

# Effect of green tea extract on body weight, serum glucose and lipid profile in streptozotocin-induced diabetic rats

## *A dose response study*

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### ABSTRACT

**الأهداف:** اختبار مدى تأثير خلاصة الشاي الأخضر على وزن الجسم، ومستويات الغلوكوز في مصلى الدم، ومستويات الدهون لدى مجموعة من الجرذان التي حُفّز مرض السكري لديهم باستخدام الستريبتوزوتوسين.

**الطريقة:** أُجريت هذه الدراسة في مركز أبحاث مرض السكري، جامعة أهفاز للعلوم الطبية، إيران وذلك خلال الفترة من يناير إلى مارس 2011م. شملت الدراسة 48 جرذ ذكراً من النوع ويست (200-250 غ)، وقد تم تقسيم الحيوانات عشوائياً إلى 6 مجموعات. لقد قمنا بتحفيز مرض السكري لدى الحيوانات بحقن جرعة أحادية من الستريبتوزوتوسين داخل الصفاق (55 ملغ/كغ). وبعد ذلك قمنا بإعطاء خلاصة الشاي الأخضر لمجموعات الدراسة (100 ملغ/كغ و200 ملغ/كغ) ولمدة 4 أسابيع خلالها قمنا بقياس وزن الجسم يومياً. وأخيراً قمنا بجمع عينات الدم من كافة الحيوانات من أجل تحليل مستويات الغلوكوز والدهون.

**النتائج:** أشارت نتائج الدراسة إلى أن إعطاء خلاصة الشاي الأخضر بمقدار 200 ملغ/كغ قد أدى إلى خفض مستويات الغلوكوز ومجموع مستويات الكوليسترول، كما أنه قد أدى إلى تحسين خسارة الوزن بشكل كبير من الناحية الإحصائية وذلك عند مقارنة مجموعات الدراسة بمجموعة الشاهد المصابة بالسكري ( $p < 0.05$ ). ولم نلاحظ أي تغيرات واضحة من الناحية الإحصائية في مستويات ثلاثي الغليسريد ( $p = 0.04$ )، والكوليسترول منخفض الكثافة ( $p = 0.000$ )، والكوليسترول مرتفع الكثافة ( $p = 0.01$ ) بعد إجراء التجربة.

**خاتمة:** أثبتت هذه الدراسة بأن خلاصة الشاي الأخضر أثر في خفض سكر الدم والكوليسترول لدى الجرذان المصابة بالسكري. وبالرغم من ذلك فنحن بحاجة لمزيد من الدراسات لإثبات ودراسة ميكانيزمات عمل الشاي الأخضر.

**Objectives:** To examine the effect of green tea extract on body weight, serum levels of glucose, and lipids in streptozotocin-induced diabetic rats.

**Methods:** This experimental study was carried out in the Diabetes Research Center, Ahvaz University of Medical Sciences, Ahvaz, Iran from January 2011 to March 2011. Forty-eight male wistar rats (200-250g) were divided randomly into 6 groups. Diabetes was induced by a single intraperitoneal injection of streptozotocin (55 mg/kg). The experimental groups received alcohol extract of green tea leaves (100 mg/kg and 200 mg/kg) for 4 weeks and the body weight of animals were measured every day. Finally, blood samples were collected and analyzed for glucose and lipid profile levels.

**Results:** Administration of green tea extract caused a significant decrease in serum glucose and total cholesterol levels and significantly improved the body weight loss in diabetic rats treated with 200 mg/kg green tea in comparison to diabetic control group. No significant changes were observed in triglyceride ( $p = 0.04$ ), low-density-lipoprotein cholesterol ( $p = 0.000$ ), and high-density-lipoprotein cholesterol levels ( $p = 0.01$ ) following intervention.

**Conclusion:** It appears that green tea extract had both antihyperglycemic and hypocholesterolemic effects in diabetic rats, although further work is needed to determine their mechanism.

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Diabetes is a significant public health issue. At least 177 million people worldwide have diabetes. This figure is predicted to reach 366 million by 2030.<sup>1</sup> One of the outcomes of diabetes is oxidative stress that is caused by the effect of hyperglycemia. Recent studies indicate that oxidation agents in diabetes result in many complications such as cardiovascular disease nephropathy, retinopathy, and neuropathy.<sup>2,3</sup> Regarding the high prevalence of diabetes in the worldwide, there is a need for novel therapies which are more effective with less adverse effects. Herbal productions are used for decreasing of symptoms in diabetes.<sup>4</sup> One of the medicinal plants, which have been getting increasing attention lately, is green tea (*Camellia sinensis*). For many years green tea and its catechins (epigallocatechin-3-gallate (EGCG) epigallocatechin (EGC), epicatechin-3-gallate (ECG), epicatechin (EC)) has been considered as an antioxidant and anti diabetic plant.<sup>5</sup> Several human and animal studies show that the consumption of green tea can decrease blood glucose in diabetic patients in a dose response manner.<sup>4,6</sup> Potenza et al<sup>7</sup> suggested that dietary supplementation with EGCG can improve glucose tolerance and insulin sensitivity. Igarashi et al<sup>6</sup> found that administration of green tea catechins to type 2 diabetic rats decreased blood glucose levels than rats not fed catechins. Furthermore, anti-obesity features of green tea and its catechins especially EGCG have been reported in several studies.<sup>8,9</sup> There are also considerable epidemiological studies that suggest the drinking of green tea lowers the risk of cardiovascular disease.<sup>10,11</sup> But the responsible mechanisms are still unknown for scientists. Changing lipid and lipoprotein profiles is one of the possibility ways. Recently, Serisier et al<sup>12</sup> indicate that green tea had a modulator effect on the lipid profile in obese dogs. However, its effect has not been confirmed in diabetes yet and very little is known about its mechanisms. Moreover, there are some other studies that show green tea does not appear to have any direct effects on body weight, glucose, and lipid profile and so it requires further investigations to determine the effect of green tea on this parameters.<sup>13-15</sup> This investigation is based on the hypothesis that bioactive compounds found in green tea (*Camellia sinensis*) have antidiabetic properties. The present study was conducted to examine the effect of 2 doses of green tea extract (100 mg/kg and 200 mg/kg) on glucose and lipid profile as well as, body weight changes in streptozotocin (STZ) induced diabetes rats.

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**Methods.** *Preparation of green tea extract.* Green tea (*Camellia sinensis*) leaves used in this study were purchased from a local market in Ahvaz, Iran. The dry green tea leaves were powdered by electrical mill. In order to prepare the extract, 150 g of powdered green tea leaves was mixed with 1000 ml 95% ethanol and shaken constantly for 48 hours. After filtration (Whatman filter paper No. 1), the suspension was evaporated in a rotary evaporator (extractive value: 95%). The extracts were stored in 4°C refrigerator until usage.

*Animals.* In this experimental study, 48 male wistar rats (200-250 g), aged 6-8 weeks, were obtained from the Physiology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. All animals were maintained on a 12 hours/12 hours light/dark cycle and at controlled temperature (22±3°C) and humidity were kept at 50%. The animals were fed with a standard laboratory diet and allowed food and water ad libitum. They were handled according to the recommendation of the Ethics Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Ethical Approval No. a/54/47b, 28/11/2010). This experimental study was carried out in Diabetes Research Center, Ahvaz University of Medical Sciences, Iran from January 2011 to March 2011.

*Study design.* The experimental animals were divided randomly into 6 groups (n=8) and treated as follows: Group 1: non-diabetic control rats; Group 2: non-diabetic rats treated with 100 mg/kg green tea extract; Group 3: non-diabetic rats treated with 200 mg/kg green tea extract; Group 4: diabetic control rats; Group 5: diabetic rats treated with 100 mg/kg green tea extract; and Group 6: diabetic rats treated with 200 mg/kg green tea extract. Diabetes was induced by a single intraperitoneal injection of 55 mg/kg STZ (Sigma, Aldrich, USA), that was dissolved in citrate buffer (0.1 M, PH: 4.6). Fasting blood glucose levels were measured 4 days after STZ injection from tail vein for confirming diabetic. Rats with fasting blood glucose 250 mg/dl or greater were considered diabetic.<sup>16</sup> One week after injection of STZ, green tea extract was administered orally by gavage for 4 weeks. During the intervention, the animals were carefully monitored and weighed day by day.

*Biochemical analysis.* At the end of the experimental period, the rats were anesthetized by light ether and fasting blood samples were drawn directly from cardiac. Then blood samples were centrifuged at 3000 rpm for 15 minutes and serum was separated and used for the biochemical analysis. Serum glucose, triglycerides (TG), total cholesterol (TC) and high-density

lipoprotein-cholesterol (HDL-c) levels were determined enzymatically using the standard methods. Low-density lipoprotein-cholesterol (LDL-c) level was calculated by Friedwald formula as follows: LDL-cholesterol = total cholesterol - HDL-cholesterol - (triglyceride/5).

**Statistical analysis.** Statistical analyses were carried out by Statistical Package for the Social Sciences, Version 17 for windows (SPSS Inc, Chicago, IL, USA). All data were expressed as mean  $\pm$  SD. Statistical analysis was performed using Independent sample t-test and one way Analysis of Variance followed by Post hoc Tukey honestly significant difference (HSD) test with 95% confidence interval. *P*-value less than 0.05 was considered statistically significant.

### Results. Effect of green tea extract on body weight.

The means of initial and final body weight in 6 groups

are summarized in Table 1. The results showed that the means of final body weight in both of diabetic control rats and diabetic rats treated with 100 mg/kg green tea were significantly lower than those of normal control rats ( $p=0.006$ ,  $p=0.01$ ). But at the end of the study, the body weight of the diabetic rats treated with 200 mg/kg green tea was not statistically different from that of normal control rats ( $p>0.05$ ). In the present study, supplementation with 2 doses of green tea extract had no significant effect on body weight in normal groups ( $p>0.05$ ).

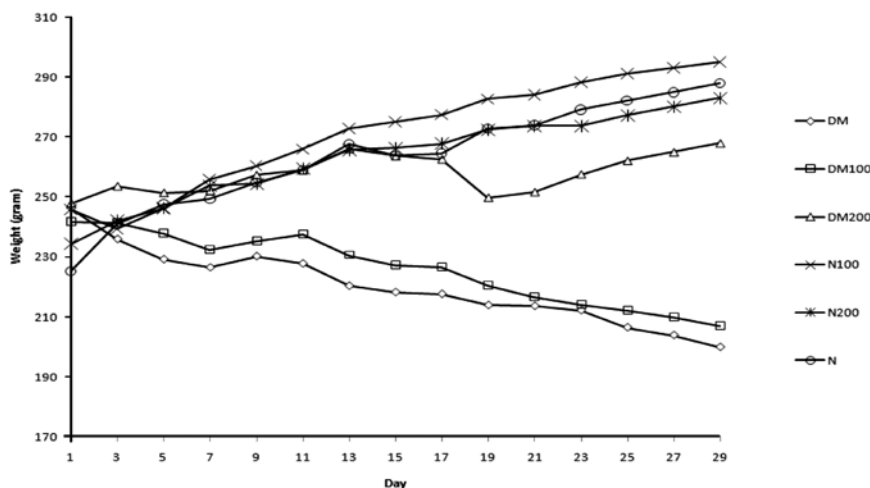
The body weight changes during the study in normal and diabetic groups are presented in Figure 1. As it is shown in Figure 1, the treatment of the diabetic rats with 200 mg/kg green tea extract improved their body weight loss compared to the diabetic control group ( $p=0.01$ ).

**Table 1** - The means of initial and final body weight in 6 groups at the beginning and at the end of the study.

Groups	Initial weight <sup>a</sup>	Final weight	<i>P</i> -value <sup>c</sup>	<i>P</i> -value <sup>d</sup>
	(g) Mean $\pm$ SD	(g) Mean $\pm$ SD		
Normal control	225.77 $\pm$ 23.16	282.16 $\pm$ 36.90	-	0.005
Normal+green tea (100mg/kg)	241.77 $\pm$ 13.76	291.16 $\pm$ 15.12	0.990	0.001
Normal+green tea (200mg/kg)	256.50 $\pm$ 23.24	277.16 $\pm$ 29.31	1.000	0.016
Diabetic control	246.28 $\pm$ 32.15	206.57 $\pm$ 60.67	0.005	-
Diabetic+green tea (100mg/kg)	246.00 $\pm$ 10.41	212 $\pm$ 18.24	0.006	1.000
Diabetic+green tea (200mg/kg)	234.40 $\pm$ 17.14	277.2 $\pm$ 24.77	1.000	0.010

<sup>a</sup>Initial weight was not different between groups ( $p=0.207$ , One way Analysis of Variance)

<sup>c</sup>indicates *p*-value between normal control and other groups. <sup>d</sup>indicates *p*-value between diabetic control and other groups. One way Analysis of Variance was used for statistical significance assessment, with 95% confidence interval



**Figure 1** - Effect of green tea extract on body weight changes. DM - Diabetic control, DM100 - Diabetic + green tea (100 mg/kg), DM200 - Diabetic + green tea (200 mg/kg), N - normal control, N100 - normal + green tea (100 mg/kg), N200 - normal + green tea (200 mg/kg).

**Effect of green tea extract on serum glucose levels.** As it is shown in Table 2, oral administration of 100 mg/kg green tea extract in diabetic rats did not reduce serum glucose levels significantly in comparison to the diabetic control group, but the 200 mg/kg green tea extract treated diabetic group had significant lower levels of glucose in comparison to the control ( $p=0.04$ ). In normal groups, green tea administration did not change serum glucose levels in comparison to normal control group.

**Effect of green tea extract on lipid profiles.** The effects of oral administration of green tea extract on serum lipid profiles are shown in Table 3. As it is shown, serum TC was significantly higher in the untreated diabetic group than those of normal control group ( $p=0.000$ ). Diabetic control group had also significant lower levels of HDL-c than those of normal control group ( $p=0.05$ ). The present data also indicated that only the administration of 200 mg/kg green tea extract in diabetic rats caused a significant decrease in TC levels compared to the diabetic control ( $p=0.02$ ). Serum concentrations of TG, LDL-c, and HDL-c did not change significantly

following treatment of these animals with 100 mg/kg or 200 mg/kg green tea extract. In normal groups, the effect of green tea extract (100 mg/kg and 200 mg/kg) on lipid profiles was not statistically significant.

**Discussion.** In the present study, we showed that green tea extract administration at high dose (200 mg/kg) was able to reduce serum glucose and TC levels and improve weight loss in diabetic rats. Weight loss in diabetic untreated rats in this investigation was in agreement with other studies<sup>17,18</sup> and could be due to poor glycemic control, and subsequently the excessive catabolism of proteins and muscle wasting that arisen from insulin deficiency.<sup>17</sup> Dietary supplementation with green tea extract at dose 200 mg/kg resulted in improved glycemic control, which significantly prevented the weight loss trend of diabetic rats. The lower dose (100 mg/kg) of green tea extract did not change glucose levels in the treated animals, and so it could not inhibit the weight loss in this group. In the same study, Babu et al<sup>16</sup> reported that the administration of green tea extract (300 mg/kg) caused a significant increase in body weight in STZ-diabetic rats. The investigators suggested the increasing body weight can create by improving in blood glucose level in diabetic rats.

The results also showed that the feeding of green tea extract at dosage of 200 mg/kg in diabetic rats even reached the serum glucose levels to the normal values, as the difference between the mean of glucose concentration in 200 mg/kg green tea treated diabetic rats and normal control groups were not statistically significant. This finding indicates that green tea extract at higher dose act as an anti-hyperglycemic agent rather than a hypoglycemic agent. The hypoglycemic and anti-hyperglycemic effect of green tea has been reported by other researchers. Wu et al<sup>19</sup> showed that daily ingestion of 0.5 g green tea in rats significantly reduced the fasting blood glucose compared to control diet. A study by Wolfram et al<sup>20</sup> suggested that EGCG enhances

**Table 2** - Effect of the orally administered green tea extract on serum glucose levels.

Groups	Fasting blood glucose (mg/dl) Mean±SD	P-value*	P-value†
Normal control	153.16 ± 12.73	-	0.006
Normal+green tea (100mg/kg)	180.16 ± 20.98	0.980	0.030
Normal+green tea (200mg/kg)	172.6 ± 31.64	0.990	0.030
Diabetic control	299.14 ± 83.11	0.006	-
Diabetic+green tea (100mg/kg)	284.11 ± 89.14	0.010	0.990
Diabetic+green tea (200mg/kg)	182.50 ± 41.20	0.970	0.040

One way Analysis of Variance was used for statistical significance assessment, with 95% confidence interval. \*indicates  $p$ -value between normal control and other groups. †indicates  $p$ -value between diabetic control and other groups.

**Table 3** - Effect of the orally administered green tea extract on serum lipid profiles levels.

Groups	TG (mg/dl) Mean±SD	TC (mg/dl) Mean±SD	LDL-C (mg/dl) Mean±SD	HDL-C (mg/dl) Mean±SD
Normal control	63.00 ± 15.11	78.66 ± 2.58 <sup>††</sup>	43.56 ± 5.24	22.50 ± 2.42 <sup>†</sup>
Normal+green tea (100mg/kg)	63.68 ± 22.08	77.50 ± 7.52 <sup>††</sup>	40.06 ± 11.87 <sup>†</sup>	24.46 ± 3.14 <sup>††</sup>
Normal+green tea (200mg/kg)	71.40 ± 41.94	79.00 ± 3.24 <sup>††</sup>	40.12 ± 9.53 <sup>†</sup>	24.60 ± 1.51 <sup>††</sup>
Diabetic control	110.42 ± 32.93	99.28 ± 9.72 <sup>††</sup>	59.77 ± 15.21	17.42 ± 3.55 <sup>†</sup>
Diabetic+green tea (100mg/kg)	99.33 ± 44.82	95.11 ± 8.85 <sup>††</sup>	56.95 ± 13.89	18.22 ± 3.63
Diabetic+green tea (200mg/kg)	73.50 ± 19.20	82.33 ± 4.76 <sup>†</sup>	48.16 ± 4.65	19.50 ± 2.73

Independent-sample t-test was used for statistical significance assessment, with confidence interval 95%. \* $p=0.03$  versus normal control group, <sup>††</sup> $p=0.000$  versus normal control group, <sup>†</sup> $p=0.02$  versus diabetic group, <sup>†††</sup> $p=0.04$ , versus normal group, <sup>††††</sup> $p=0.01$  versus normal group, <sup>†††††</sup> $p<0.001$  versus diabetic control group. TG - triglyceride, TC - total cholesterol, LDL-c - low density lipoprotein-cholesterol, HDL-c - high density lipoprotein-cholesterol



oral glucose tolerance in severely diabetic db/db mice. Several mechanisms have been suggested for anti-hyperglycemic effect of green tea that include enhancing insulin-stimulated glucose uptake, suppressing glucose absorption by sodium dependent glucose transporter SGLT1,<sup>16</sup> suppressing gluconeogenesis by decreasing the expression some genes such as phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-phosphatase (G6Pase)<sup>4</sup> and ameliorating insulin resistance by increasing expression of glucose transporter IV (GLUT IV).<sup>21</sup> In the present study, following treatment of normal rats with 2 dosage of green tea extract for 4 weeks the serum glucose concentration did not significantly change. In the study of Babu et al,<sup>16</sup> fasting blood glucose was not also changed in green tea treated normal rats. This property of green tea in normal groups could be considered as an advantage for this medicinal plant; because of the excessive lowering of the glucose level in the circulation beyond that of the normal range might even be counterproductive. Several animal studies indicate that green tea or its catechins improved plasma lipid profiles.<sup>11,12</sup> Babu et al<sup>22</sup> found that the green tea extract (300 mg/kg body weight for 4 weeks) containing 80% catechins caused a significant increase in HDL-c, but reduced circulating LDL-C in diabetic rats. The results of the present study demonstrated a significant increase in serum TC and decrease in HDL-c in diabetic control rats ( $p < 0.05$  and  $p < 0.001$ ). These findings may be due to the elevated lipolytic activity of tissues and consequently the increased serum lipid profiles in diabetic rats.<sup>23</sup> The results also exhibited that the green tea extract at dose 200 mg/kg significantly reduced the TC levels in diabetic rats, but could not change the serum concentrations of TG, LDL-c, and HDL-c significantly. However, other studies showed drinking green tea appeared to be characterized by decreasing serum triglyceride, LDL cholesterol and increasing HDL cholesterol.<sup>15</sup> The results regarding the effect of green tea on lipid profile are controversial because of the difference in the dose and duration of these studies. The lipid profiles in normal groups did not also alter following the intervention. The possible mechanisms by which green tea extract can exert cholesterol lowering effect are reducing the absorption of dietary and biliary cholesterol and promoting its fecal excretion.<sup>11</sup> Furthermore, in the recent study by Singh et al<sup>24</sup> indicated that green tea extract caused to decrease the synthesis of cholesterol in cultured rat hepatoma cells. Nevertheless, in the present study we used only 2 doses of green tea extract (100 mg/kg and 200 mg/kg) and intervention last only for 4 weeks, so maybe higher doses of green tea and long-term administration of it have favorable effect on these parameters.

In conclusion, the current results demonstrated that the administration of green tea extract in dose of 200 mg/kg may reverse weight loss-related diabetes by improving the serum glucose concentration and also decrease TC in STZ-diabetic rats during 4 weeks. The results of this study also imply that green tea as a common and inexpensive drink can have hypocholesterolemic and hypoglycemic properties. The exact mechanisms underlying the protective effects of green tea in diabetes are unknown yet. Thus, further studies should be carried out to determine the effect of green tea on diabetes complications.

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