

## The Comparison of Green Tea Aqueous Extract and Catechin Effect on Pituitary-Gonadal Axis in Rat Models of Type 1 Diabetes

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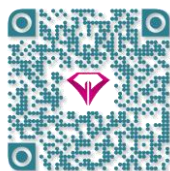
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### ABSTRACT

**Background & Objective:** Diabetes causes fertility disorders by interfering with the endocrine gland function. There are reports that, green tea and catechins could have anti-oxidant and hypoglycemic properties. Therefore, in the present study, we evaluated the effects of green tea aqueous extract and catechin influence on pituitary-gonadal axis in rat models of type 1 diabetes.

**Materials & Methods:** Six groups of Wistar rats (8 in each group), including control, diabetic control (intraperitoneal injection (IP) of 0.5 mL saline solution for 30 days after induction of diabetes), diabetic treated with 100 and 200 mg/kg doses of green tea aqueous extract (IP injection of 0.5 mL green tea extract for 30 days), and diabetic treated with 100 and 200 mg/kg doses of catechin (IP injection 0.5 mL of catechin for 30 days) were used. The induction of diabetes was conducted through an IP injection of 240 mg/kg alloxan. At the end of the treatment course, the serum levels of LH, FSH, estrogen, testosterone, dihydrotestosterone and cytoplasmic HOdG-8 in testicular tissue were measured by ELISA method. ANOVA and Tukey post hoc test ( $P < 0.05$ ) were used to perform the data analysis.

**Results:** The incorporation of 200 mg/kg green tea extract and 100 and 200 mg/kg concentrations of catechin, in comparison with the diabetic control group, led to a significant dose-dependent increase in the serum level of LH, FSH, estrogen, testosterone, and dihydrotestosterone. A dose-dependent significant decrease was observed in HOdG-8 in the testicular tissue of diabetic rats ( $P < 0.05$ ).

**Conclusion:** Based on the obtained data, compared to green tea, catechin considerably enhanced the hormonal parameters and reduced HOdG-8 in testicular tissue of diabetic rats.

**Keywords:** Catechin, Diabetes mellitus, Green tea, Oxidative Stress, Rats, Testis



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### Introduction

Diabetes refers to a heterogeneous set of metabolic disorders and its sign is a chronic increase in blood glucose level as a result of a failure in insulin secretion (1). Studies have indicated that diabetes is associated with some complications, including oxidative stress and decreased activity of antioxidant enzymes (2), increased lipid peroxidation (3), and DNA oxidative damage (4). In addition, this disease causes cell death by disrupting oxidative phosphorylation and reducing energy production (5). Based on the literature, guanine is the most readily oxidized DNA base among the purine and pyrimidine bases, in a way that a combination called 8-Oxo-2'-deoxyguanosine (8-OHdG) is created because of attacking the eighth position of the guanine molecule by hydroxyl radicals. Since 8-OHdG indicates a dynamic balance between DNA oxidative stress and its recovery speed, it is important to measure this combination in the evaluation of DNA damage (6).

Diabetes plays a significant role in the emergence of infertility and hormonal disorders through weakening the antioxidant defense system in testicular tissue (7); this reduces the protection of testicular tissue against oxidative damage, increases the accumulation of free radicals, and ultimately, damages germ cells (7).

Clinical and experimental studies have demonstrated that diabetes causes a defect in the activity of hormonal pituitary-testis axis, causing a reduction in the secretion of gonadotropins and testosterone, which eventually leads to the impairment of spermatogenesis (8). Also, some laboratory studies showed that the lack of insulin among diabetic rats results in a reduced section of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (9). Furthermore, insulin is required to maintain LH receptors in Leydig cells and can adjust cell division and metabolism of Leydig cells (9). Therefore, the decreased level of insulin in body can

cause impairments in the activity of Leydig cells and reduce testicular steroid hormones (9). Endogenous estrogen is vital in male reproduction, especially to sperm count. Moreover, it has been indicated that spermatogenesis alterations in men with genetically deficient estrogen levels could appear both in terms of motility and number of spermatozoa (10). Medicinal herbs are a good option for treating diabetes as complementary supplements or an appropriate alternative to reduce the side effects of chemical drugs. Based on previous studies, the compounds in medicinal plants can reduce the complications of diabetes and modify some of the associated metabolic abnormalities (11). Green tea is part of the angiosperm branch, the dialypetalae category, the partial order, the Teaceae family, and the genus *Camellia* and is recognized with the scientific name of *Camellia sinensis* (12). As indicated, consuming green tea can decrease the serum levels of inflammatory factors, such as CRP, IL-6, and TNF- $\alpha$  in women with type II diabetes (T2D) (13). Review of the literature revealed that prescribing the extract of green tea can significantly improve mobility, sperm motility, diameter of seminiferous tubes and lumen, and reproductive epithelium thickness in rats consuming sodium arsenite. As a result, green tea extract, as a strong antioxidant, reduces lipid peroxidation in sperm by inhibiting oxidative stress caused by sodium arsenite, which prevents sperm death (14). Symptoms of polycystic ovary syndrome (PCOS) could be extraordinarily improved by green tea as a result of its influence on oxidative stress pathways. Treatment of PCOS, insulin resistance, and T2D could be highly attributed to the consumption of green tea as a possible medication (15). Studies have revealed that catechins contribute to the improvement of T2D and can be a good supplement for metformin due to its ability to reduce blood glucose before and after diabetes (16). Some evidence reported that the incorporation of green tea in the treatment of rat models with type 1 diabetes (T1D) significantly reduced serum glucose levels (17). Based on the literature, the consumption of green tea increases catalase and glutathione peroxidase enzymes among the patients with T2D, indicating the antioxidant effect of green tea, which is mainly attributed to one of its components called catechin (18). Furthermore, according to some existing data, green tea is effective in reducing LH, testosterone, and progesterone levels (19).

As far as the researchers investigated, this study is the first research to compare the influence of green tea extract and catechin on pituitary-gonad axis and DNA oxidative damage of testicular tissue in rat models of T1D. Considering the antioxidant effects and different applications of green tea and its effective compounds in traditional medicine, this study aimed to compare green tea aqueous extract to catechin effect on pituitary-gonadal axis in rat models of T1D.

## Materials and Methods

This experimental study was implemented in the research laboratory of the Biology Department of Islamic Azad University of Damghan, Iran in the time period between 2018 and 2019. All test stages were carried out based on the instructions by the committee for ethics in animal research of Islamic Azad University (IR.IAU.DAMGHAN.REC.1398.001), which were similar to international guidelines. The sample of this study included 48 male Wistar rats (mean weight=160 $\pm$ 5 gr; age=140 $\pm$ 7 days) kept in standard transparent polycarbonate cages at a temperature of 24 $\pm$ 3 $^{\circ}$ C, relative humidity of 35 $\pm$ 4%, and 12/12 light-darkness cycle. All animals had access to sufficient water provided by 500-mL plastic bottles, and they were fed by compressed food with a standard formula. In order to make the samples adapted to the environment, the experiments were carried out at least 10 days after keeping the animals in cages (19). The samples were randomly divided into six groups (eight rats in each group) as follows: control, diabetic control, diabetic treated with 100 mg/kg dose of green tea extract, diabetic treated with 200 mg/kg dose of green tea extract, diabetic treated with 100 mg/kg dose of catechin (Sigma-Aldrich, Germany), and diabetic treated with 200 mg/kg dose of catechin. The control and diabetic control groups intraperitoneally received 0.5 mL of saline solution as curcumin solvent for 30 days.

The green tea specimens were identified and confirmed by the herbarium department of Payam Noor University of Mashhad (herbarium code: 14/60858). Next, 100 g of dried green tea powder was poured into the percolator and distilled water was added. Then, it the solution was placed in a laboratory environment for 72 hours and filtered using a filter paper. The extract was placed at 45 $^{\circ}$ C for 48 hours to dry (20). After the removal of the solvent, aqueous extracts were obtained at concentrations of 100 and 200 mg/kg.

One intraperitoneal injection of alloxan monohydrate (240 mg/kg) was used to induce the empirical model of T1D to rat samples (Sigma-Aldrich, Germany). In addition, citrate buffer (pH=5.4) was applied as alloxan solvent. In fact, alloxan was administered to the groups of diabetic control and diabetic treated with green tea extract and catechin. Since the present study considered chronic diabetes, blood samples were drawn to measure the blood glucose of samples by a glucometer (IGM-0002A, EasyGluco, Korea) 30 days after the injection of alloxan and induction of empirical diabetes to confirm the disease. In this regard, the blood glucose above 300 mg/dl was regarded as an indicator of diabetes and zero test day (21).

Diethyl ether was incorporated to anesthetize rats, which were separated by groups, in the final stage of the treatment. Following that, the skin of the chest, sternum, and ribs was cut open. Then, 2 mL blood sample was taken from the left ventricle of the heart with a syringe by pulling away the sternum and ribs. The drawn samples were poured into test tubes with no

anti-coagulation agent and incubated for 12 minutes (device: INB400, Memmert, Germany) at 37°C. Once coagulation occurred, the tubes were positioned in the centrifuge (model: EBA280, Hettich, Germany) for 12 minutes at 5000 rpm/min. Subsequently, blood serum on the clotted part was isolated by a sampler (Transferrpette®S, Brand, Germany) and transferred to another test tube and kept in a freezer at -80°C (21).

The serum levels of LH, FSH, estrogen, testosterone, and dihydrotestosterone hormones were estimated by Elisa reader (Stat Fax 2100, USA) and kits of Tinestest Co. (Finetest, China) with sensitivities above 0.938 mIU/L within the range of 1.100-563 mIU/L, 1.406 mIU/L within the range of 2.344-150 mIU/L, 9.375 pg/mL within the range of 15.6-1000 pg/mL, 0.188 ng/mL within the range of 0.313-20 ng/mL, and 23.438 pg/mL within the range of 39.063-2500 pg/mL, respectively. Furthermore, testicles were removed from the body for tissue evaluation. After being washed by saline solution along with Tris buffer, the samples were homogenized for two minutes by a homogenizer (Ultra Turrax T25, IKA, Germany) at 5000 rpm. Then, the cell cytoplasm was isolated from homogenized tissue by a centrifuge (Z366, Hermle, Germany) and used for evaluation. Since it was preferred to prevent enzyme and protein demolitions, all phases of the experiments were implemented at 4°C (refrigerated centrifuge) using 0.5 µm phenylmethylsulfonyl fluoride solution (Sigma-Aldrich, Germany) as the inhibitor of cell proteases (22). In addition, the level of 8-OHdG in tissue was assessed with sensitivity of >0.938 ng/mL within the range of 1.563-100 ng/mL of testicular tissue by ELISA method and kits of Finetest Co.

The normal frequency distribution of the data was analyzed by incorporating the Kolmogorov-Smirnov test in SPSS version 20, while data analysis was performed using the one-way analysis of variance (ANOVA) and Tukey post-hoc test. In addition, the mean±standard error of the mean was presented as data along with a P-value=0.05 being accepted as statistically significant.

In the first group, the patients whose *H. pylori* infection were not eradicated (UBT was positive in the first month) or the patients who had recurrent infection (UBT was positive at the end of the six<sup>th</sup> month) were transferred from group I to group III and data analysis was done with and without them. These groups received standard treatment for ITP. The platelet count was measured every month up to six months after the start of the treatment. All data required for this study included age, sex, time of entry into the study, tests requested, and date of treatment which were entered into the questionnaires.

Inclusion criteria were as follows: 1) Patients over eighteen years of age, 2) Patients who have not been elapsed from disease onset more than six months (acute ITP), 3) Other causes of thrombocytopenia were excluded. Exclusion criteria for the study were as follows: 1) A serious illness such as heart, liver and

kidney diseases, and neoplastic disorders, 2) History of previous treatment for *H. pylori*, 3) Allergic reaction to therapies used for *H. pylori*, 4) Distinct gastrointestinal signs and symptoms for the pharmacologic intervention as well as treatment for *H. pylori*, 5) Secondary causes of ITP.

Chi-square (for qualitative variables), independent t-test (in the case of normally distributed quantitative variables) and Mann-Whitney U test (in the case of non-normal distribution of quantitative variables) were used for the statistical analysis.

In view of medical ethics, there was no compulsion to participate in the study. All patients were initially explained that the information was completely confidential and used solely for the scientific goals. Also, unknown effect of *H. pylori* treatment on patients with ITP was explained to the patients and a written informed consent was obtained from all the participants.

Ethically, there was no need to treat all patients with positive UBT, because all the patients with *H. pylori* did not have indications for treatment. Additionally, cases with indication for *H. pylori* treatment (like peptic ulcer histories) were excluded.

## Results

Based on the results obtained in this study, the serum level of LH, FSH, estrogen, testosterone, and dihydrotestosterone hormones significantly decreased in the diabetic control group in comparison with the control group ( $P<0.05$ ). Nevertheless, there was a significant increase in the serum level of LH, FSH, estrogen, testosterone, and dihydrotestosterone hormones in the group of diabetic rats treated with 100 mg/kg dose of green tea extract in comparison with the diabetic control group ( $P<0.05$ ). Compared to the diabetic control group, there was no significant difference in the serum level of the mentioned hormones in the group of diabetic rats treated with 100 mg/kg dose of green tea extract ( $P>0.05$ ). Nevertheless, a significant increase was found in the serum level of LH, FSH, estrogen, testosterone, and dihydrotestosterone hormones in the groups of diabetic rats treated with 100 and 200 mg/kg doses of catechin in a dose-dependent manner ( $P<0.05$ ). Compared to the groups of diabetic rats which were treated with the 100 and 200 mg/kg doses of green tea extract, the serum level of LH, FSH, estrogen, testosterone, and dihydrotestosterone hormones was meaningfully improved in the groups of diabetic rats treated with 100 and 200 mg/kg doses of catechin in a dose-dependent manner ( $P<0.05$ ) (Table 1).

Based on the results, a significant increase was observed in the level of HOdG-8 in the diabetic control group compared to the control group ( $P<0.05$ ). Nonetheless, the level of HOdG-8 was significantly decreased in the group of diabetic rats treated with 200 mg/kg dose of green tea extract compared to the

diabetic control group ( $P < 0.05$ ). No substantial difference was observed in the level of HODG-8 between the groups of diabetic control and diabetic rats treated with 100 mg/kg dose of green tea extract ( $P > 0.05$ ). In comparison to the diabetic control group, a major reduction was observed in the level of HODG-8 in the groups of diabetic rats treated with 100 and 200

mg/kg doses of catechin depending on the dose ( $P < 0.05$ ) (Table 1). After comparing the groups of diabetic rats treated with 100 and 200 mg/kg doses of green tea extract, a substantial decrease was observed in the level of HODG-8 in the groups of diabetic rats treated with 100 and 200 mg/kg doses of catechin depending on the dose ( $P < 0.05$ ) (Table 2).

**Table 1. Mean serum level of dihydrotestosterone, testosterone, and estrogen in groups (n=8)**

Groups	Parameter	Dihydrotestosterone (pg/mL)	Testosterone (ng/mL)	Estrogen (pg/mL)
Control		185.32 ± 5.41	8.39 ± 0.98	47.18 ± 2.12
diabetic control		52.36 ± 6.25 <sup>a</sup>	2.61 ± 0.55 <sup>a</sup>	20.51 ± 2.07 <sup>a</sup>
diabetic + green tea 100 mg/kg		60.50 ± 4.23 <sup>a</sup>	2.63 ± 0.45 <sup>a</sup>	21.57 ± 3.44 <sup>a</sup>
diabetic + green tea 200 mg/kg		88.64 ± 5.10 <sup>bc</sup>	4.17 ± 1.07 <sup>bc</sup>	27.61 ± 3.20 <sup>bc</sup>
diabetic + catechin 100 mg/kg		96.47 ± 6.23 <sup>bc</sup>	4.95 ± 0.78 <sup>bc</sup>	30.45 ± 1.47 <sup>bc</sup>
diabetic + catechin 200 mg/kg		110.92 ± 10.55 <sup>bcd</sup>	5.84 ± 1.15 <sup>bcd</sup>	38.05 ± 4.00 <sup>bcd</sup>
Analysis of variance (p)		0.004	0.006	0.009

Data are expressed as mean±standard error; a:  $P < 0.05$ , compared to the control group; b:  $P < 0.05$ , compared to the diabetic control group, c:  $P < 0.05$ , compared to the group of diabetic rats treated with 100 mg/kg green tea extract, d:  $P < 0.05$ , compared to the group of diabetic rats treated with 100 mg/kg catechin.

**Table 2. Mean serum level of HODG-8, FSH, and LH in groups (n=8)**

Groups	Parameter	HODG-8 (ng/mL)	FSH (mIU/mL)	LH (mIU/mL)
Control		3.86 ± 0.29	4.11 ± 0.54	3.92 ± 0.74
diabetic control		20.87 ± 1.59 <sup>a</sup>	1.07 ± 0.21 <sup>a</sup>	0.69 ± 0.28 <sup>a</sup>
diabetic + green tea 100 mg/kg		18.74 ± 3.09 <sup>a</sup>	1.20 ± 0.19 <sup>a</sup>	0.91 ± 0.51 <sup>a</sup>
diabetic + green tea 200 mg/kg		10.87 ± 2.15 <sup>bc</sup>	2.71 ± 0.20 <sup>bc</sup>	2.11 ± 0.54 <sup>bc</sup>
diabetic + catechin 100 mg/kg		8.67 ± 2.09 <sup>bc</sup>	3.11 ± 0.35 <sup>bc</sup>	2.41 ± 0.34 <sup>bc</sup>
diabetic + catechin 200 mg/kg		6.20 ± 0.49 <sup>bcd</sup>	3.11 ± 0.45 <sup>bcd</sup>	3.20 ± 0.67 <sup>bcd</sup>
Analysis of variance (p)		0.002	0.013	0.008

Data are expressed as mean±standard error; a:  $P < 0.05$ , compared to the control group; b:  $P < 0.05$ , compared to the diabetic control group, c:  $P < 0.05$ , compared to the group of diabetic rats treated with 100 mg/kg green tea extract, d:  $P < 0.05$ , compared to the group of diabetic rats treated with 100 mg/kg catechin.

## Discussion

This study compared the effect of green tea extract and catechin on the serum level of LH, FSH, estrogen, testosterone, dihydrotestosterone and HODG-8 in the testicular tissue of rat models of T1D. According to our results, experimental diabetes induced by alloxan monohydrate reduced the activity of the pituitary-testis hormone axis. In this regard, the reduced secretion of

pituitary gonadotropins decreased the amount of testicular hormones secretion. A different study was carried out to determine the influence of diabetes on the genital system and hypothalamic-pituitary-gonadal axis hormones; the results showed that the biosynthesis of testicular androgens reduced in diabetic cases. In addition, with regard to the direct relationship between

the secretion level of testosterone and activity of Leydig cells, it has been demonstrated that diabetes reduces the activity of Leydig cells and synthesis of steroid hormones of testicles by decreasing the secretion of gonadotropins (7). Also, research has showed that there is a direct association between the ultrastructural changes of spermatogenesis cell line with hormonal disorders in pituitary-testis axis (23).

Diabetes initiates disorders in the spermatogenesis process by reducing the activity of pituitary-testicle hormone axis and causing structural and functional changes in the testicular tissue (23). Moreover, it has been reported that the mean testicular weight in diabetic rats declines in comparison with healthy rats, which may be due to the shrinkage of testicular tissue or reduced weight of epididymis (23). In the present study, after inducing the experimental T1D, the tissue level of HODG-8 significantly increased compared to the healthy rats. In addition, oxidative stress emerged in diabetic patients due to the increased serum level of blood glucose and related metabolic disorders, which led to DNA oxidative damage in the samples (24). In addition, the level of oxidative stress imposed on DNA was directly related to the level of blood glucose (24). Another study indicated that diabetes caused changes in cell metabolism and decreased gene expression level by increasing the condition of oxidative stress and DNA oxidative damage (25).

Based on the results of the present study, treating diabetic rats with 200 mg/kg dose of green tea extract, as well as 100 and 200 mg/kg doses of catechin, increased the dose-dependent activity of pituitary-gonad axis and reduced DNA oxidative damage. Based on the literature, green tea extract can prevent the reduction of epithelial cells produced by sodium arsenite and maintain it at the level of the control group. In a previous study, it was shown that green tea could reduce the spermatogenesis by toxic substances, such as lead and doxorubicin, through increasing the activity of the pituitary-testicle axis. Such a prevention may be due to an antioxidant feature of green tea, which exists due to the high percentage of polyphenols inhibiting free radicals. Therefore, green tea can reduce oxidative stress and DNA oxidative damages by increasing the activity of antioxidant enzymes (25). Researchers have also investigated the effect of green tea on serum estrogen, progesterone, and gonadotropin concentrations in female rats. Based on the obtained results, green tea increased the serum level of LH, estrogen, and progesterone, which is in line with the findings of this study. However, it was reported that green tea had no impact on the serum level of FSH (11).

In another study, it was observed that treating rats with green tea for seven days increased the serum level of  $\beta$ -Estradiol and LH (22). One of the major drawbacks of this study was the inability to assess the effect of green tea and catechin on other aspects of infertility disorders in male diabetic rats, such as assessing the impact of green tea and catechin on testicular tissue damage and sperm parameters. Further studies are needed to better analyze the mechanism of green tea and catechin and their impact on controlling oxidative stress and infertility and hormonal disorders in diabetic laboratory samples.

## Conclusion

Our results showed that catechin improved the hormonal parameters more efficiently and reduced HODG-8 in testicular tissue, compared to green tea aqueous extract in type 1 diabetic rats. In addition, presumably, green tea and catechin can increase the activity of pituitary-gonadal axis and the testicular hormonal secretion by increasing the secretion of previous pituitary gonadotropins. Therefore, it is suggested to conduct more studies on the effect of green tea and catechin as natural antioxidant compounds on reducing infertility disorders in patients with T1D.

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## Conflict of Interest

Authors declared no conflict of interest.

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