	2.01	36.70	3.31	3.670	0.002*
AST	29.10	1.84	32.70	3.97	2.673	0.016*
Urea	28.10	5.16	32.80	3.60	2.407	0.027*
Creatinine	1.01	0.15	0.98	0.23	0.227	0.823

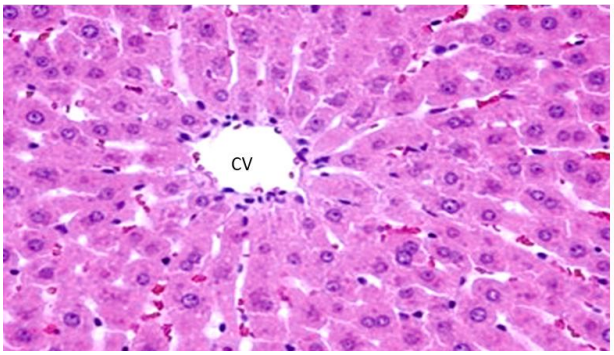

Figure 1. Photmicrograph of the liver in negative control group, showing normal hepatic lobule, where hepatic cells arranged

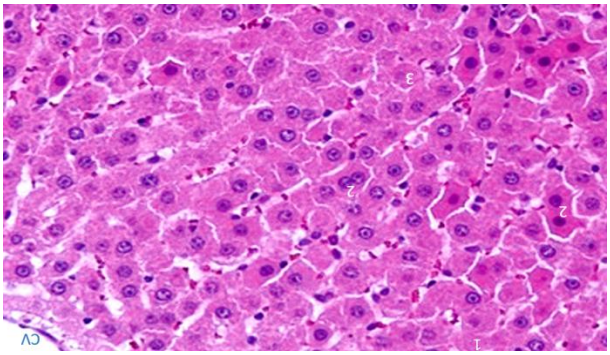

Figure 2. Loss of normal architecture with numerous apoptotic dark-stained shrunken hepatocytes with (absent nuclei [1], bi-

NB: Pictures were treated digitally to improve

Discussion

Several studies in recent years, have shown that ginger consumption could have profitable effects on glucose and lipid metabolism in patients with diabetes. Our results showed significant reductions in fasting blood glucose, total cholesterol, LDL, and triglycerides as well as an increase in HDL. In the present work, we presented the potential protective effects of anti-diabetic gliclazide and Ginger on both laboratory findings and histopathology of the liver. Results revealed that, both gliclazide and Ginger provided protective effects, as both normalized blood sugar and triglycerides. Gliclazide additionally normalizes HDL. When both medications used simultaneously, all laboratory tests were nearly normalized except ALT and AST. Histopathological examination revealed harmful effects on liver tissues, both medications were able to prevent development of pathological effects of liver tissue. Gliclazide found to be superior in prevention of alterations in LDL, total cholesterol, ALT, AST and urea.

Our work agree with Makhdoomi et., al. 2017 who showed that consumption of 500mg ginger daily in diabetic patients reduce fasting blood glucose and LDL/ HDL-ratio significantly. Also, Amir et., al.2018 reported that Treatment with ginger ameliorate hyperglycemia, hyperlipidemia and kidney function. In addition, ginger exerts a protective role against diabetes-induced renal injury by ameliorating oxidative stress, inflammation and apoptosis.

Results of the present work support the results obtained by Al-Amin ,2006 who reported that 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 aqueous extracts of ginger can affect carbohydrate and lipid metabolism as well as insulin sensitivity. The mechanism by which ginger can exert these anti-diabetic effects is hypothesized to occur through the inhibition of several transcriptional pathways, lipid peroxidation, carbohydrate metabolizing enzymes, and the activation of antioxidant effect (Li et., al. 2012).

Results of the present work are consistent with Abdulrazaq et al. (2011) who reported that, adose-dependent antihyperglycaemic effect of ginger revealed a decrease of plasma glucose levels by 38% to 68% at 15th and 30 th day of administration of ginger in dose dependent manner 100, 300 and 500mg/kg respectively.

In summary, This study suggests a direct effect of ginger for the treatment of diabetes.The biochemical and histopathological data from this study revealed that, the combination of Ginger with oral hypoglycemic gliclazide represent a valuable combination to prevent hyperglycemia and its complications. However, further studies are needed to evaluate its safety uses and to clearly establish what dosage provides the greatest efficacy for the treatment of diabetes.

Significance of the study

This study provided an evidence on the efficacy of ginger to protect against diabetes and its complications and compared the pharmacodynamics of gliclazide with ginger. We must stress that, at the present time, ginger alone could not be used as antidiabetic drug, although serum glucose levels were controlled among studied animals.Ginger can be used as an adjuvant with classic antidiabetic drugs. Further clinical evidence is required to search the anti-diabetic mechanisms of ginger.

REFERENCES

1. Abdulrazaq N.B., Cho M.M. and Win N.N. (2011): Beneficial Effects of Ginger (Zingiber officinale) on Carbohydrate Metabolism in Streptozotocin-Induced Diabetic Rats. British Journal of Nutrition, 108, 1194-1201.
2. Akash M.S.H., Rehman K., Tariq M. and Chen S. (2015): Zingiber officinale and Type 2 Diabetes Mellitus: Evidence from Experimental Studies. Critical Reviews in Eukaryotic Gene Expression, 25, 91-112.
3. Al-Amin Z.M., Thomson M. and Al-Qattan K.K. (2006): Antidiabetic and Hypolipidemic Properties of Ginger (Zingiber officinale) in Streptozotocin-Induced Diabetic Rats. British Journal of Nutrition, 96, 660-666.
4. Amir M. , Al HroobaMohammad H. , Abukhalil R. D., Alghonmeena A. and Mahmoud M. (2018): Ginger alleviates hyperglycemia-induced oxidative stress, inflammation and apoptosis and protects rats against diabetic nephropathy. Biomedicine & Pharmacotherapy, 106, 381-389.
5. Ballagi P. G., Koszeghy A., Koltai MZ., Aranyi Z. and Pogatsa G (1990): Divergent cardiac effects of the first- and second-generation hypoglycemic sulfonylurea compounds. Diabetes Res Clin Pract. 8(2):109-14.
6. Daily J.W., Yang M. and Kim S.S. (2015): Efficacy of Ginger for Treating Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Journal of Ethnic Foods, 2, 36-43.
7. Ghlissi Z., Atheymen R., Boujbih M.A., Sahnoun Z., Makni A. F., Zeghal K., El Feki A. and Hakim A. (2013): Antioxidant and Androgenic Effects of Dietary Ginger on Reproductive Function of Male Diabetic Rats. International Journal of Food Sciences and Nutrition, 64, 974-978.
8. Ghosh S. and Collier A. (2012): Churchill's pocketbook of diabetes (2nd ed.). Elsevier.
9. Kota N., Panpatil V.V., Kaleb R., Varanasi B. and Polasa K. (2012): Dose Depen-dent Effect in the Inhibition of Oxidative Stress and Anti Clastogenic Potential of Ginger in STZ Induced Diabetic Rats. Food Chemistry, 135, 2954-2959.
10. Li Y., Tran V.H., Duke C.C. and Roufogalis B.D. (2012): Preventive and Protective Properties of Zingiber officinale (Ginger) in Diabetes Mellitus, Diabetic Complications, and Associated Lipid and Other Metabolic Disorders: A Brief Review. Evidence-Based Complementary and Alternative Medicine: 516870.
11. Loren D., Roscoe R. and Shack A. (2018): Complementary and Alternative Medicine for Diabetes. Canadian Journal of Diabetes, 42, 154-161.
12. Mahluji S. (2013): Effects of Ginger (Zingiber officinale) on Plasma Glucose Level, HbA1c and Insulin Sensitivity in Type 2 Diabetic Patients. International Journal of Food Sciences and Nutrition, 64, 682-686.
13. Makhdoomi A. M., Mohammadzadeh H. N. and Saedisomeolia A. (2018): The Effects of Ginger on Fasting Blood Sugar, Hemoglobin A1c, and Lipid Profiles in Patients with Type 2 Diabetes. Int J Endocrinol Metab. 15:57927.
14. Massud A., Shadi J. and Kareen M. (2019): Complementary and Alternative Medicine: A Review on the Effects of Ginger, Cinnamon and Camellia Sinensis Leaf Tea in Diabetes. Journal of Diabetes Mellitus 9, 126-136.
15. Preethi P.J., Koorapalayam P. and Erode T.N. (2013): Herbal medicine for diabetes mellitus. International Journal of Phytopharmacy. 3, 1-22.
16. Shanmugam K.R. (2011): Neuroprotective Effect of Ginger on Antioxidant Enzymes in Streptozotocin-Induced Diabetic Rats. Food and Chemical Toxicology, 49, 893-897.
17. Shanmugam K.R., Mallikarjuna K., Nishanth K., Kuo C.H. and Reddy K.S. (2011): Protective Effect of Dietary Ginger on Antioxidant Enzymes and Oxidative Damage in Experimental Diabetic Rat Tissues. Food and Chemical Chemistry, 124, 1436-1442.