Effects of curcumin and its nanomicelle form on body weight, insulin resistance, adiponectin, and blood parameters of streptozotocin-induced diabetic rats

Hamed Dadgar
Department of Animal Science, Faculty of Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran
Hassan Kermanshahi (kermansh@um.ac.ir)
Department of Animal Science, Faculty of Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran
Mahmoud Reza Jaafari
Nanotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
Ali Javadmanesh
Department of Animal Science, Faculty of Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran

Research Article

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Abstract

Curcumin can be used for diabetes treatment. However, it rapidly degrades and has low absorption in gastrointestinal system. Its nanomicelle form might improve its efficiency. Therefore, they both assessed in streptozotocin-induced diabetic rats. Fifty male wistar rats were induced diabetes and divided into 5 groups and treated with 1) no dietary supplement, 2 and 3) 40 and 80 mg/kg curcumin, 4 and 5) 40 and 80 mg/kg nanomicelle curcumin. A group of 10 untreated rats was considered as healthy control. Serum concentrations of AST, ALT, glucose, insulin, insulin resistance, triglycerides, cholesterol, HDL-C, LDL-C and adiponectin were assessed. Body weight and weights of liver, heart and pancreas were also evaluated. Induction of diabetes increased the serum concentrations of AST, ALT, glucose, triglycerides, cholesterol, LDL-C and insulin resistance and decreased the serum concentrations of insulin, adiponectin, and HDL-C, and also body weight and weights of heart and pancreas ($P<0.05$). Nanomicelle form of curcumin alleviated the negative effects of diabetic rats for glucose, lipid profile, and liver enzymes ($P<0.05$). In conclusion, nanomicelle form of curcumin showed better efficiency for alleviating the adverse effects of diabetes. It can be suggested that nanomicelle form of curcumin at specific doses can be used for diabetes treatment.

Introduction

Diabetes is a major challenge for most people in all over the world and type 2 diabetes mellitus is known by insulin resistance, faulted glucose, lipid metabolism and deficiency of insulin production[1]. It is also characterized by an increased in fasting and postprandial glucose[2]. Insulin resistance is the first sign for type 2 diabetes mellitus in most of the individuals. Beta cells increase insulin secretion for maintaining normal glucose levels and the response is observed as hyperinsulinemia. Patients that hyperinsulinemia cannot maintain normoglycemia, fasting glucose and glucose tolerance are faulted[3]. Defaulted fasting glucose progresses type 2 diabetes mellitus[4]. Several factors such as glucotoxicity, lipotoxicity, inflammation, and accumulation of amyloid fault β-cell function[2]. Deficiencies in lipid and glucose metabolism promote the pathogenesis of type 2 diabetes mellitus[4]. Adiponectin is an insulin-sensitizing hormone with anti-apoptotic and anti-inflammatory effects that is produced in adipose tissues and its levels are decreased in patients with type 2 diabetes[5].The serum concentrations of aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are increased in diabetes[6]. Increased levels of the enzymes shows hepatic injury in the hepatocellular cytosol and mitochondria[7]. A significant correlation between increased ALT and AST with insulin resistance, and type 2 diabetes mellitus is already reported[8].

The management of diabetes is a challenge for the medical system. Different interventions are used for the treatment of diabetes, such as anti-diabetic drugs, and lifestyle intervention[9] (healthy nutrition and daily physical activity). Using synthetic compounds cause severe side effects such as hypoglycemic coma and hepatorenal disorders[9]. A high efficacy of medical plant supplements for the prevention and management of type 2 diabetes mellitus are recommended[10, 11, 12, 13]. Curcumin is an active molecule

found in the rhizome of turmeric. It has antioxidant, anti-inflammatory, anti-microbial, immunomodulatory, hypoglycaemic and anti-rheumatic effects[14, 15]. Curcumin controls glycaemia and lipidaemia in the body system[16] and can be used as an appropriate compound for the treatment of diabetes. Using natural isolates from the plants is an appropriate strategy for the treatment of different disorders, but their uses are faced with major limitations due to their formulation, application and degradation during processing[17, 18]. Using nanomicelle form of curcumin may prevents its degradation during processing and digestion and helps to increase its efficiency. Therefore, this study was conducted to investigate the effects of curcumin and its nanomicelle form on body weight, insulin resistance, adiponectin secretion, and blood biochemical parameters of streptozotocin-induced diabetic rats.

Materials And Methods

Animals. All the methods were performed in accordance with the Ferdowsi University of Mashhad, Iran regulations and guidelines and approved by its Ethics Committee (No: 3.44995). The study was also carried out in compliance with the ARRIVE guidelines. A total number of sixty male wistar rats with mean weight of 180-200 g and 60 days of age were purchased from the Pasture Institute (Tehran-Iran). The animals were kept at standard individual cages for 49 days (7 days adaptation and 42 days of study) under 12h L: 12h D lighting cycle at 20-25°C. The animals had free access to standard pellet feed and fresh water. Feed was prepared from Javaneh Khorasan Company (Mashhad-Iran).

Preparation of curcumin and nanomicelle curcumin. Pure turmeric rhizome extract as powder was purchased from Sami Lab Limited (Bengaluru, Karnataka, India). The powder contained 79.4% curcumin, 17.6% demethoxycurcumin, and 3.0% bisdemethoxycurcumin. Nanomicelle form of this extract as nanomicelle curcumin was purchased from Exir Nano Sina Co., Tehran, Iran, IRC: 1228225765). The measured size of nanomicelle curcumin was about 10 nanometer (nm) as described by Hatamipour et al.[19].

Induction of diabetes. At the beginning of the study, diabetes was induced in 50 male wistar rats by one dose of intraperitoneal administration of streptozotocin (Sigma, St. Louis, MO, USA) (60 mg/kg body weight) in 0.05 M cold citrate buffer (pH 4.5) to the overnight fasted rats. To stabilize the streptozotocin in an aqueous media, cold citrate buffer was used. A group of 10 rats were not treated with streptozotocin and considered as healthy control animals. An Accu-check blood glucose meter (Roche Diagnostics) was used for monitoring fasting blood glucose. The rats with fasting blood glucose higher than 250 mg/dl for five consecutive days after the administration of streptozotocin were considered as diabetic rats.

Following induction of diabetes, the animals were divided into five groups and administrated with no dietary supplement of curcumin or nanomicelle curcumin (Diab-Con), 40 mg/kg curcumin into the pelleted feed (Diab-Cur40), 80 mg/kg curcumin into the pelleted feed (Diab-Cur80), 40 mg/kg nanomicelle curcumin into the pelleted feed (Diab-Nano40), and 80 mg/kg nanomicelle curcumin into the pelleted feed (Diab-Nano80). A group of 10 rats was considered as healthy control and did not receive any streptozotocin or curcumin forms (Healthy-Con). All formulations were fed to rats for 42 days.

Body and organ weights. At the end of the experiment, the animals were weighted and then killed by CO^2. Weights of liver, heart, and pancreas were calculated as percentage of body weight.

Blood biochemical parameters. At the end of the study and after 12 h fasting, blood samples were collected from left ventricle, centrifuged and stored at -20°C and investigated for blood biochemical parameters. The serum concentrations of AST, ALT, glucose, insulin, triglycerides, cholesterol, HDL-C and LDL-C were evaluated by an enzyme-linked immunosorbent assay (ELISA) commercial Kit (PARS-Azmoon, Tehran-Iran). Homeostatic Model Assessment score for insulin resistance (HOMA-IR) was calculated as reported by Matthews et al.[20].The level of adiponectin was assessed by commercial Kits of Otsuka Pharmaceutical Co., Tokyo, Japan.

Data analysis. The obtained data were analyzed by SPSS software (version 24) and the significance designated at P<0.05 for the differences among the six groups for all studied parameters. The significance was considered by one-way ANOVA between all the studied groups.

Results

The effects of treatments on the serum concentrations of glucose, insulin, adiponectin and insulin resistance of the rats are shown in Figure 1. The results showed that induction of diabetes increased the serum concentrations of glucose (P<0.0001), and decreased the serum concentrations of insulin (P<0.0001), HOMA-IR (P<0.0001) and adiponectin (P<0.0001). The results showed that administration of curcumin at the level of 40 mg/kg rat diet and nanomicelle curcumin in both doses decreased the serum concentrations of glucose (P<0.05), and increased insulin (P<0.05), HOMA-IR (P<0.05) and adiponectin (P<0.05). The best responses were observed in nanomicelle curcumin groups, especially in the rats received 80 mg/kg diet (P<0.05).

The effects of treatments on the serum lipid profile of the rats are presented in Table 1. The results showed that induction of diabetes significantly increased the serum concentrations of triglycerides (*P<0.0001*), cholesterol (*P<0.0001*), and LDL-C (*P<0.0001*) and decreased HDL-C (*P<0.0001*). Administration of curcumin had no significant effect when compared to control diabetes (*P*>0.05). The administration of nanomicelle curcumin decreased the serum concentrations of triglycerides (*P<0.0001*), cholesterol (*P<0.0001*), and LDL-C (*P<0.0001*) and increased HDL-C (*P<0.0001*). No significant difference between the Nano treatments (*P*>0.05) was observed.

Table 1. Effects of treatments on the serum lipid profile (mg/dl) of the diabetic rats

	Triglycerides	Cholesterol	HDL-C	LDL-C
Healthy Control	50.20±5.49^{c}	116.60±4.21^{c}	52.80±3.96^{a}	53.76±7.08^{c}
Diabetic Control	89.60±3.64^{a}	185.60±8.56^{a}	26.75±1.50^{c}	142.10±8.41^{a}
Diabetic Cur40	89.00±3.74^{a}	182.40±2.51^{a}	26.20±2.28^{c}	138.40±4.36^{a}
Diabetic Cur80	88.60±3.78^{a}	179.80±2.58^{a}	28.60±2.60^{c}	133.50±4.50^{a}
Diabetic Nano40	82.80±3.56^{b}	171.60±2.07^{b}	32.75±2.07^{b}	122.20±2.12^{b}
Diabetic Nano80	81.20±2.77^{b}	166.40±2.96^{b}	34.20±2.68^{b}	116.00±3.90^{b}
P-value	0.000	0.000	0.000	0.000
SEM	2.640	4.420	1.850	5.960

$^{a-c}$ Means in each column with different superscripts are significantly different (P<0.05). SEM: Standard error of means. Curcumin (Cur) and Nano-micelle curcumin (Nano) with specified doses of 40 and 80 mg/kg diet.

The effects of treatments on body weight (g) and relative percentages of pancreas, heart and liver of the diabetic rats are shown in Table 2. The results showed that induction of diabetes decreased body weight (*P<0.0001*), relative weights of pancreas (*P<0.05*), and heart (*P<0.05*), but did not have any significant effects on liver weight (*P*>0.05). The results did not show any significant differences between the diabetic treatments for relative weights of pancreas and heart. Supplementing curcumin 40 decreased body weight compared to those of the rats in diabetic control (*P<0.05*).

Table2. The effects of treatments on body weight (g) and relative weights (w/w*100) of pancreas, heart and liver of the diabetic rats

	Body weight	Pancreas	Heart	Liver
Healthy Con	308.80±16.65^{a}	0.51±0.35^{a}	1.18±0.04^{a}	10.04±0.45
Diabetic Con	224.60±3.71^{b}	0.23±0.02^{b}	0.98±0.03^{b}	10.22±1.16
Diabetic Cur40	191.00±27.48^{c}	0.36±0.06^{ab}	0.90±0.13^{b}	10.37±2.50
Diabetic Cur80	243.40±53.90^{b}	0.40±0.19^{ab}	0.89±0.10^{b}	10.59±1.13
Diabetic Nano40	209.00±15.17^{bc}	0.35±0.04^{b}	0.87±0.06^{b}	11.13±0.90
Diabetic Nano80	225.00±15.00^{bc}	0.42±0.09^{ab}	0.85±0.03^{b}	10.34±1.07
P-value	0.000	0.013	0.000	0.848
SEM	8.250	0.023	0.024	0.023

$^{a-c}$ Means in each column with different superscripts are significantly different (P<0.05). SEM: Standard error of means. Curcumin (Cur) and Nano-curcumin (Nano) with specified doses of 40 and 80 mg/kg diet.

The effects of treatments on serum levels of liver enzymes of the diabetic rats are shown in Table 3. Induction of diabetes increased the serum concentrations of ALT and AST (*P<0.0001*). The results showed that the administration of Nano-curcumin at both doses decreased the serum concentrations of ALT and AST (*P<0.0001*). Serum concentration of ALT was not affected by 40 and 80 mg/kg curcumin (P>0.05).

Table3. The effects of treatments on serum levels of liver enzymes of the diabetic rats

Treatments	ALT	AST
Healthy Control	22.11±0.84^{c}	320.90±0.97^{e}
Diabetic Control	37.58±0.49^{a}	381.60±5.90^{a}
Diabetic Cur40	36.62±0.49^{a}	370.60±5.39^{b}
Diabetic Cur80	36.02±0.44^{a}	363.80±2.55^{b}
Diabetic Nano40	35.36±0.83^{b}	350.20±4.71^{c}
Diabetic Nano80	34.64±1.14^{b}	334.60±1.14^{d}
P-value	0.000	0.000
SEM	0.980	3.930

$^{a\text{-}e}$ Means in each column with different superscripts are significantly different (P<0.05). SEM: Standard error of means. Curcumin (Cur) and Nano-curcumin (Nano) with specified doses of 40 and 80 mg/kg diet. ALT, alanine aminotransferase. AST, aspartate aminotransferase.

Discussion

The results showed that induction of diabetes increased the level of glucose and decreased the level of insulin that are already confirmed by others[1, 2, 3]. Diabetes destroys β-cells and increases level of glucose and decreases level of insulin. The results showed that oral administration of curcumin 80 and Nano-curcumin decreased the level of glucose and increased the serum concentration of insulin. The difference between curcumin 40 and control-diabetic groups was not significant. It means that Nano-curcumin can alleviate adverse effects of diabetes on glucose and insulin. Curcumin is known to have the anti-hyperglycaemic effect in diabetic subjects[21, 22, 23]. Previous studies have shown that the administration of curcumin improves insulin sensitivity by reducing glycaemia and dyslipidemia in high fat-fed rats[24, 25, 26]. In agreement with the results of this study, Lu et al.[27] showed that curcumin supplementation improve glucose and insulin intolerance by activating the AMPK pathway in diabetic animals. Administration of nanomicelle curcumin showed better response compared to curcumin. Low absorption rate and rapid degradation of curcumin in intestinal system are reported[28]. Use of nanomicelle structure form of curcumin prevents rapid degradation and increases more absorption in intestinal system and helps to increase curcumin absorption so it shows better anti-hyperglycaemic function. Since diabetes disturbs oxidant-antioxidant balance, it may destroy pancreas function and insulin secretion. It seems that use of nanomicelle structure form of curcumin increases antioxidant properties and prevents pancreas injury. Therefore, administration of nanomicelle curcumin decreases the level of glucose and subsequently decreases the serum concentration of insulin. Following improved insulin concentration and pancreas injury insulin resistance improves, as seen in the current study.

The results showed that diabetes decreases adiponectin. However, administration of curcumin in higher dose and nanomicelle form of curcumin in both levels increased level of adiponectin and the best response observed in nanomicelle groups. Adiponectin is produced in adipose tissue, and its tissue levels directly correlates with underlying tissue function. Adiponectin is an insulin-sensitizing hormone with anti-apoptotic and anti-inflammatory effects. In the adipose tissues of patients with type 2 diabetes the level

of adiponectin decreases[5]. Curcumin suppresses the improper functionality of NF-kB in adipocytes and may improve adiponectin level[29]. NF-kB links to cancer, inflammatory and autoimmunity diseases, and improper immune development. It controls transcription of DNA, cytokine production and cell survival. A well-known function of NF-kB is regulation of inflammatory responses[30]. Our findings showed a direct relation between insulin and adiponectin. It means that administration of curcumin increases insulin level and subsequently increases adiponectin level.

Diabetes increased level of triglycerides, cholesterol, and LDL-C, and decreased HDL-C, and only administration of curcumin in the form of nano could improve serum lipid profile of rats. Diabetes disturbs lipid metabolism[1]. Administration of curcumin in the form of nano improved lipid profile of diabetic rats when compared to diabetic control group that is in agreement with those of other studies[29, 31]. Improved lipid profile could be attributed to increasing lipoprotein lipase activity that decreases serum triglycerides. Diabetes also induces lipid peroxidation and increases lipid profile of triglycerides, cholesterol and LDL-C. Curcumin decreases lipid peroxidation by normalizing antioxidant enzyme levels, such as superoxide dismutase, catalase and glutathione peroxidase[31]. Apparently, administration of nano structure form of curcumin spares antioxidant enzymes and improves antioxidant properties and thereby improves lipid profile.

Induction of diabetes increased the level of liver enzymes, and administration of curcumin decreased their activities. Increased levels of transaminase enzymes is directly associated to liver cell damages. Increased levels of the enzymes shows hepatic injury in the hepatocellular cytosol and mitochondria[7]. Increased levels of ALT and AST in type 2 diabetes mellitus is already reported[8]. Seemingly, curcumin protects liver hepatocytes against oxidative injuries and decreases level of antioxidant enzymes.

Current study showed that diabetes decreased body weight, pancreas and heart weights and administration of curcumin only at the level of 80 alleviated the adverse effects of diabetes on pancreas weight. It is reported that diabetes decreases body weight[32, 33]. Diabetes decreases energy, increases urinary excretion and catabolic processes[34] and the output is decreased body weight. Diabetes damages pancreas and decreases body weight. Curcumin in any forms couldn't alleviate the adverse effects of diabetes on body weight. Hodaei et al.[35] showed that curcumin supplementation did not improve body weight in patients with type 2 diabetes. Consumption of curcumin decreased body weight in patients with metabolic syndrome[36]. It seems more time was needed to recover the body weight or organ weights disrupted by streptozotocin injection in rats. However, the weights of pancreas partly improved. It might be needed to optimize the level and time of curcumin or nanomicelle curcumin administration, or diabetes inducers such as streptozotocin. The priorities for diabetic subjects are to lower the glucose level, and protect endocrine/exocrine secretion balances such as adiponectin, ALT, or AST from disruption and in all cases, positive results were obtained. More research is needed to clarify the suitable doses of curcumin, and nanomicelle curcumin along with other nutrients in diabetic subjects.

Conclusion

In conclusion, diabetes induced damages on pancreas and changed the serum concentrations of glucose, lipid profile, insulin resistance and decreased adiponectin, liver enzymes, and body weight, and pancreas weights. Administration of nanomicelle form of curcumin improved insulin resistance and the serum concentrations of glucose, insulin, lipid profile, adiponectin, and liver enzymes. We suggest nanomicelle form of curcumin for diabetic patients with special care of used doses might be effective.

Declarations

Acknowledgement

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Author contributions

H.D performed the experiment and wrote the main manuscript. H.K. contributed to the experiment as supervisor and corresponding author. M.R.J. and A.J. contributed to the manuscript as advisors. All authors reviewed the manuscript.

Competing interests

The authors declare no conflict of interests.

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Figures

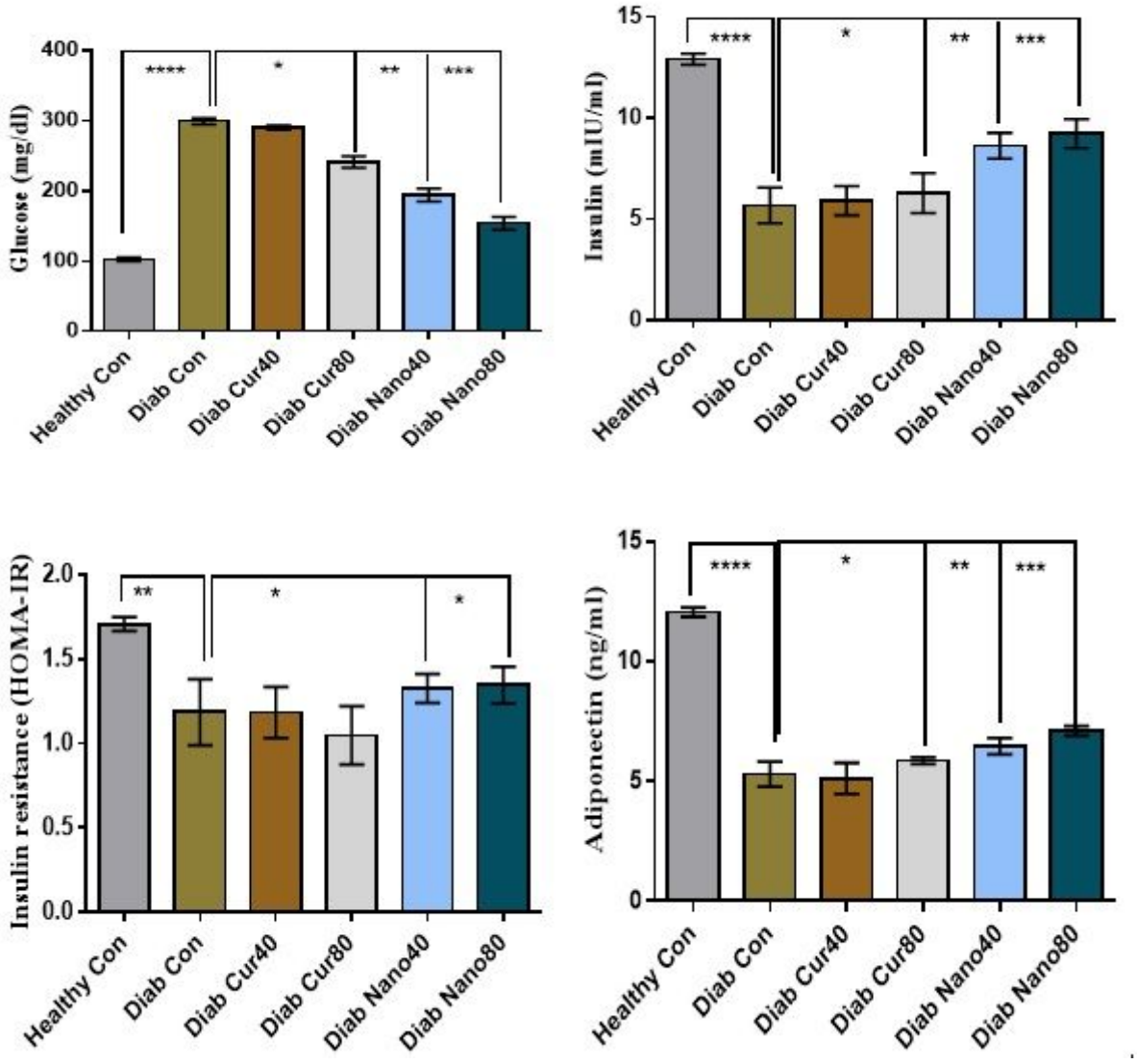

Figure 1

Effects of treatments on the serum concentrations of glucose (top-left), insulin (top-right), insulin resistance (bottom-left) and adiponectin (bottom-right) of the diabetic rats. Superscripts *, **, *** and **** show significant differences at 0.05, 0.01, 0.001, and 0.0001, respectively. Curcumin (Cur) and nano-micelle curcumin (Nano) with specified doses of 40 and 80 mg/kg diet.