

ORIGINAL ARTICLE

Comparison of the Effects of Combination of Turmeric, Ginger and Cinnamon Hydroalcoholic Extracts with Metformin on Body Weight, Glycemic Control, Inflammation, Oxidative Stress and Pancreatic Histopathological Changes in Diabetic Rat

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ABSTRACT

Background: Type 2 diabetes is a progressive disease. This study compared effects of combination of turmeric, ginger and cinnamon hydroalcoholic extracts with metformin on body weight, glycemic control, inflammation, oxidative stress and pancreatic histopathological changes in diabetic rat.

Methods: Rats were randomly assigned to four groups of 13 animals. Diabetes was induced by a single injection of streptozotocin (STZ, 65 mg/kg) and nicotinamide (110 mg/kg, 15 min before STZ injection). Normal control (NC) and diabetic control (DC) rats received 1 mL of distilled water and two other diabetic groups received either 300 mg/kg (HETGCC) or 100 mg/kg metformin for 6 weeks.

Results: HETGCC and metformin significantly decreased serum glucose, glycated hemoglobin (HbA1c), Homeostatic Model Assessment for Insulin Resistance (HOMA index), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and malondialdehyde (MDA) levels and significantly increased high-density lipoprotein cholesterol (HDL-C) concentrations compared to DC group. A significant increase in the number and diameter of the islets of Langerhans (IL) and body weight was seen in HETGCC group compared to DC rats and a significant increase in quantitative insulin sensitivity check index (QUICKI) was observed in metformin treated group. HETGCC and metformin did not have significant effects on hsCRP, insulin and triglyceride (TG) concentrations in diabetic rats.

Conclusion: HETGCC was shown to reduce the risk of diabetes and improve complications associated with diabetes such as hyperglycemia, dyslipidemia, oxidative stress, inflammation, histopathological status of islets of Langerhans and weight loss in T2D patients.

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Introduction

Diabetes mellitus is a chronic disorder of carbohydrate, protein and fat metabolism. This worldwide health problem caused by either impaired insulin secretion or reduced tissue insulin sensitivity (1). In 2010, the prevalence of diabetes in the 20-79 year old population of the world was 6.6 percent (2). It's predicted that the number of people with diabetes will rise from 171 million in 2000 to 366 million in 2030 (3), by reasons such as inactivity, high- density calorie diets, obesity, and increased life expectancy (4).

Macro-vascular (stroke, heart attacks) and micro-vascular (retinopathy, nephropathy, neuropathy) disorders are chronic complications of this disease (5). More than 90% of diabetes incidences are attributed to type 2 diabetes mellitus (T2D) (6). According to the American Diabetes Association guidelines, metformin is recommended as the first-line drug for T2D management (7). Use of hypoglycemic drugs accompanies with numerous side effects and contraindications (1), for these reasons, the World Health Organization has considered herbs and medicinal plants as a way to manage T2D (5).

Many herbs and spices like turmeric, ginger and cinnamon show hypoglycemic, hypolipidemic, anti-inflammatory and antioxidant activities (8-11). Turmeric (*Curcuma longa*, family Zingiberaceae, rich in curcuminoids, 3-5%) (4), ginger (*Zingiber officinale*, family Zingiberaceae, rich in gingerols and shogaols, 1-3%) (4) and cinnamon (*Cinnamomum zeylanicum* L, Family Lauraceae, rich in Cinnamaldehyde) (4, 8, 12) have been widely used as flavoring agents in food, and they have also been used for treatment of various diseases in traditional medicine since ancient times (4, 8). Although clinical and experimental studies support the glycemic control, hypolipidemic, anti inflammatory effects and antioxidant activity of these spices and herbs (8-11). No study have assessed the effects of combination of these three together. Therefore, the present study aimed to examine the effects of HETGCC on body weight, glycemic control, lipid profile, inflammatory markers, oxidative stress and histopathology of the pancreas of diabetic rats and compare these effects with metformin.

Materials and Methods

Laboratory Animals

Fifty two male Sprague Dawley rats (weighing 200-250 g) were obtained from the Laboratory Animals Center of Shiraz University of Medical Sciences, Shiraz, Iran. The animals were acclimatized to the laboratory for one week prior to starting the experiments and were fed with standard rodent food

pellets (Behparvar Co., Tehran, Iran), and distilled water was ad libitum during the study. The standard rodent food pellets contained 10% ash, 20% protein, 4.5% fiber, and 4% fat and minerals. Animals were kept in a controlled temperature (22-25°C); lighting of 12 h and 12 h dark cycle, while the humidity was 50%±5%.

Induction of Diabetes

Type 2 diabetes was induced intraperitoneally (IP) in the overnight fasted rats through the injection of freshly prepared streptozotocin (STZ) (65 mg/kg; Sigma, USA), 15 min following the IP administration of nicotinamide (NA, 110 mg/kg; Merck, Germany). STZ and nicotinamide were dissolved in citrate buffer (pH=4.5) and physiological saline, respectively. A glucometer (Accu-Chek Active, Roche, Germany) was used for the estimation of blood glucose levels. The stable blood glucose concentration, three days after STZ-NA injection was used for the confirmation of diabetes. Blood glucose levels above 200 mg/dL were considered as diabetes.

Experimental Design

Animals were randomly divided into four groups of 13 including one healthy (non-diabetic) group and three STZ–nicotinamide induced diabetic groups. The treatment period for the study was 6 weeks. Distilled water; metformin and hydroalcoholic extract of turmeric, ginger, and cinnamon combination (HETGCC) were administered to rats by oral gavage. Group I was the normal control (NC) rats given 1 mL of distilled water; Group II was the diabetic control (DC) rats receiving 1 mL of distilled water; Group III was diabetic rats getting 100 mg/kg/day metformin; and Group IV was diabetic rats given 300 mg/kg/day of HETGCC (100 mg/kg/day).

Preparation of Extract

Turmeric, ginger root and cinnamon bark were shade dried at room temperature before being pulverized with a grinder. Spice powders were separately extracted with 70% ethanol for 24 hours and filtered. The produced solutions were condensed using rotator and dried by oven under the temperature of 37°C, for 3 days. The extracts were then stored in a refrigerator until use.

Determination of Biochemical Parameters

On day 42nd, the overnight fasted rats were subjected to intraperitoneal anesthesia with 45 mg/kg sodium thiopental. Approximately 5 mL of blood was collected by cardiac puncture, 2 mL collected into a tube containing EDTA for measuring HbA1c, and the remaining centrifuged at 3000 rpm for 15

Analysis of Serum

for the separation of serum. Serum samples were stored in clean sterile microcentrifuge tubes at -80°C until analysis.

Analytical Measurements

A digital scale was used for weighing rats. Serum concentration of glucose, triglyceride, total cholesterol, HDL-C and LDL were determined using the specific enzyme kits (Pars Azmoon Co., Tehran, Iran). A commercial kit (Rat Insulin ELISA) was used for measuring of serum insulin. hsCRP concentration was determined using the ELISA kit and thiobarbituric acid (TBARS) colorimetric analysis method was used to assess MDA. Samples were then analyzed spectrophotometrically at 532 nm. HbA1c levels were measured by Hb Gold device. All analyses were performed in accordance with the manuals provided by the manufacturers. For Insulin resistance, HOMA-IR index and QUICKI index were used to determine insulin sensitivity. The formulas used were as follows:

$\text{HOMA-IR} = \frac{[\text{fasting insulin } (\mu\text{U/ml})] \times [\text{fasting glucose } (\text{mmol/l})]}{22.5}$. $\text{QUICKI} = 1 / [\log (\text{fasting insulin, } \mu\text{U/ml}) + \log (\text{fasting glucose, mg/dl})]$.

Pancreatic Histopathology

Pancreas tissues obtained from all the experimental groups were washed with saline and then fixed in 10% buffered neutral formalin solution. The tissues were dehydrated with a graded series of ethanol and embedded in paraffin wax. Sections of 5 μm were cut using a microtome, stained with hematoxylin and eosin (HE). The number and diameter of the islets of Langerhans were assayed and photographed by microscope.

Statistical Analysis

Data were presented as means with their standard errors. The statistical analysis was performed using SPSS software (version 22.0, Chicago, IL, USA). One-way analysis of variance (ANOVA) was used, followed by post-hoc Duncan's multiple range tests to

identify significance of difference between groups. A P value <0.05 was considered statistically significant.

Results

Glycemic Control

Diabetic control rats had significantly higher levels of serum glucose compared to healthy control group ($P < 0.05$) (Table 1). Serum glucose concentrations significantly decreased in diabetic rats treated with either metformin or HETGCC compared to the DC group ($P < 0.05$). However, no significant differences were seen between metformin and HETGCC treated rats (Table 1). There was no significant difference in serum insulin levels among the treated diabetic rats compared to the DC group (Table 1).

HbA1c in all treated diabetic rats were significantly reduced compared to DC group ($P < 0.05$). The HETGCC treated group exhibited more reduction compared to metformin group. HOMA index in diabetic control groups significantly increased compared to NC rats ($P < 0.05$) (Table 1). All treated diabetic rats showed significantly lower HOMA index compared to diabetic control group ($P < 0.05$), while there was no significant difference between rats treated with metformin and HETGCC, regarding this parameter (Table 1).

QUICKI significantly decreased in DC rats compared to the non-diabetic rats ($P < 0.05$) (Table 1). Metformin treated rats showed a significant increase in QUICKI compared to DC group ($P < 0.05$). HETGCC treated group had also tendency toward higher QUICKI than DC group, although no significant differences were observed between these two groups (Table 1).

Serum Lipids

The effects of treatments on serum lipids were shown in Table 2. DC rats showed significantly higher level of total cholesterol, triglyceride, LDL-C and lower HDL-C concentration compared to NC group ($P < 0.05$). HETGCC and metformin did not

Table 1: Serum glucose, insulin levels, Hb A1C, HOMA index and QUICKI in normal control, diabetic control, metformin, and HETGCC groups during 42-day trial period

Groups	FBS (mg/dL)	Insulin ($\mu\text{g/L}$)	HbA1C (%)	HOMA	QUICKI
NC	101.15 \pm 4.59 ^a	0.62 \pm 54 ^a	3.04 \pm 0.38 ^a	4.05 \pm 3.43 ^a	0.32 \pm 0.02 ^b
DC	444.22 \pm 97.66 ^c	0.45 \pm 0.43 ^a	12.77 \pm 2.64 ^c	13.10 \pm 14.05 ^b	0.28 \pm 0.03 ^a
HETGCC	200.80 \pm 100.43 ^b	0.38 \pm 0.13 ^a	6.20 \pm 2.78 ^b	4.31 \pm 1.51 ^a	0.31 \pm 0.01 ^{ab}
Met	256.100 \pm 97.19 ^b	0.33 \pm 0.26 ^a	7.48 \pm 2.73 ^b	4.99 \pm 4.54 ^a	0.31 \pm 0.03 ^b

NC: Normal control, DC: Diabetic control, HETGCC: Hydroalcoholic extract of turmeric, ginger, and cinnamon combination, Met: Metformin, FBS: Fasting blood glucose, HbA1c: Glycated hemoglobin, HOMA index: Homeostatic Model Assessment for Insulin Resistance, QUICKI: Quantitative insulin sensitivity check index. Values are expressed as mean \pm SD. In each column, figures bearing different superscripts were significantly different (One way ANOVA and Duncan test, a, b and c: $P < 0.05$)

Table 2: Serum TG, TC, LDL-C, HDL-C in normal control, diabetic control, metformin, and HETGCC groups during 42-day trial period

Group	TG (mg/dL)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
NC	92.53±39.82 ^a	75.23±7.5 ^a	30.07±5.17 ^a	37.76±6.52 ^b
DC	170.77±41.38 ^b	140.33±12.14 ^c	90.22±6.61 ^d	25±8.81 ^a
HETGCC	135.30±53.79 ^{ab}	115±11.1 ^b	60.1±6.24 ^c	35.4±8.44 ^b
Met	140.40±77.66 ^{ab}	110.3±26 ^b	40.2±6.32 ^b	37±15.17 ^b

NC: Normal control, DC: Diabetic control, HETGCC: Hydroalcoholic extract of turmeric, ginger, and cinnamon combination, Met: Metformin, TG: Triglyceride, TC: Total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol. Values are expressed as mean±SD. In each column, figures bearing different superscripts are significantly different (One way ANOVA and Duncan test, a, b and c and d: P<0.05)

Table 3: Body weight, serum hsCRP, MDA, islets number, islets size in normal control, diabetic control, metformin, and HETGCC groups during 42-day trial period

Group	Weight (g)	hsCRP (ng/mL)	MDA (μM)	IL number	IL size (mm)
NC	317.15±13.88 ^c	5.86±1.3 ^a	2.21±0.58 ^a	26.84±11.89 ^c	0.63±0.28 ^b
DC	182.22±12.86 ^a	7.87±87 ^b	4.52±0.38 ^d	3.55±2 ^a	0.21±0.09 ^a
HETGCC	233.2±33.2 ^b	6.94±1.23 ^b	2.8±0.35 ^b	13.6±8.01 ^b	0.58±0.31 ^b
Met	198.4±38.38 ^a	7.45±1.05 ^b	3.54±0.68 ^c	10.1±12.56 ^{ab}	0.39±0.3 ^{ab}

NC: Normal control, DC: Diabetic control, HETGCC: Hydroalcoholic extract of turmeric, ginger, and cinnamon combination, Met: Metformin, MDA: Malondialdehyde, IL: Islets of Langerhans. Values are expressed as mean±SD. In each column, figures bearing different superscripts were significantly different (One way ANOVA and Duncan test, a, b and c and d: P<0.05)

alter triglyceride concentrations in treated diabetic rats compared to the DC group. Total cholesterol levels in metformin and HETGCC treated groups significantly decreased (P<0.05) (Table 2). However, no significant differences were observed between HETGCC treated rats compared to metformin treated group (Table 2).

LDL-C concentrations demonstrated a significant decline in all treated groups, while metformin treated group showed more reduction compared to the HETGCC group (P<0.05) (Table 2). HDL-C concentration of all treated diabetic rats illustrated a significant rise in comparison to the DC group (P<0.05), but there was no significant difference between metformin and HETGCC groups (Table 2).

Body Weight, Oxidative Stress and Inflammatory Markers

A significant decrease in body weight was seen in diabetic control rats compared to normal control (P<0.05) (Table 3). This weight reduction was significantly prevented by HETGCC in diabetic rats (P<0.05), while metformin did not reveal significant improvements on body weight (Table 3). Diabetic rats displayed a significant increase in level of hsCRP compared to the normal control (P<0.05), while no significant differences were noted among treated rats compared to DC group (Table 3). MDA significantly increased in DC group compared to normal control (P<0.05) (Table 3). Significant decreases in MDA level were visible in all treated diabetic rats with

more reduction in the HETGCC group compared to diabetic control rats (P<0.05) (Table 3).

Histopathology of Pancreas

The number and diameter of islets of Langerhans in the diabetic control significantly decreased compared to the normal control group (P<0.05). HETGCC group showed a significant increase in the number and diameter of islets of Langerhans compared to DC group (P<0.05), while metformin treated group demonstrated no changes (Table 3 and Figure 1).

Discussion

Diabetic rats treated with either HETGCC or metformin in this study showed a significant reduction in serum glucose, HbA_{1C} and HOMA index compared to DC group. Hypoglycemic effects of turmeric, ginger, cinnamon and metformin have been observed in other studies as well (3, 4, 13-19). The hypoglycaemic potency of turmeric is related to curcumin (6), which may decrease hepatic glucose production, increase the expression of Glut 4 gene (20) and AMP-activated protein kinase activity (6).

Turmeric also inhibits the activity of α-glucosidase (9). Phenolic components of ginger have shown hypoglycemic activity through the inhibition of α-glucosidase and α-amylase activity, increasing GLUT4 protein expression, transmission to cell membranes (21) and stimulating glucose uptake in

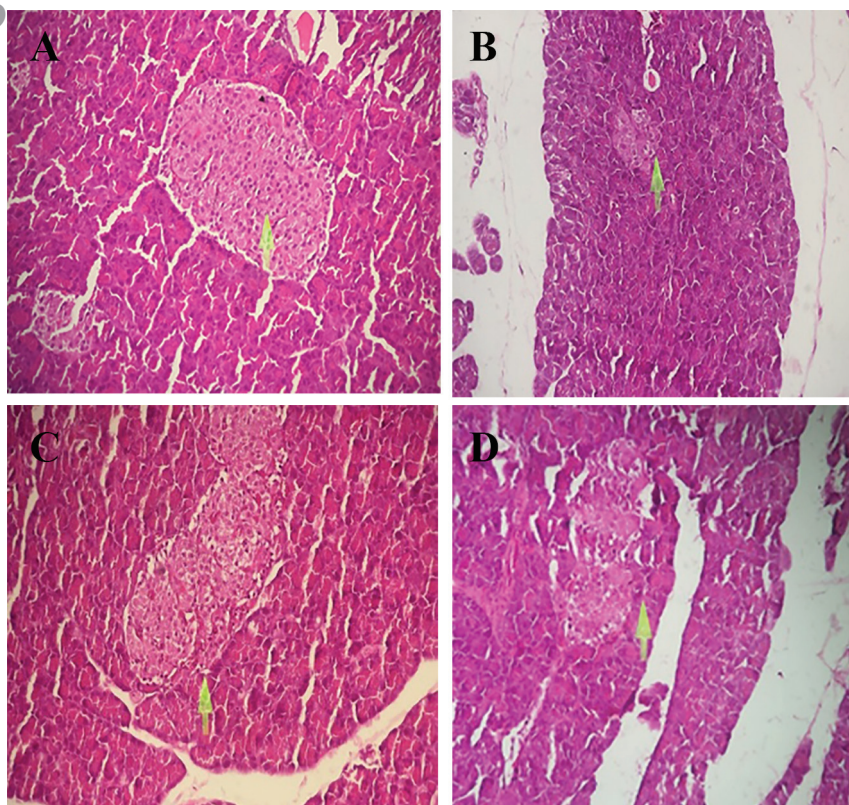


Figure 1: Microphotographs of pancreatic tissue. (A): normal control group, (B): streptozotocin-nicotinamid diabetic rats with no treatment, (C): HETGCC-treated group, and (D): metformin-treated group.

muscle and fat cells (9). Cinnamon reduces blood glucose and insulin resistance (9) by reducing the gene expression of enzymes related to glucose production, like glucose-6-phosphatase (10).

In the present study, HETGCC and metformin did not alter the insulin level in diabetic rats. Our findings agrees with Blevins et al.'s report and some human studies which reported no significant changes in serum insulin following administration of cinnamon, turmeric and metformin in diabetic patients (22-24). Although these results differ from Madkor et al.'s study (2010) (4) and other researchers that have shown increased serum insulin level of diabetic rats treated with ginger, turmeric and cinnamon (14).

A reduction in TC and LDL-C and an increase in HDL-C was seen in both metformin and HETGCC groups compared to DC rats, which all are in agreement with other studies as well (14, 17, 25). HETGCC and metformin decreased TG level, but this reduction was not significant. These findings are supported by two studies that showed no significant reduction in serum TG in diabetic patients treated with ginger and cinnamon (18, 22).

The hypolipidemic effect of metformin is related to activating 5-AMP-activated protein kinase, reducing lipogenesis and finally increasing fatty acid oxidation (26). Turmeric increases the activity of liver cholesterol 7-hydroxylase enzyme,

fecal excretion of cholesterol (27) curcumin in the turmeric also reduces fatty acid synthase activity (20) and mRNA levels of lipogenesis transcription factors (ChREBP and SREBP1-c) (28). Ginger also improves hyperlipidemia via a reduction in expression of fatty acid synthase, acetyl-CoA carboxylase 1, stearoyl-CoA desaturase 1 and an increase in lipoprotein lipase activity (29).

Vasanthi et al. suggested that the hypolipidemic effects of cinnamon on lipid indicators was possibly through activating transcription factors that regulate adipogenesis (PPAR α , γ) and inhibition of HMG-CoA reductase activity and cholesterol biosynthesis (8). The current study showed a significant reduction in body weight in diabetic rats compared to NC group. This reduction is partly associated with increased catabolic reactions during diabetes (dehydration, fat and muscle cells degeneration and frequent conversion of glycogen to glucose) (4, 30). HETGCC significantly improved body weight. It seems that these spices reduce protein and fat catabolism by improving glucose metabolism and reversing proteinuria (4, 20).

In consistent with previous studies, both HETGCC and metformin treated rats showed a significant reduction in MDA levels compared to DC group (13, 31-34). Metformin inhibits lipid oxidation through decreasing plasma glucose (35). Curcumin reduces lipid peroxidation by induction

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of glutathione S-transferase (10), while the protective effects of ginger and cinnamon against lipid peroxidation and reactive oxygen species formation are attributed to their gingerols and polyphenol contents, respectively (4, 8).

In agreement with other studies, HETGCC and metformin did not change hsCRP levels compared to DC group (32, 36, 37). Although anti-inflammatory activity of turmeric, ginger, cinnamon has been highlighted previously (13, 31, 33). The modulatory effects of these spices on inflammation is possibly through inhibition of NF- κ B and cytokines transcription, expression and signaling (10, 29, 38).

HETGCC treated rats showed a significant increase in the number and diameter of the islets of Langerhans. This observation agrees with Jothi et al. (2016) and Osman et al.'s report (2016), which reported the improvement of histopathological statue of islets of Langerhans in diabetic rats treated with zingeron and Cinnamon (39, 40). These spices may increase pancreatic β -cells viability and protect them via reactivating the antioxidant defence system (4, 21).

Conclusion

In summary, the present study showed that HETGCC may reduce the risk of diabetes and improve complications associated with diabetes such as hyperglycemia, dyslipidemia, oxidative stress, inflammation, histopathological statue of islets of Langerhans and weight loss in T2D patients.

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Conflict of Interest

None declared.

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