

Modulatory effects of garlic, ginger, turmeric and their mixture on hyperglycaemia, dyslipidaemia and oxidative stress in streptozotocin–nicotinamide diabetic rats

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Abstract

Spices which show hypoglycaemic, hypolipidaemic and antioxidant activities may have a role in the treatment of diabetes and its complications. The present study aimed to compare the modulatory effects of garlic, ginger, turmeric and their mixture on the metabolic syndrome and oxidative stress in streptozotocin (STZ)–nicotinamide diabetic rats. Diabetes was induced in overnight fasted rats by a single intraperitoneal injection of STZ (65 mg/kg body weight) and nicotinamide (110 mg/kg body weight, 15 min before STZ injection). Diabetic rats orally received either distilled water (as vehicle) or 200 mg/kg body weight of garlic bulb, ginger rhizome or turmeric rhizome powder suspension separately or mixed together (GGT mixture) for twenty-eight consecutive days. The results showed that these spices and their mixture significantly alleviated (80–97%, $P < 0.05$ – 0.001) signs of the metabolic syndrome (hyperglycaemia and dyslipidaemia), the elevation in atherogenic indices and cellular toxicity in STZ–nicotinamide diabetic rats by increasing the production of insulin (26–37%), enhancing the antioxidant defence system (31–52%, especially GSH) and decreasing lipid peroxidation (60–97%). The greatest modulation was seen in diabetic rats that received garlic and the GGT mixture (10–23% more than that in the ginger and turmeric groups). In conclusion, garlic or the mix including garlic appears to have an impact on each of the measures more effectively than ginger and turmeric and may have a role in alleviating the risks of the metabolic syndrome and cardiovascular complications.

Key words: Albino rats: Antioxidant activity: Complementary/alternative medicine: Metabolic syndrome: Streptozotocin–nicotinamide diabetes

The number of individuals suffering from diabetes worldwide is predicted to reach 325 million by the year 2025 due to sedentary lifestyle, consumption of energy-rich diet, obesity, longer life span, etc.⁽¹⁾. There are two forms of diabetes mellitus: type 1 and type 2. In type 1 or insulin-dependent diabetes, pancreatic β -cells are progressively destroyed and secrete little or no insulin. Type 2 or non-insulin-dependent diabetes is a heterogeneous disorder of insulin resistance and pancreatic β -cell dysfunction⁽¹⁾. Cardiovascular complications due to the metabolic syndrome, a clustering of pathological conditions including obesity, dyslipidaemia, hepatic steatosis and insulin resistance, are a major cause of morbidity and mortality in diabetic patients⁽²⁾. Dyslipidaemia (lipid abnormalities) resulting from uncontrolled hyperglycaemia and insulin resistance in diabetic patients is a major risk factor for coronary artery disease, stroke and peripheral vascular disease⁽³⁾.

Streptozotocin (STZ) has been widely used for inducing type 1 diabetes in a variety of animals by causing severe degeneration of pancreatic β -cells⁽⁴⁾. Recently, a new rat model of type 2 diabetes that shares a number of features with human type 2 diabetes mellitus has been described⁽⁵⁾. In this model, the diabetic syndrome is experimentally induced in adult rats by the administration of a low dose of STZ after the pancreatic β -cells were partially protected from STZ-induced necrosis by a suitable dose of nicotinamide⁽⁶⁾. Therefore, this model is characterised by only 40% reduction in β -cell mass, which results in moderate and stable hyperglycaemia, glucose intolerance, altered but significant glucose-stimulated insulin secretion and *in vivo* as well as *in vitro* responsiveness to sulfonylureas⁽⁶⁾. This model may provide a particularly advantageous tool for pharmacological investigations of new insulinotropic agents⁽⁶⁾. Recently, attention has been focused on the

Abbreviations: ALAT, alanine aminotransferase; GGT mixture, mixture of garlic, ginger and turmeric; STZ, streptozotocin; TBARS, thiobarbituric acid-reactive substances.

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relationship between production of free radicals, especially reactive oxygen species, and the pathogenesis as well as progression of diabetes mellitus. Mechanisms that contribute to the formation of free radicals in diabetes mellitus may include metabolic stress resulting from changes in energy metabolism, inflammatory mediators and impaired antioxidant defence mechanisms⁽⁷⁾. STZ induces oxidative stress and depletion of antioxidant systems in both blood and tissues, causing membrane lipid peroxidation and hence cellular injury^(5,7). Therefore, the STZ-diabetic rat model may be suitable for investigating the antioxidant properties of hypoglycaemic agents^(5,7). GSH is the first line of defence against lipid peroxidation⁽⁸⁾. It is an essential electron donor to glutathione peroxidases in reducing hydroperoxides and serves as a nucleophilic co-substrate to glutathione *S*-transferases in detoxifying xenobiotics⁽⁸⁾.

Many spices show hypoglycaemic and antioxidant activities and are less toxic than Western medicines^(9–11). Garlic (*Allium sativum*, family Alliaceae), ginger (*Zingiber officinale*, family Zingiberaceae) and turmeric (*Curcuma longa*, family Zingiberaceae) have been widely used as dietary spices and for the treatment of various ailments in folk medicine since ancient times^(9–11). Asian people typically consume 2–4 g/d of these spices in culinary use. Garlic bulb (rich in alliin, a precursor of allicin, 1–2.5%), turmeric rhizome (rich in phenolic curcuminoids, 3–5%) and ginger rhizome (rich in pungent phenolic compounds, gingerols and shogaols, 1–3%) in the form of dried powders or their extracts are important ingredients of many traditional and alternative medicines worldwide^(12–14). The present study compared the modulatory effects of pure dried powder of garlic bulb as well as ginger and turmeric rhizomes separately and mixed together (for the first time to our knowledge) on hyperglycaemia, dyslipidaemia and impaired antioxidant defence system (especially GSH) in STZ–nicotinamide diabetic rats. Moreover, the present study examined any deleterious effects caused by feeding healthy rats these spices. Because these plants are used as dietary spices and supplements, their antidiabetic effects were investigated in the present study via oral administration.

Materials and methods

Chemicals

STZ ($C_8H_{15}N_3O_7$; molecular weight 265.22 Da) and nicotinamide ($C_6H_6N_2O$; molecular weight 122.12 Da) were purchased from Sigma-Aldrich (St Louis, MO, USA). Pure (100%) dried powder of garlic bulb as well as ginger and turmeric rhizomes (AL-AMEER Brand) was authenticated and purchased from a herbal-specialised company (Kazerooni Brothers Establishment Company, Manama, Bahrain).

Animals

Adult male Wistar albino rats (*Rattus norvegicus*), weighing about 120–130 g, were obtained from the College of Veterinary Medicine and Animal Resources, King Faisal University, Al-Hufuf, KSA. Animals were housed in suitable cages and acclimatised to laboratory conditions for a period of 1 week before the commencement of the experiments. Rats were fed standard rodent food pellets (ARASCO, Riyadh, KSA) and distilled water. The standard rodent food pellets contain cereals, wheat bran, soya, molasses, alfalfa, minerals and vitamins. The amount of ash and crude proteins, fibres and fats in the food pellets are 80, 130, 100 and 20 g/kg, respectively. All animals were humanely treated in accordance with the WHO guidelines for animal care, and the study design was approved by the King Faisal University Research Ethics Committee.

Induction of diabetes

Diabetes was induced in overnight fasted rats by STZ (a single intraperitoneal injection of 65 mg/kg body weight) and nicotinamide (a single intraperitoneal injection of 110 mg/kg body weight, 15 min before STZ injection) as described previously⁽⁵⁾. STZ and nicotinamide were dissolved in citrate buffer (pH 4.5) and physiological saline, respectively. Rats with blood glucose level more than 2000 mg/l (72 h after STZ injection) were used in the present study as diabetic rats.

Experimental design and treatment schedule

Animals were randomly divided into ten groups of six animals each: five healthy (non-diabetic) groups and five STZ–nicotinamide diabetic groups. Non-diabetic rats were intraperitoneally injected with saline and orally received (by gavage) either distilled water (healthy control group) or 200 mg/kg body weight of garlic bulb, ginger rhizome or turmeric rhizome powder suspension separately or mixed together (GGT mixture) for twenty-eight consecutive days. STZ–nicotinamide diabetic rats orally received either distilled water (diabetic control group) or 200 mg/kg body weight of garlic bulb, ginger rhizome or turmeric rhizome powder suspension separately or mixed together (GGT mixture) for twenty-eight consecutive days.

Blood and tissue sampling

Animals were fasted overnight and subjected to light diethyl ether anaesthesia before killing on day 29. Blood was collected into clean and dry test-tubes without EDTA to separate serum, which was divided into aliquots and preserved at $-40^{\circ}C$ until used for biochemical analysis. The liver was quickly perfused *in situ* (via the hepatic portal vein) with a PBS solution to remove erythrocytes

and clots, and then homogenised in cold PBS solution containing 1 mM-EDTA (pH 7.4) after the gall bladder was dissected away. The homogenate was collected, and its protein content was assayed by the method of Lowry *et al.*⁽¹⁵⁾. Thereafter, it was divided into aliquots and stored at -40°C until used for the determination of tissue thiobarbituric acid-reactive substances (TBARS, for monitoring lipid peroxidation) and GSH.

Measurements

Food intake (on a per-group basis) was measured weekly. Body-weight change was assessed. Serum glucose concentration was estimated using glucose oxidase and peroxidase⁽¹⁶⁾. Quantitative measurement of serum insulin concentration was performed using an insulin (rat) EIA kit (Alpco Diagnostics, Salem, NH, USA) according to the manufacturer's recommendations. Serum total lipid concentration was chemically determined by the phosphovanillin method⁽¹⁷⁾. Serum TAG⁽¹⁸⁾, total cholesterol⁽¹⁹⁾ and HDL-cholesterol⁽²⁰⁾ concentrations were colorimetrically determined using peroxidase-coupled methods. Serum LDL-cholesterol concentration was calculated according to the equation of Friedewald *et al.*⁽²¹⁾:

$$\text{LDL-cholesterol} = \text{total cholesterol} - (\text{TAG}/5) - (\text{HDL-cholesterol}).$$

Atherogenic indices were calculated as follows:

$$\text{Atherogenic index (1)} = \frac{\text{total cholesterol}}{\text{HDL-cholesterol ratio}},$$

$$\text{Atherogenic index (2)} = \frac{\text{LDL-cholesterol}}{\text{HDL-cholesterol ratio}}.$$

Serum alanine aminotransferase (ALAT) and aspartate aminotransferase activities were colorimetrically measured⁽²²⁾. Serum alkaline phosphatase activity was estimated from the rate of conversion of *p*-nitrophenylphosphate to *p*-nitrophenol⁽²³⁾. Serum total antioxidants and liver TBARS concentrations were determined by the methods of Miller *et al.*⁽²⁴⁾ and Ohkawa *et al.*⁽²⁵⁾, respectively. Liver GSH concentration was determined from the reaction of the sulfhydryl group with Ellman's reagent to give 5-thio-2-nitrobenzoic acid⁽²⁶⁾. The percentage of difference of any parameter = $((T - C)/C) \times 100$, where *T* is the mean value of the parameter in the treated group and *C* is the mean value of the parameter in the healthy control group.

Statistics

Data are presented as means with their standard errors. Statistical analysis was performed with one-way ANOVA, and the differences among groups were determined by Bonferroni's multiple comparison test⁽²⁷⁾ using GraphPad Prism version 4.03 for Windows (GraphPad Software, Inc., San Diego, CA, USA). *P* values of <0.05 , <0.01 and <0.001 were considered statistically significant, highly significant and very highly significant, respectively.

Results

Effects of garlic, ginger, turmeric and their mixture on body-weight gain and food intake in healthy and diabetic rats

The present study showed that neither ginger nor turmeric significantly affected body-weight gain in non-diabetic rats ($P > 0.05$), but both garlic and the GGT mixture significantly decreased weight gain by 83% ($P < 0.001$) and 43% ($P < 0.01$), respectively (Fig. 1(a)). Diabetic rats that received vehicle showed a significant decrease in

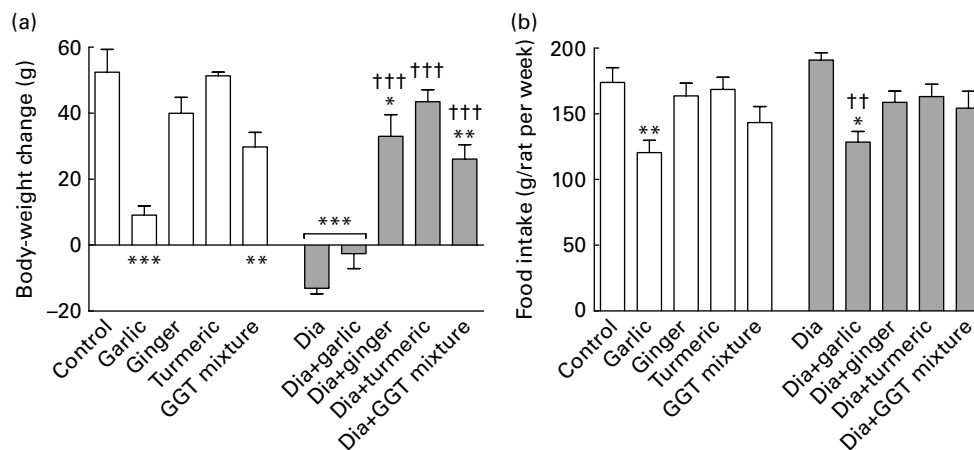


Fig. 1. Body-weight change (a) and food intake (b) in control (□) and diabetic (■) rats (Dia) given vehicle or vehicle plus garlic, ginger, turmeric or their mixture for 28 d. GGT mixture, mixture of garlic, ginger and turmeric. Values are means, with their standard errors represented by vertical bars. Mean values were significantly different from that of the control group: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Mean values were significantly different from that of the diabetic group that received vehicle only: †† $P < 0.01$, ††† $P < 0.001$.

body-weight gain (125% less, $P < 0.001$, $t = 10.42$, difference between means 65.53, 95% CI 46.46, 84.60, compared with healthy rats that received vehicle). This loss was completely prevented by turmeric ($P > 0.05$ and $P < 0.001$ compared with healthy and diabetic rats that received vehicle, respectively, Fig. 1(a)). On the other hand, food intake was significantly decreased by garlic in healthy and diabetic rats (26–31% less, $P < 0.05$ – 0.01 , Fig. 1(b)).

Effects of garlic, ginger, turmeric and their mixture on serum glucose and insulin levels in healthy and diabetic rats

Garlic, ginger, turmeric or the GGT mixture did not significantly alter ($P > 0.05$) the serum glucose (Fig. 2(a)) and insulin (Fig. 2(b)) levels in healthy rats. On the other hand, diabetic rats that received vehicle showed hyperglycaemia (203% more, $P < 0.001$, $t = 17.55$, difference between means -1672 , 95% CI -1961 , -1383) and hypoinsulinaemia (35% less, $P < 0.01$, $t = 4.094$, difference between means 0.339, 95% CI 0.088, 0.589). These effects were completely prevented by garlic, turmeric or the GGT mixture ($P > 0.05$; Fig. 2). Although ginger prevented hypoinsulinaemia in diabetic rats (Fig. 2(b)), its modulation on hyperglycaemia was partial, but significant ($P < 0.05$ and $P < 0.001$ compared with healthy and diabetic rats that received vehicle, respectively, Fig. 2(a)).

Effects of garlic, ginger, turmeric and their mixture on serum lipid profile and atherogenic indices in healthy and diabetic rats

Serum lipid profile (Table 1) and atherogenic indices (Fig. 3) did not significantly differ in healthy rats treated with garlic, ginger, turmeric or the GGT mixture

($P > 0.05$), except that the total lipids and total cholesterol significantly decreased by 37–47% ($P < 0.05$ – 0.01) in those treated with the GGT mixture, compared with healthy rats that received vehicle. On the other hand, diabetic rats that received vehicle showed a significant decrease in the HDL-cholesterol level (42% less, $P < 0.05$, $t = 3.061$, difference between means 10.14, 95% CI 0.10, 20.18) and a significant increase ($P < 0.05$ – 0.001) in total lipids, TAG, total cholesterol and LDL-cholesterol levels (31–333% more; Table 1) as well as atherogenic indices (286–766% more; Fig. 3) compared with healthy rats that received vehicle. All of these changes in serum lipids and atherogenic indices of diabetic rats were completely prevented by garlic, ginger, turmeric or the GGT mixture (Table 1 and Fig. 3), except that the modulation on hypertriacylglycerolaemia was partial, but significant, in diabetic rats that received ginger ($P < 0.05$ and $P < 0.001$ compared with healthy and diabetic rats that received vehicle, respectively, Table 1).

Effects of garlic, ginger, turmeric and their mixture on cellular toxicity markers and antioxidants in healthy and diabetic rats

Garlic, ginger, turmeric or the GGT mixture did not significantly change ($P > 0.05$) the cellular toxicity markers (serum ALAT, aspartate aminotransferase and alkaline phosphatase activities as well as liver TBARS level) in addition to serum total antioxidants and liver GSH levels in healthy rats (Table 2). On the other hand, diabetic rats that received vehicle showed a significant increase in cellular toxicity markers (29–207% more, $P < 0.05$ – 0.001) and a significant decrease in serum total antioxidant level (30% less, $P < 0.01$, $t = 3.855$, difference between means 0.095, 95% CI 0.02, 0.17) as well as liver GSH level (49% less, $P < 0.05$, $t = 3.433$, difference between means 1.646, 95% CI 0.19, 3.10) compared with healthy rats that received

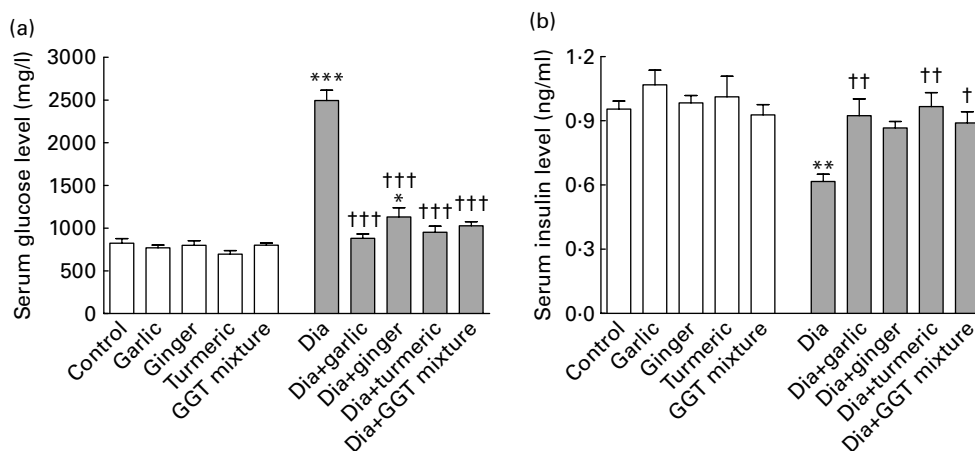


Fig. 2. Levels of serum glucose (a) and insulin (b) in control (□) and diabetic (■) rats (Dia) given vehicle or vehicle plus garlic, ginger, turmeric or their mixture for 28 d. GGT mixture, mixture of garlic, ginger and turmeric. Values are means, with their standard errors represented by vertical bars. Mean values were significantly different from that of the control group: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Mean values were significantly different from that of the diabetic group that received vehicle only: † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$.

Table 1. Levels of lipids in control and diabetic rats (Dia) given vehicle or vehicle plus garlic, ginger, turmeric or their mixture for 28 d (Mean values with their standard errors)

	Total lipids (mg/l)		TAG (mg/l)		Total cholesterol (mg/l)		HDL-cholesterol (mg/l)		LDL-cholesterol (mg/l)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Control	3304	291	716	84	524	36	246	24	135	30
Garlic	2694	101	506	34	330	24	181	19	47	6
Ginger	2703	184	561	48	392	24	206	19	75	23
Turmeric	2642	186	495	45	417	47	225	23	94	26
GGT mixture	2095**	159	440	48	276*	32	167	22	21	4
Dia	4327*	242	1719***	103	1072***	80	144*	27	584***	65
Dia + garlic	2958†††	251	890†††	99	527†††	49	163	16	187†††	29
Dia + ginger	3336†	219	1067*†††	89	617†††	68	179	21	225†††	43
Dia + turmeric	3076††	263	817†††	76	603†††	66	205	25	234†††	46
Dia + GGT mixture	2736†††	90	786†††	127	546†††	85	204	32	184†††	58

GGT mixture, mixture of garlic, ginger and turmeric.

Mean values were significantly different from that of the control group: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Mean values were significantly different from that of the diabetic group that received vehicle only: † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$.

vehicle (Table 2). All of these harmful changes were prevented by garlic and the GGT mixture ($P > 0.05$ compared with healthy rats that received vehicle). Also, turmeric completely prevented all of the aforementioned changes in diabetic rats, except that the increase in serum ALAT activity was partially modulated ($P < 0.01$, $t = 4.08$, difference between means -17.26 , 95% CI -30.08 , -4.43 , compared with healthy rats that received vehicle). In addition, the increase in serum alkaline phosphatase activity and the decrease in serum total antioxidants and liver GSH levels were completely modulated ($P > 0.05$), but the increase in serum ALAT and aspartate aminotransferase activities as well as liver TBARS level was partially modulated ($P < 0.05-0.01$), in diabetic rats that received ginger compared with healthy rats that received vehicle (Table 2).

Discussion

The present study showed that garlic, ginger, turmeric and their mixture significantly alleviated (80–97%,

$P < 0.05-0.001$) most signs of the metabolic syndrome including hyperglycaemia and dyslipidaemia, the elevation in atherogenic indices, and cellular toxicity in STZ–nicotinamide diabetic rats by increasing the production of insulin (26–37%), reactivating the antioxidant defence system (31–52%, especially GSH) and decreasing lipid peroxidation (60–97%). The greatest effect was observed in diabetic rats that received the GGT mixture and garlic (10–23% more than that in ginger and turmeric). The hypolipidaemic effect and the marked decrease in atherogenic indices shown in the present study in diabetic rats that received the aforementioned spices (Table 1 and Fig. 3) suggest that they might lower the risk of atherosclerosis. The decrease in serum ALAT, aspartate aminotransferase and alkaline phosphatase activities as well as liver TBARS level and the increase in the liver GSH level induced in diabetic rats by garlic, ginger, turmeric and the GGT mixture (Table 2) suggest that the chemical components of these spices prevented hepatocellular damage by stabilising the integrity of the cell

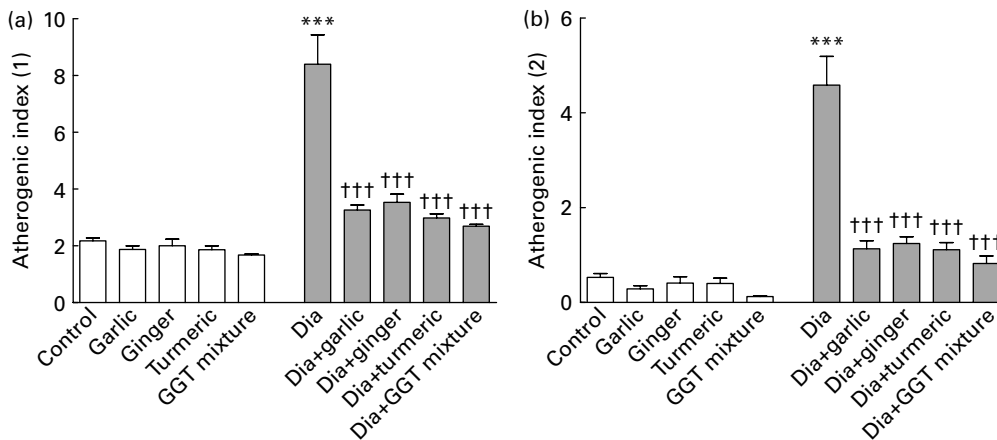


Fig. 3. Atherogenic indices in control (□) and diabetic (■) rats (Dia) given vehicle or vehicle plus garlic, ginger, turmeric or their mixture for 28 d. Atherogenic index (1), total cholesterol:HDL-cholesterol ratio; atherogenic index (2), LDL-cholesterol:HDL-cholesterol ratio; GGT mixture, mixture of garlic, ginger and turmeric. Values are means, with their standard errors represented by vertical bars. Mean values were significantly different from that of the control group: *** $P < 0.001$. Mean values were significantly different from that of the diabetic group that received vehicle only: ††† $P < 0.001$.

Table 2. Levels of cellular toxicity markers and antioxidants in control and diabetic rats (Dia) given vehicle or vehicle plus garlic, ginger, turmeric or their mixture for 28 d

(Mean values with their standard errors)

	Serum								Liver			
	ALAT activity (IU/l)		ASAT activity (IU/l)		ALP activity (IU/l)		Total antioxidant level (mmol/ml)		TBARS level ($\mu\text{M}/\text{mg}$ protein)		GSH level ($\mu\text{M}/\text{mg}$ protein)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Control	43.0	1.2	88.9	1.8	54.5	2.1	0.318	0.024	0.273	0.032	3.38	0.23
Garlic	40.5	1.3	81.5	4.4	49.2	2.2	0.367	0.030	0.244	0.033	3.22	0.31
Ginger	46.4	1.2	86.3	2.4	50.4	3.4	0.387	0.006	0.257	0.014	3.14	0.32
Turmeric	40.2	1.2	86.2	2.6	48.6	2.9	0.377	0.021	0.254	0.035	2.98	0.42
GGT mixture	37.1	1.1	76.1	2.0	46.7	3.0	0.390	0.008	0.277	0.038	3.29	0.49
Dia	77.3***	2.0	151.7***	6.8	70.2*	2.1	0.223**	0.012	0.837***	0.051	1.74*	0.12
Dia + garlic	51.3†††	1.4	96.4†††	3.8	50.0††	2.5	0.352†††	0.010	0.291†††	0.031	2.48	0.40
Dia + ginger	60.5***††	6.4	123.4***†	12.4	56.6	5.2	0.341†††	0.022	0.500***†††	0.076	3.33†	0.23
Dia + turmeric	60.3***††	5.8	103.5***††	6.9	57.4	6.2	0.382†††	0.009	0.333†††	0.028	2.86	0.46
Dia + GGT mixture	47.5†††	1.3	86.5†††	5.3	48.9††	3.8	0.374†††	0.013	0.458†††	0.090	3.62††	0.22

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; ALP, alkaline phosphatase; TBARS, thiobarbituric acid-reactive substances; GGT mixture, mixture of garlic, ginger and turmeric.

Mean values were significantly different from that of the control group: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Mean values were significantly different from that of the diabetic group that received vehicle only: † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$.

membrane, keeping the membrane intact and the enzymes enclosed, through scavenging free radicals. The significant increase in body-weight gain ($P < 0.001$), despite similar food consumption ($P > 0.05$), shown in diabetic rats that received ginger, turmeric or the GGT mixture compared with diabetic control rats that received vehicle suggested that these spices may have a positive anabolic effect through improving glucose metabolism. This effect may decrease the degeneration of the adipocytes and muscle tissues in diabetic patients, which occur to compensate for the energy lost from the body due to frequent urination and overconversion of glycogen to glucose.

Several studies have reported that garlic has hypoglycaemic and antioxidant effects^(7,28). Others have reported that consumption of a diet containing 5% garlic powder significantly decreased serum glucose and total cholesterol in type 2 diabetic db/db mice⁽²⁹⁾. Commercially available garlic preparations in the form of oil, powder and pills are widely used for certain therapeutic purposes to lower blood sugar and to improve lipid profile. The hypoglycaemic potency of garlic has been attributed to allicin-derived organosulphur compounds, which protect insulin from -SH inactivation by reacting with endogenous thiol-containing molecules such as cysteine, glutathione and serum albumin⁽⁹⁾. Garlic significantly decreased the blood glucose level in glucose-loaded diabetic rats, which may be due to the inhibition of glucose absorption from the intestine and/or the enhancement of glucose utilisation by restoring the impaired insulin response through increasing the pancreatic secretion of insulin from existing β -cells^(9,29). Moreover, the antidiabetic effect of garlic was more effective than that of glibenclamide, a sulphonylurea drug that is used clinically to lower serum glucose by stimulating β -cells to release insulin and by promoting

peripheral tissue uptake as well as utilisation of glucose⁽⁹⁾. The hypolipidaemic effect (TAG- and cholesterol-lowering properties) of garlic was probably due to the inhibition of enzymes involved in fatty acid and cholesterol synthesis⁽⁹⁾. On the other hand, lipid peroxidation (TBARS and malondialdehyde levels) was significantly reduced in diabetic rats that received garlic. This antioxidant activity of garlic has also been attributed to the presence of organosulphur compounds that increase glutathione content and the activity of antioxidant enzymes, such as superoxide dismutase as well as glutathione *S*-transferases^(7,28).

The hypoglycaemic and hypolipidaemic effects of ginger and its extracts has been reported previously in diabetic rats and mice^(10,30–31). Additionally, ginger was effective in reversing the diabetic proteinuria and body-weight loss observed in diabetic rats⁽¹⁰⁾. Ginger ethanolic extract has shown insulinotropic action similar to chlorpropamide, a sulphonylurea drug, and enhanced insulin sensitivity at the cellular level⁽³¹⁾. Also, ethanolic ginger extract reduced plasma cholesterol and inhibited LDL oxidation in atherosclerotic apoE-deficient mice⁽³²⁾. Moreover, addition of ginger (1%) to a normal diet prevented the formation of free radicals and maintained the integrity of rat erythrocytes⁽³³⁾. The antioxidant potency of ginger has been attributed to gingerols that prevent reactive oxygen species production⁽¹⁴⁾. Aldose reductase inhibitors, which reduce sorbitol formation as well as its accumulation in human tissues such as erythrocytes and protect cells from osmotic damage, are now considered to have remarkable potential for the treatment of diabetes mellitus and its complications. At least two active components, 2-(4-hydroxy-3-methoxyphenyl) ethanol and 2-(4-hydroxy-3-methoxyphenyl) ethanoic acid, of ginger have shown aldose reductase inhibitor properties⁽¹⁴⁾. Also, ginger

inhibited serotonin-induced hyperglycaemia and hypoinulinaemia by blocking its receptors⁽¹⁰⁾.

Curcumin, one of the major phenolic curcuminoids of turmeric, has been shown to reduce hyperglycaemia and hyperlipidaemia in type 2 diabetic KK-Ay mice as well as STZ-diabetic and alloxan-diabetic rat models^(5,12). Also, it prevents the oxidation of LDL⁽¹²⁾. Tetrahydrocurcumin (one of the major metabolites of curcumin) exhibited antidiabetic and antioxidant properties in STZ–nicotinamide diabetic rats⁽⁵⁾. Curcumin and tetrahydrocurcumin protected pancreatic β -cells from reactive oxygen species generated in diabetes by scavenging free radicals and reactivating the antioxidant defence system⁽³⁴⁾. They significantly increased the tissue GSH level in STZ–nicotinamide diabetic rats, which in turn activated the GSH-dependent antioxidant enzymes (such as glutathione peroxidases and glutathione *S*-transferases) and detoxified the highly reactive intermediates of STZ⁽⁵⁾. However, the antioxidant activity of tetrahydrocurcumin is more potent than that of curcumin⁽³⁵⁾. Feeding STZ-diabetic rats with turmeric decreased the TBARS level and increased the activities of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidases and glutathione *S*-transferases in erythrocytes⁽¹¹⁾. The present results are consistent with the aforementioned reports, which may explain the beneficial effects of garlic, ginger and turmeric as well as their mixture shown in the present study.

According to the data obtained in the present study, the modulatory effects of the GGT mixture were, in general, equal to that of garlic and more than that of turmeric and ginger. On the other hand, the modulatory effect of garlic on severe body-weight loss shown in diabetic rats was weak in the present study (Fig. 1(a)), which may be, in part, due to an effect of garlic on appetite, since it significantly decreased food intake in non-diabetic rats ($P < 0.01$; Fig. 1(b)). Addition of ginger and turmeric to garlic alleviated the decrease in food intake and body-weight loss induced by garlic in non-diabetic rats and ameliorated its modulatory effect on the severe body-weight loss of diabetic rats. No other harmful effects were detected for garlic, ginger, turmeric and the GGT mixture on any parameters measured in the present study. Moreover, the GGT mixture decreased significantly serum total lipids and total cholesterol levels in healthy rats, which may be beneficial as a prophylaxis against hypercholesterolaemia. In conclusion, garlic or the mix including garlic appears to have an impact on each of the measures made here and, overall, is more effective than ginger or turmeric in alleviating the risks of the metabolic syndrome and cardiovascular complications in STZ–nicotinamide diabetic rats.

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