Available online at http://www.sjomr.org

SCIENTIFIC JOURNAL
OF MEDICAL RESEARCH

Vol. 6, Issue 22, pp 17-22, 2022

ISSN: 2520-5234

ORIGINAL ARTICLE

Use of Streptozotocin to Investigate the Effect of 6-paradol Nanoparticles on Sexual and Hormonal Markers in Diabetic rats

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ARTICLE INFORMATIONS

Article history:
Received:10 April 2022
Revised: 19 May 2022
Accepted: 28 May 2022
Published: 24 June 2022

Keywords: , Antioxidant, Anti-inflammatory, Anti-diabetic anti-tumor, Streptozotocin.

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ABSTRACT

Objectives: The study aimed to explore the effect of 6-paradol nanoparticles in the therapy of changes in body weight, testis, and epididymis in male rats caused by Streptozotocin.

Methods: : In diabetic rats, different concentrations of 6-paradol nanoparticles (20 mg and 40 mg/kg) were employed as a treatment for 60 days in several hormonal and histological parameters. The criteria evaluated were body weight, testis and epididymis weight, and the concentration of sex hormones (LH, FSH, and testosterone) in Rattus norvegicus produced by Streptozotocin.

Results: The results showed a significant decrease in body weight and weight of testis and epididymis, as well as a decrease in testosterone, LH, and FSH concentrations, and a significant decrease in sperm concentration, motility, and viability, but an increase in the percentage of abnormal sperms in the STZ (G3) group of rats, but a significant increase in the weight of 6-paradol nanoparticle (G4&G5) group of rats.

Conclusion: : Because of its efficacy in treating the testis and epididymis, and because it is also useful as an antibiotic or antioxidant, we can consider 6-paradol a very good substance. It is very safe on the body and has a nanometer-sized size that allows it to enter the cell and produce good results easily.

CITATION: Abdullah JA, Al-Mayali HK, Hassan AJ. "Use of Streptozotocin to Investigate the Effect of 6-paradol Nanoparticles on Sexual and Hormonal Markers in Diabetic rats". Sci. J. Med. Res. 2022;6(22):17-22. DOI: 10.37623/sjomr.v06i22.04.

INTRODUCTION

Because medical plants offer antioxidant, anti-inflammatory, anti-diabetic, and anti-tumor properties, they have biological benefits in treating disorders.[1] Ginger is regarded to be unsuccessful in treating dysmenorrhea due to a lack of well-conducted research.[2] There was also minimal indication that its analgesic qualities were present. 6-parazol is a bioactive chemical with anti-tumor, anti-diabetic, and antioxidant activities. It can also be identified using ginger (Zingiber officinale) grains, paradise (Amomum melegueta), and plants. 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone[3] 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone, 6-paradol in its chemical form. 6-paradol has been demonstrated to influence insulin sensitivity,

glucose metabolism, and lipids in both in-vivo and in-vitro animal experiments. These trials found promising results in diabetic kidney, liver, and nerve issues.[4] Nanomedicine is one of the essential scientific techniques since it delivers microscopic gadgets and sensor technologies that may accurately identify diseases quickly. Several nanotechnology applications have been in drug delivery and simplifying the oral absorption of protein and peptide nanocarriers that specific ligands have altered.5 The nanoparticles transport proteins and RNA to diagnose and track sickness progression. Aside from nanocarriers, pulmonary medicine administration has also been identified as a viable option.[6,7]

MATERIAL AND METHODS

Using a Sol Gel, prepare Nanoparticles 6-paradol with Zinc Oxide via ion exchange.

The method8was modified by dropping 50 mL of the 6-paradol compound into a zinc oxide solution made by dissolving 1 g of zinc oxide in 50% ethanol, stirring the mixture at room temperature for two hours, then placing the mixture in a shaking incubator at 37°C for 24 hours, then placing the mixture in an incubator at 40°C for 24 hours, and finally centrifuging the precipitate. According to the scheme, the precipitate was crushed in a ceramic mortar and then stored at 40°C.1

6-paradol solution + zinc oxide solution. Stir the mixture for two hours at room temperature. Stir the mixture for 24 hours at room temperature in a shaking incubator. Incubate the mixture for 24 hours at 40 degrees Celsius

in an incubator. For 20 minutes, centrifuge at 5000 (rpm). Several times with deionized distilled water Hybrid nanoparticles are a type of hybrid nanoparticle that combines Dry at 40°C Crushing and preserving Hybrid nanoparticle diagnosis Preparation of 6-paradol nanoparticles with Zinc Oxide using a Sol gel for ion exchange.

Animals

The Kerbala University's Pharmacy College animal facility supplied forty 8-week-old adult Wister albino male rats weighing 230–10 g. Before being employed in the experiment, the male rats were maintained in rooms with controlled temperatures (25°C), a constant humidity (between 40 and 70%), and 12 hours dark/light cycles. The Lab Animal Care Principles were applied to all of the animals. The experimentation procedures were approved by the Animal Ethical Committee based on Kerbala University's Pharmacy College's Animal House's criteria for the care and use of lab animals. For 60 days, all of the rats were given water and a normal diet.

Streptozotocin-induced Diabetes

One intraperitoneal (i. p.) STZ injection at a dose of 60 mg/kg body weight in 0.1M citrate buffer (pH4) was used to induce diabetes.[9] The changes in blood glucose levels and body weight were regularly observed.

Dose of Streptozotocin

Streptozotocin dosages of 60 mg/kg body weight were made,[9] which involved dissolving the required concentration on the animal's average weight.

Dose of ZnO

Zinc oxide dosages were generated by dissolving the necessary concentration on the animal's average weight[10] at a concentration of 20 mg/kg of body weight.

Dose of 6-paradol nanoparticle

Doses of 6-paradol nanoparticles at concentrations of 20 mg and 40 mg /kg of body weight were generated by dissolving the required concentration on the average weight of the animal.[11] As a result, male wister rats have been divided into five groups, each with eight rats:

Group 1 (G1): the control group was only given DW everyday for 60 days.

Group 2 (G2): received 20 mg/kg/day zinc oxide as a control.

Group 3 (G3): induced diabetes control (60 mg/kg streptozotocin, single i.p. injection)

Group 4 (G4): The Nano 6-paradol was administered to the induced diabetes group at a dose of 20 mg/kg every day.

Group 5 (G5): The induced diabetic group was administered 40 mg/kg of Nano 6-paradol per day.

Surgical procedure

Rats were slaughtered on the 60th day after a ketamine solution was mixed with a Xylazine solution (2 mL of 20 mg/kg) was supplied via i.p. as anesthesia and the peritoneal cavity was accessed by a lower transverse abdominal incision (at the end of the treatment period). The experimental and control groups had their testicles and epididymis removed immediately. After the testes and epididymis were fixed in formalin solution, each group member underwent histological tests, testes weight, and epididymis weight

RESULT

Bodyweight

The group (G3) exhibited a considerable reduction in body weight as compared to the control group (G1) and the nanoparticle 6-paradol treatment group (G3) (P 0.05). G4, G5, G6, G7, G8, G9, G10, G11. The treated group with nanoparticle 6-paradol (G4, G5) exhibited a substantial rise in body weight as compared to the control and other groups, whereas the group treated with Zinc oxide (G2) had no change in body weight.

Testis weight.

Table 1 demonstrates that when compared to the control group (G1) and the 6-paradol-treated groups (G4, G5, and G2), group (G3) exhibits a significant decrease in testes weight (P 0.05). The testes weight increased significantly in the group treated with 6-paradol nanoparticles (G4,G5) (P 0.05), but there was no difference between (G4) and (G5) (G5). A statistical analysis found no difference in testes weight between groups treated

with (ZnO) G2 and (G1) at (p> 0.05), but a significant difference between treated groups (G4&G5) and G3 at (P >0.05). (p> 0.05)

Epididymis Weight

Table 1 shows a significant decrease in epididymis weight for group (G3) (p> 0.05) when compared to the control group and the 6-paradol-treated group (G4, G5). The group treated with 6-paradol nanoparticle (G4, G5) had a significant increase in epididymis weight (p> 0.05) as compared to (G1, G2), but there was no significant difference between (G4) and (G5) (p> 0.05). When compared to the control and treatment groups, statistical analysis demonstrates that the zinc oxide (G2) group has a significant reduction (p> 0.05) in epididymis weight.

Testosterone Hormone

Table 2 shows that group (G3) has a significant drop in testosterone hormone concentration when compared to control group (G1) and group (G3) has a significant decrease in testosterone hormone concentration when compared to the G1 control group (G2). When compared to (G1) and (G2), the group treated with 6-paradol nanoparticle (G4,G5) showed a significant increase in testosterone hormone concentration (p> 0.05). (G2). There was also a significant difference (p 0.05) in (G4,G5). When comparing group (G2) to control group, statistical analysis showed that testosterone hormone concentrations have not decreased significantly (p> 0.05)

Luteinizing Hormone (LH)

When compared to the control group (G1) and 6-paradol-treated groups (G4,G5), the results in table (2) demonstrate a substantial decrease in luteinizing hormone concentration (P 0.05) for group (G3) (G2). There was also a substantial rise in luteinizing hormone concentration (p 0.05) compared to the control group in the group treated with 6-paradol nanoparticles (G4,G5) (G1, G2), and statistical analysis revealed no difference between (G4) and (G5) at p> 0.05 (G5). Furthermore, there is no difference in luteinizing hormone levels between the experimental and control groups (G2). On the other hand, the treated group showed a significant drop at p 0.05.

Follicle-stimulating Hormone (FSH)

The results in table (2) reveal a significant decrease in follicle-stimulating hormone levels when compared to the control group (G1) and the Zinc oxide-treated group (G3) (p> 0.05). Similarly, when compared to (G4,G5), (G2) has a significant drop (p> 0.05). The levels of folicle stimulating hormone increased significantly (p> 0.05) in the 6-paradol nanoparticle (G4,G5) group, but did not alter significantly in the other groups. The p 0.05 in the (G4) and (G5) groups (G5). There is no significant difference in follicle stimulating hormone levels between the groups treated with zinc oxide (G2), (G1), and (G3), according to statistical analysis (p> 0.05). However, when it came to (p> 0.05), there was a significant decrease.

Concentration of Sperms (million /mL)

Table (3) showed that when compared to the control group (G1) and other animal groups, the group treated with 6-paradol nanoparticles (G4 and G5) had a significant increase in sperm concentration (p 0.05), while there was a significant difference in sperm concentration (p 0.05) between (G4) and (G5) (G5). Furthermore, when compared to the control and other groups, there was a significant decrease in sperm concentration in animal group (G3) (p> 0.05). Compared to the control group, there was no significant difference in sperm concentration in animal groups treated with (G2) (p 0.05).

Percentage of Sperms Motility (%)

As demonstrated in Table, there was no difference in sperm motility between the animal groups treated with (G2) and the control group (G1) in this investigation (3) (p = 0.04). Simultaneously, there is no difference in sperm motility between (G4) and (G5) at p> 0.05 (G5). Furthermore, sperm motility in the animal group (G3) was significantly reduced (p> 0.05) when compared to the control group and the 6-paradol-treated groups (G4,G5) (G2). Compared to the control group, the animal group treated with 6-paradol nanoparticle (G4,G5) demonstrated a substantial increase in sperm motility (p> 0.05) (G1). Between (G6) and (G7), there is a considerable difference in sperm motility (p> 0.05).

Percentage of Sperms Abnormalities (%)

Compared to the control and 6-paradol-treated groups, the aberrant sperm ratio for animal group (G3) rose considerably at p> 0.05. (G4,G5, and G2). Furthermore, the animal group treated with 6-paradol nanoparticles (G4,G5) had a considerably lower aberrant sperm ratio than the control group (p> 0.05). (G1). At p> 0.05, the abnormal sperm ratio of amidst (G4) and the aberrant sperm ratio of amidst (G5) did not differ. (G5)

Percentage of Sperms Viability (%)

As indicated in table, the percentage of sperm viability in the animal group (G3) was significantly lower at p> 0.05 when compared to the control group (G1) and other groups (3). Furthermore, when compared to (G1,G2), The sperm viability percentage of the animals treated with 6-paradol nanoparticles (G4,G5) increased significantly (p> 0.05). Simultaneously, the percentages of sperm viability in the middle (G4) and overall sperm viability (G4) grew dramatically (p> 0.05). (G5).

DISCUSSION

A study[12] exhibited a considerable reduction in average bodyweight regarding the STZ-induced diabetes group. The rise in body weight is significant after STZ were given cinnamon, ginger, or a combination of cinnamon and ginger, which agrees with our findings. The results related to body weight, liquid and food intake have been summarized and evaluated, while the initial body weights have been comparable in diabetic and normal groups, while the final body weights are considerably reduced in diabetic controls when compared with normal control. On the other hand, the body weights witnessed considerable differences in 6-paradol treated diabetic rats.

The amounts of fluid and food intake have been considerably higher in the diabetic group compared to normal[13], which deal with our results. Reduced body weight and increased food consumption have been seen in STZ-induced diabetic rats, indicating polyphagia and weight loss due to tissue protein breakdown.[14] A study[15] indicated that the decreased body weight in diabetic rats might be because of catabolism and dehydration of proteins and fats which also agrees with our results. In diabetic rats, administration of 6-paradol enhanced the body weight. It reduced the consumption of food and this might be because of the better control regarding hyperglycemic state in diabetes rats decreased level of sugar blood might enhance the weight of the body in the diabetes rats via STZ[16] which also agree with our results because it showed an increase in the body weight when treated rats by 6-paradol and decrease in the body weight by treated with STZ. The reason for the reduction in body weight is due to the effects caused by STZ due to oxidative stress and the process of oxidation of fats, which causes an imbalance in the functions of the organs, as free radicals affect the cells and tissues of the body, especially the organs responsible for metabolism, specifically the liver, in addition to nucleic acids, the high fat oxidation in the blood It causes an imbalance in the metabolic processes from the destruction of proteins and fats and then a decrease in weight[17] perhaps agree this results with our results. and also improvement in the groups treated with 6-paradol because it a flavonoids possessing the mitigating effect of oxidative stress, which in turn affects the improvement of the metabolic rate and the increase in the metabolism rate. Promote health, reduce the risk of disease, and act as antioxidants18 that agree with our results. The considerable rise in the absolute weight related to epididymis and testis might thus be because of the increase in androgen synthesis indicated via considerable rise testosterone concentration on experience rats. In addition, androgen were vital for growth, development and normal functions regarding the male accessory reproductive glands and testes, while research showed that the levels are positively-associated to the weight of testes and epididymis.[19,20] may be match with our results. This increase in reproductive organ weight is consistent with previous research that found an increase in testicular weight in rats given Z. Officinale for an

Table 1: Effect of 6-paradole in body and testes weight in rats induced diabetes by STZ

Weights Groups	*Body weight/g*	*Testes weight/mg*	*Epididymis weight/mg*
G1	41.14 ± 0.54 d	554.87 ± 7.38 c	227.38 ± 11.78 bc
G2	40.67 ± 0.47 de	552.39 ± 9.65 c	221.99 ± 10.31 c
G3	24.27 ± 0.32 f	538.26 ± 30.65 d	202.49 ± 14.08 d
G4	47.38 ± 0.61 a	587.52 ± 10.98 a	250.19 ± 7.57 a
G5	45.65 ± 0.43 b	582.38 ± 6.99 a	243 ± 3.86 a
G6	43.37 ± 0.41 c	564.57 ± 28.88 cb	233.89 ± 6.73 b
G7	41.25 ± 0.39	574.78 ± 17.40	230.90 ± 5.57
LSD	1.58	17.3	8.51

Numbers = Mean + Standard Error
Different letters indicate a statistically significant difference (p 0.05)) G1= Control group, which received only one DW injection every day for 60 days, G2 = Control group given zinc oxide at a rate of 20 mg/kg/day, G3 = induced diabetes group (60 mg/kg STZ, intraperitoneal injection), G4= diabetic group induced by (STZ) injected at a rate of 20 mg/kg/day Nano 6-paradol
G5= diabetic group induced by (STZ) injected at a rate of 40 mg/kg/day Nano 6-paradol.

Table 2: Effect of 6-paradol on concentration of hormone in rats induced diabetes by STZ

Hormones Groups	*FSH (mIu/mL)*	*Testosterone (ng/mL)*	*LH (mIu/mL)*
G1	1.09 ± 0.12 c	1.85 ± 0.07 b	1.46 ± 0.22 c
G2	1.03 ± 0.75 c	1.79 ± 0.08 b	1.39 ± 0.74 cd
G3	0.91 ± 0.11 d	0.81 ± 0.28 c	0.93 ± 0.32 d
G4	3.99 ± 0.90 a	2.01 ± 0.06 a	2.04 ± 0.26 a
G5	2.82 ± 0.64 b	1.97 ± 0.30 a	1.87 ± 0.19 ab
G6	1.28 ± 0.46 c	1.89 ± 0.10 ab	1.52 ± 0.36 bc
G7	1.34 ± 0.36 c	1.88 ± 0.07 ab	1.51 ± 0.41 bc
LSD	0.51	0.15	0.42

Numbers = Mean + Standard Error
Different letters indicate a statistically significant difference (p> 0.05)), G1= Control group, which received only one DW injection every day for 60 days, G2 = Control group given zinc oxide at a rate of 20 mg/kg/day, G3 = induced diabetes group (60 mg/kg STZ, intraperitoneal injection), G4= diabetic group induced by (STZ) injected at a rate of 20mg/kg/day Nano 6-paradol
G5= diabetic group induced by (STZ) injected at a rate of 40mg/kg/day Nano 6-paradol.

Table 3: Effect of 6-paradol on semen parameters in rats induced diabetes by STZ

Sperms Groups	Sperms con (million/mL)	Sperms motility %	Sperms abnormality %	Sperms Viability %
G1	81.64 ± 0.97 d	10.30 ± 11.30d	73.54 ± 3.40 b	86.46 ± 0.75 d
G2	80.55 ± 1.20 d	10.43 ± 0.98 b	73.41 ± 4.10d	85.78 ± 1.72d
G3	53.05 ± 2.14e	14.65 ± 0.73e	43.36 ± 2.91a	62.26 ± 1.86e
G4	89.57 ± 1.27a	7.79 ± 1.01a	88.64 ± 3.38d	91.73 ± 1.40a
G5	G486.68 ± 1.37b	7.84 ± 1.17a	85.75 ± 2.52d	89.82 ± 0.34b
G6	G584.54 ± 1.25c	8.76 ± 1.14 b	82.10 ± 4.04 c	87.45 ± 3.48 c
G7	G684.90 ± 0.88 bc	8.74 ± 0.90 c	79.17 ± 5.17 c	88.95 ± 1.24c
LSD	1.59	3.32	0.87	1.2

Numbers = Mean + Standard Error
Different letters indicate a statistically significant difference (p> 0.05)), G1= Control group, which received only one DW injection every day for 60 days, G2 = Control group given zinc oxide at a rate of 20 mg/kg/day, G3 = induced diabetes group (60 mg/kg STZ, intraperitoneal injection), G4= diabetic group induced by (STZ) injected at a rate of 20 mg/kg/day Nano 6-paradol, G5= diabetic group induced by (STZ) injected at a rate of 40mg/kg/day Nano 6-paradol.

8-days period, along with a rise in testosterone levels. Yet, the effects because of only the changes in testosterone must result in a rise in all accessory organs' weight; thus, there is high importance that the increased weight of the epididymis and testis is reflecting the dual effects of the increased levels of testosterone and sperm that is contained in such organs also agree with our results.[21] There were demonstrated the data clearly indicates a decrease in the testicular weight following treatment with STZ with respective doses, statistical analysis shows that there has been a significant reduction (p> 0.05) in testicular weights in all groups compared with the control group and to each other these results also matching with our results because illustrated increase the weight of testis and epididymis when treated by 6-paradol. The reason of decreased in weight of the epididymis and testis may be due to the toxic effects of free radicals generated from the use of the drug on the tissues of the testis and epididymis, as the free radicals interact with the lipids that make up cell membranes, thus producing MDA, which is considered one of the indicators of oxidation.[22] It causes degeneration, necrosis and cell death, especially the spermatocyte cells inside seminiferous tubules. It also lead to degeneration and non-proliferation of Leidg's cells, which causes a reduction in the diameter of epididymis tubules and seminiferous tubules. It is the functional and structural unit of epididymis and testis, perhaps the cause of the decrease in the weight of the epididymis in males rats which treated with STZ is a decrease in the epithelial cells lining the epididymis.[23] In other researches, the results indicated that the ginger might be increasing the caudal of epididymis sperm reserves (CESR) related to rats via the increase in the testicular spermatogenesis. It is reported that administra-tion of ginger could be conquest the reproductive toxicity of the STZ on sperm's count. The administrations of finger increased the testosterone levels in rats even despite receiving 5 mg/kg daily of the stz compared to the stz treated groups or control groups.[24] Research utilizing the pure compounds related to plant origin improved testosterone concentration in the diabetic animal models. One of the phenols, curcumin, increased testosterone concentration in certain diabetic rats after treatment for 8 weeks.[25] Flavonoids such as rutin and quercetin enhanced the concentration of testosterone in specific diabetic rats.[26, 27] Research conducted by showed that administering ginger at 100mg/kg for each rat and 50mg/kg for each rat for 20 successive days did not show significant effects on the concentration of FSH and LH in the serum between control and treated group. Yet, the FSH and LH in the control group have been the levels of total testosterone were significantly increased (p> 0.05) in animals receiving 100 mg/kg for each rat, ginger compared to the controls these result do not agree with our results. STZ-induced diabetes led to a reduction in the levels of testosterone, when putting to comparison the healthy controls against the STZ-treatment group It has been shown that all three treatments (cinnamon, ginger, and combined cinnamon and ginger) result in a substantial increase in total testosterone levels, with combined cinnamon and ginger having the highest increase (p> 0.05).[28] The STZ-induced diabetes control group had significantly lower serum FSH and LH levels (p> 0.05). Furthermore, the STZ-treatment groups with cinnamon, ginger, and combination cinnamon and ginger all showed a substantial increase in FSH and LH levels, with combined cinnamon and ginger showing the greatest increase (p> 0.05). [29] perhaps deal with our results. Yet, diabetic rats that have been given ginger exhibited a significant ameliorating effect, increased FSH and LH levels, damaged sperm parameters, and rise level of the antioxidants with a decrease level of (MDA), then a positive fertility outcome (p> 0.05). The research specified that ginger could have synergetic protection effect on the testes, this study showing the positive synergetic effect ginger on the spermatogenesis in the diabetic rats. Also, this has been in accordance with other research results[30,31] showing similar destructive results in the diabetic individuals. Even though

there were a few discussions over the approaches playing a role in such changes, oxidative stress is considered the major key factor for most changes.[32]

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