POTENTIALS PROTECTIVE EFFECT OF RUTA GRAVEOLENS AS ANTIOXIDANT ON CISPLATIN INDUCED TESTICULAR DAMAGE IN ALBINO RATS

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ABSTRACT

The present study was established to investigate that *Ruta graveolens'* ability to alleviate cisplatin-induced testicular dysfunction in albino rats. Thirty rats were randomly divided into six groups (A–F) of 5 rats each: Group A which attended as control (-) received water; Group B was intraperitoneally (i.p) injected 10 mg kg^{-1} bw. cisplatin on 6 weeks as control (+). Groups C and D were assumed 50 and 100 mg of *R. graveolens* via oral administration, respectively, for ٦ weeks and then exposed to i.p administration of 10 mg kg^{-1}bw cisplatin on the 6^{st} week ; Groups E and F received 10 mg kg^{-1} bw of cisplatin intraperitoneally and then recieved 50 and 100 mg kg^{-1} bw of *R. graveolens* for 6 weeks orally. Cisplatin-exposed Group B rats had decreased sperm characteristics and higher sperm morphological abnormalities, as well as altered histological architecture of seminiferous tubules and lower glutathione (GSH) levels in the testes. These parameters in *R. graveolens* alone treated Groups C and D were not markedly different compared with negative control group ;such as sperm count recorded **102.54±3.91** compared with **146.25±3.12** in the control (-) and **56.41±4.10** in the control (+). The rats with the combined treatment in Groups E and F showed significantly improved sperm parameters, testicular histology architecture and antioxidant enzymatic activities. Conclusively, *R. graveolens* has protective potential against cisplatin damage

Keywords : cisplatin, *Ruta graveolens*, testis, male albino rats

INTRODUCTION

Cisplatin (CP) is a DNA alkylating anti-neoplastic drug created from platinum that is commonly utilised as a front-line adjuvant therapy for malignancies such as testicular, gut, stomach, head, neck, ovarian, cervical, germ cell tumours, and non-small cell lung carcinoma ***(Yildirim et al.,2011).*** Although the use of CP in the treatment of testicular cancer, even at an advanced stage of the disease, has encouraging results, it is also associated with undesired side effects such as testicular weight loss, azoospermia, and transient or permanent loss of male reproductive capability ***(Türk et al.,2008)***. Spermatogenesis is a complex process that is influenced extensively by hormonal levels and environmental factors, particularly temperature. Sertoli cells, Leydig cells, and peritubular cells are among the testicular cells involved in this occurrence ***(Huleihe et al.,2004 and Yamaguchi et al.,2008)***. Because of its alkylating properties, CP therapy inhibits nucleic acid synthesis in germ cells, particularly in spermatogonia ***(Seaman et al.,2003)***. Damage to Leydig cells caused by CP resulted in testosterone secretion suppression ***(Lirdi et al.,2008).*** The pathogenesis of reproductive abnormalities caused by CP exposure is commonly related to oxidative stress, which causes the antioxidant immune system to deteriorate.Within the human body protection against oxidative stress is achieved by self-defense enzymes that catalytically remove the free radicals and other reactive species. Superoxide dismutase, catalase, and glutathione peroxidase are examples of these enzymes ***(Farias-Silva et al.,2007),*** CP, on the other hand, inhibits the activity of these enzymes, causing oxidative damage in testicular tissue. Chemotherapeutic treatments are currently non-selective in their potency and kill rapidly dividing cells, including cancer, normal cells, and stem cells. Such harmful substances also affect spermatogenic cells and cause infertility in men ***(Chirino and Pedraza-Chaverri,2009)***. Antioxidant supplementation may be effective in reducing cisplatin-induced toxicity, according to a growing body of research. ***(Ali et al.,2006 and Yagmurca et al.,2007).*** As a result, developing combinatorial medicines that minimise CP resistance

while minimising its negative effects is critical. Plants have a variety of elements that can help avoid oxidative stress-related illnesses, such as male reproductive diseases ***(Shah et al.,2014)***, As a result, it's regularly included in recipes with chemotherapy medications to help safeguard against their negative effects ***(HemaIswarya and Doble, 2006)***. Flavonoids are potent antioxidants that prevent lipid peroxidation and platelet aggregation ***(Lirdi et al., 2008),*** protect the tissue from free radicals by direct scavenging ROS, reactive nitrogen species (RNS), and activating antioxidant enzymes.

Ruta graveolens (R. graveolens) has long been used in folk medicine to cure a variety of ailments, including eye difficulties, rheumatism, dermatitis, pain, and a variety of inflammatory disorders ***(Ratheesh and Helen,2007).*** A variety of chemical compounds have been identified from various portions of the plant, including alkaloids, coumarins, volatile compounds, terpenoids, flavonoids, and furoquinolines ***(Kuzovkina et al.,2004).*** Additional pharmacological applications of R. graveolens have been discovered in contemporary pharmaceutical trials, including antioxidant and antiinflammatory properties ***(Ratheesh and Helen, 2007)***, antinociceptive and antipyretic ***(Loonat, Amabeoku,2014)*** antiulcerogenic***(Tarique et al.,2016)***, antidiabetic, antibacterial ***(Toserkani et al.,2011)*** and antifungal ***(Meepagala et al., 2005)*** as well as antiandrogenic effects ***(Khouri et al.,2005)***.

The goal of this study was to see if ethanolic extracts of S. officinalis and R. graveolens could protect albino rats from testicular and cardiac toxicity caused by two regularly used insecticides, chlorpyrifos and methomyl. With the protective benefits of *R. graveolens* in mind, this study was conducted to assess *R. graveolens'* ability to protect against CP-induced histamine release.

The present study aimed to estimate the protective role of *R. graveolens* on the improvement of reproductive function in cisplatin induced toxicity of testes in male albino rats.

Materials and Methods

1-chemicals:-

CP injection (Sigma-Aldrich, St. Louis, MO, United States of America) was dissolved in saline and a dose of 10 mg/kg body weight of CP was chosen based on previous research to produce testicular toxicity ***(Afsar et al.,2015).***
R. graveolens were obtained from Experimental Station of Medical Plants (ESMP), Faculty of Pharmacy, Cairo University.

Preparation of Ethanolic Extracts of R. graveolens

The leaves of and *R. graveolens* were washed and dried in good aerated shaded area. The dried leaves were powdered by an electric grinder. The powder of *R. graveolens* was soaked in absolute ethyl alcohol for 72 hours and the mixture was filtered. The solvent in the filtrate was evaporated by rotatory evaporator at 50^{o}C and high pressure. The obtained viscous extract was kept in deep freezer until used.

2- Experimental animals:-

Male adult albino rats (30) (60 days- old, weighing 130:150g) were collected from the National Research Center's animal house in Cairo, Egypt and fed on a basal diet for eight days. The basal diet consisted of corn starch 70%, casein 10% corn oil 10%, salt mixture 4%, vitamin mixture 1% and cellulose 5% according to (AOAC, 2005). Rats were raised and kept in an air-conditioned animal housing under particular pathogen-free conditions, with a 12:12 h daylight/dark cycle and unlimited access to food and water. Animal facilities followed and supervised all ethical guidelines for animal treatment. All animal experiments received approval from the animal care committee, National Research Center.

3- Experimental design:-

30 male albino rats were divided into 6 groups as follows: -

A. Control: rats orally received water (5 ml kg^{-1} bw) for 6 weeks.

B. Cisplatin (CIS): rats were given (10 ml kg^{-1} bw) single dose of CIS intraperitoneally on the 6st weeks of the experiment as described by ***Amin et al. (2012).***

C. 50 mg *R. graveolens*: rats received (50 ml kg^{-1} bw) of *R. graveolens* for 6 weeks orally and then administered 10 ml kg^{-1} bw of cisplatin intraperitoneally on the 6st week.

D. 100 mg *R. graveolens*: rats received 50 ml kg^{-1} bw of *R. graveolens* for 6 weeks orally and then administered 10 ml kg^{-1} bw of cisplatin intraperitoneally on the 6st week.

E. 50 mg *R. graveolens*: rats received 10 ml kg^{-1} bw of cisplatin intraperitoneally and then recieved 50 ml kg^{-1} bw of *R. graveolens* for 6 weeks orally.

F. 50 mg *R. graveolens*: rats received 10 ml kg^{-1} bw of cisplatin intraperitoneally and then recieved 100 ml kg^{-1} bw of *R. graveolens* for 6 weeks orally.

Five days after the administration of cisplatin, the rats were sacrificed for the evaluation of biochemical and histological variations in the testicular tissue. The mean body weights were noted once a week during the experimental period.

Sperm count

Five pairs of caudal epididymis were minced in distilled water and filtered through a nylon mesh to assess epididymal sperm count. As detailed by Pant & Srivastava (2003), the spermatozoa were counted using a haemocytometer and the enhanced Neubauer (Deep 1/ 10 m; LABART, Munich, Germany) chamber.

Biochemical assays

Hormone analysis Concentration of LH and FSH in the serum of different treatment groups were estimated through GenWay Biotech, Inc. Immunoassay Test Kits

Five right testes were homogenised in 50 mm Tris–HCl buffer (pH 7.4) containing 1.15% potassium chloride, and the homogenate was centrifuged at 10 000 g for 15 min at 4 °C. The supernatant was collected for the evaluation of Lipid peroxidation was quantified as MDA following the method defined by ***Farombi et al. (2000)*** and expressed as lm MDA g^{-1} tissue. CAT activity was resolute as defined by ***Aebi (1974)*** and expressed as units mg^{-1} of protein. GSH was estimated at 412 nm using the method designated by ***Jollow et al. (1974).***

Statistical analysis

Statistical analysis was passed out using one-way analysis of variance, followed by Tukey's post hoc test for multiple comparison. The results were expressed as group mean standard error of mean, while the level of significance was $P < 0.05$.

Results& Discussion

In the present research, measured several hormonal,biochemicals, and histological parameters correlated to testicular toxicity and oxidative stress in the testis tissue to assess the protective effect of *R. graveolens* against Cis common effective antineoplastic agents quite used in the treatment of numerous types of cancers including urogenital system carcinoma. However, Cis has side effects such as nephrotoxicity, ototoxicity, cardiotoxicity, hepatotoxicity,and gonadal toxicity (***Hassen et al.,2021)***.

Body weight:

Data are given in table 1, proved that the average body weights of Cis group recorded a very highly significant decrease

($p < 0.05$) as compared to the control group. At the same time the average body weights of Cis rats treated with either R(LD)+Cis or R(HD)+Cis revealed a highly significant increase ($p < 0.05$) as compared to Cis group. Moreover, data showed a very highly significant increase in the body weight gain of Cis group treated with both Cis+R(LD)and Cis+R (HD) in relation to Cis group.

The present study revealed a significant decrease in body weight of male albino rats given Cis. Similar observation was recorded by ***Hassen et al.,2021*** who used Cis intraperitoneal in rats and observed a decrease in body weight of rats.

Table 1: Effect of cisplatin and different treatments of *R. graveolens* on body weight.

Groups / Parameters	Control A	CIS B	R(LD)+CIS C	R(HD)+CIS D	CIS+R (LD) E	CIS+R (HD) F
Body weight gain (g)	***244.84 ± 8.80***	***130.79 ± 8.42***	***198.79 ± 8.42****	***201.77 ± 21.55****	***155.11 ± 19.19 ****	***176.77 ± 21.55 ****

(LD: low dose, **HD**: high dose)

Values are presented as mean ±SEM

*: statistically significant compared to corresponding value in control group ($P<0.05$)

Changes in Sperm Parameters

The data shown in Table 2 exhibited a significant ($P < 0.05$) reduction in live/dead ratio (L-D), sperm count, and motility with accompanied increased percentage of morphologically after treatment with Cis (B group) relative to the control group. On the other hand *R. graveolens* pretreatment at doses of 50 and 100 mg kg/ bw significantly ($P < 0.05$; $P < 0.01$, respectively) ameliorated these altered sperm parameters in a dose-dependant manner in

Groups C and D rats, respectively, relative to Group B. Interestingly, Groups E and F rats that did not receive pretreatment with graded doses of *R. graveolens* presented no significant difference ($P < 0.05$) in the values of sperm parameters compared with Group B . (table 1).

In the current investigation, Cis administration contributed to a reduction in sperm count as a result of Cis toxic side-effects, resulting in a diminished testicular activity. These findings agreed with several documentations on the adverse effects of Cis on sperm characteristics. The formation of free radicals and diminished Cis-induced antioxidant enzymes result in a fast loss of intracellular adenosine triphosphate (ATP), impairing sperm motility and viability ***(Türk et al.,2008)***. Also, reducing sperm motility and increasing abnormal sperm rate in rats treated with cisplatin could be caused by lipid peroxidation of unsaturated fatty acids in the sperm plasma membrane, resulting in loss of fluidity and function ***(Ateşşahin et al.,2006).***

Graded doses of *R. graveolens* pre-treatment offered marked protection against this Cis toxicity dose dependently.

Table 2: Effect of cisplatin and different treatments of *R. graveolens* on sperm count.

groups / parameters	**Control A**	**CIS B**	**R(LD)+CIS C**	**R(HD)+CIS D**	**CIS+R (LD) E**	**CIS+R (HD) F**
Sperm count (10^6 mm^3/cell)	**146.25±3.12**	**56.41±4.10**	**97.56±3.54***	**102.54±3.91***	**77.14±2.15**	**82.14±2.65***

(**LD**: low dose, **HD**: high dose)

Values are presented as mean ±SEM

*: statistically significant compared to corresponding value in control group ($P<0.05$)

Hormone Results

The results of T, LH and FSH in the control and other studied groups are illustrated in Table (3). Indicating that Cis administration altered the secretion of reproductive and pituitary hormones. Cis inoculation considerably (p0.01) lowered T, LH, and FSH concentrations, which were significantly improved (P0.05; P0.01, respectively) following *R. graveolens* Cis inoculation considerably (p0.01) lowered T, LH, and FSH concentrations, which were significantly improved (P0.05; P0.01, respectively) following *R. graveolens*, however the hormonal concentrations did not restore to normalized control values in Groups E and F rats did not receive pretreatment with graded doses of *R. graveolens*.(table3)

Serum gonadotropin releasing hormone (GnRH) including LH, FSH levels aid in making conclusions regarding reproductive pathologies. The decrease in serum T concentration in drug-treated animals indicates either a direct effect of the chemical on Leydig cells or an indirect effect via changes in hormonal regulation of the hypothalamic-pituitary axis (HPA) owing to oxidative stress. ***(Latif et al.,2008).*** It has also been found that abnormal intratesticular testosterone concentrations hinder spermatogenesis. ***(Azu et al., 2010)***. LH stimulates the generation of testosterone in Leydig cells by activating FSH to interact with Sertoli cells and stimulate spermatogenesis ***(Guideline, 2001)***. Cis displayed a notable decrease of T, LH, and FSH concentrations in serum, according to the results of the current experiment. T has already been shown to be suppressed by Cis. Administration of *R. graveolens* results in potential intensification of lowered levels of T, LH and FSH and might result in regulation of HPA. Pretreatment with *R. graveolens* in Groups C and D rats, more significantly maintained serum hormone levels compared to *Cis* plus *R. graveolens* , indicating the preventive potential of *R. graveolens*.

Table 3: Effect of Cisplatin and different treatments of *R. graveolens* on reproductive hormone.

groups / parameters	Control A	CIS B	R(LD)+CIS C	R(HD)+CIS D	CIS+R (LD) E	CIS+R (HD) F
LH (ng/ml)	**2.61±.01**	**1.23±.005**	**1.98±.004**	**2.01±.09***	**1.46±.03**	**1.84±.07***
FSH (ng/ml)	**2.11±.06**	**.97±.03**	**1.86±.06***	**1.99±.007***	**1.51±.09**	**1.65±.05**
Testesterone (ng/ml)	**4.65±.07**	**2.10±.09**	**3.05±.06***	**3.45±.04***	**2.56±.08**	**2.98±.008**

(LD: low dose, **HD**: high dose)

Values are presented as mean ±SEM

*: statistically significant compared to corresponding value in control group ($P<0.05$)

Biochemical analysis

Table 4 shows the data on the outcomes of *R. graveolens* pretreatment against Cis-induced damage of antioxidant systems and lipid peroxidation in testicular tissues. There was a significant ($P < 0.01$) decrease in the testicular catalase (CAT) and glutathione (GSH) enzymes of Group B compared with control rats. However, testicular levels of CAT and GSH enzymes of rats in Groups C and D increased significantly ($P < 0.05$) when compared to the cisplatin-treated Group B rats. Besides, lipid peroxidation raised significantly ($P < 0.01$) in Group B relative to another group. *R. graveolens* pre-treatment in Groups C and D significantly ($P < 0.01$) ameliorated the altered MDA levels when compared to Group B. The levels of the antioxidant enzymes, the CAT, GSH activity, and MDA in the *R. graveolens* treated Groups E and F rats were not significantly ($P < 0.05$) different from the Group B. (table 4)

Oxidative stress is described by an excessive reactive oxygen species (ROS) and remains a notable cause of male infertility ***(Iwasaki & Gagnon, 1992)***. Reactive oxygen formations and reactions with biological structures are usually attended by antioxidant systems **(*Riley, 1994*)**. In the current study, Cis recorded that the rat's antioxidant profile developed as testicular

MDA increased and TAC reduced, with GSH showing that enzymatic and non-enzymatic antioxidant molecules were insufficient to scavenge free radicals generated from cisplatin ***(Adejuwon et al.,2015).*** The increase in the amount of MDA may be attributed to the excess output of ROS attacking the cell membrane due to a deficiency of antioxidant enzymes ***(Nita et al.,2016).*** The decrease in their activity could be explained by the consumption of these enzymes during the transformation of free radicals into less damaging or harmless metabolites, or by the direct inhibitory effect of cisplatin on enzyme function. The testis is one of the most sensitive organs to oxidative stress and peroxidative damage, as well as low antioxidant concentration efficiency, which leads to decreased sperm vitality, motility, and infertility. ***(Beytur et al.,2012 and Hassen et al.,2021).***

In Groups C and D rats, pretreatment with R. graveolens significantly improved the damaged antioxidant defence systems in a dose-dependent manner, enhancing the profiles of cisplatin-depleted antioxidant enzymes (CAT) and intracellular GSH, as well as the level of MDA produced in the testes.These observed ameliorations are suggested to be connected to the phyto-antioxidants components particularly flavonoids in *R. graveolens* leaves. These findings are similar to earlier reports on optimizing Phyto-antioxidants benefits in alleviating cisplatin-induced testicular injury as documented by ***Jahan et al.(2018)***

It is worth discussing that the flavonoid, a group of polyphenolic compounds found mainly in plants of the Rutaceae family, have been shown to exhibit a series of biological effects among which stand out the inhibition of LPO and platelet aggregation, due to their antioxidant properties and their ability to remove free radicals and chelating divalent cations ***(Ashour et al.2017).*** *R. graveolens* was known for its free radical scavenging activity, which was revealed in the current study to be related to its phenolic and flavonoid components, which greatly increased antioxidant status and lowered lipid peroxidation.

Table 4: Effect of cisplatin and different treatments of *R. graveolens* on antioxidant and oxidative stress markers.

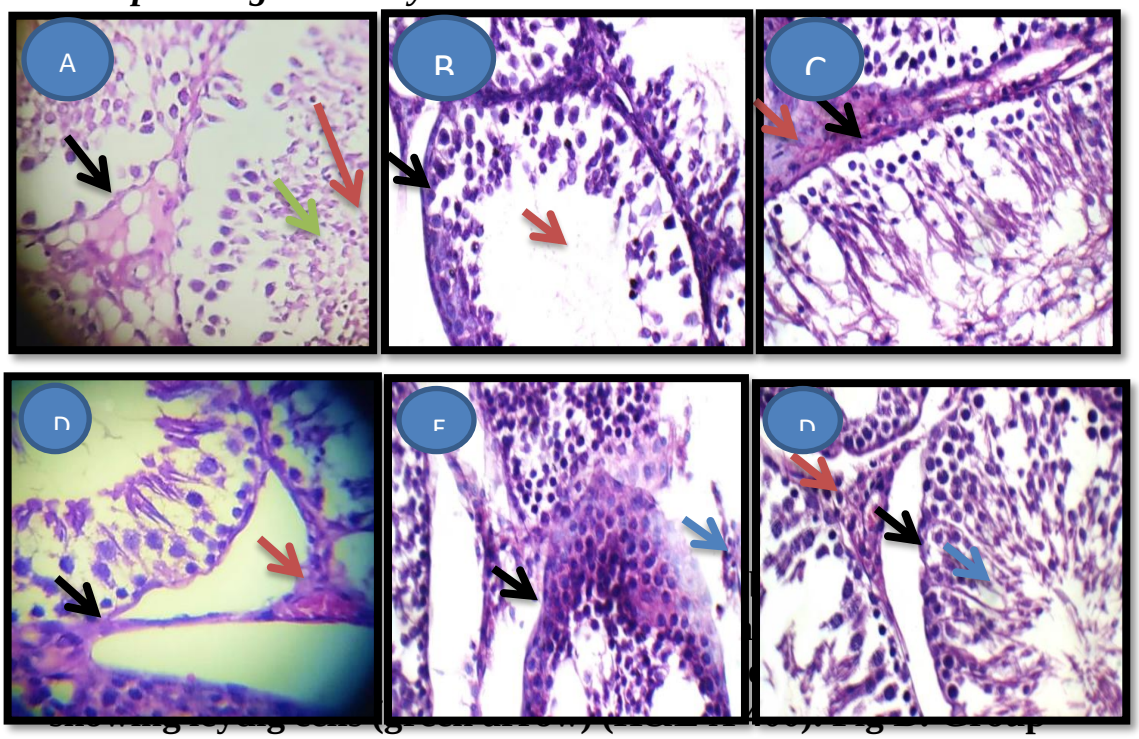
groups / parameters	Control A	CIS B	R(LD)+CIS C	R(HD)+CIS D	CIS+R (LD) E	CIS+R (HD) F
MDA (n. mol/mg)	.62±.11	2.51±.05	1.25±.10*	1.04±.16*	2.10±.15	2.06±.18
GSH (m. mol/mg)	4.65±.16	.98±.05	2.45±.15*	3.6±.26*	1.65±.14	1.98±.23*
CAT (U/min)	19.02±0.14	8.36±0.17	12.02±.09*	16.25±.18*	9.15±.15	9.99±0.24

(LD: low dose, **HD**: high dose)

Values are presented as mean ±SEM

*: statistically significant compared to corresponding value in control group (P<0.05)

Histopathological Analysis



B; rue (LD): showing tubules with mildly thick BM (black arrow), average germinal lining up to full spermatogenesis, and interstitium showing increased number of Leydig cells (red arrow) (H&E X 400). Fig C: Group C; rue (HD) : higher

power view showing tubules with mildly thick BM (black arrow), average germinal lining up to full spermatogenesis , and average interstitium with average Leydig cells (red arrow) (H&E X 400). Fig D: Group D; Cisplatin: higher power view showing tubules with thick detached BM (black arrow), marked reduction of germinal lining with few sperms (red arrow), and interstitium showing increased number of leydig cells (H&E X 400). Fig E: Group E; Cis + rue (LD): showing tubules with mildly thick BM (black arrow), mild reduction of germinal lining with moderate number of sperms , and interstitium showing increased number of leydig cells (blue arrow) (H&E X 400). Fig F: Group F; Cis + rue (HD): : higher power view showing tubules with average BM (black arrow), average germinal lining up to full spermatogenesis (blue arrow), and average interstitium with average Leydig cells (red arrow) (H&E X 400).

Conclusion

The current study substantiates that reproductive toxicity induced by *Cis* is associated with enhanced oxidative stress. *R. graveolens* as a possible antioxidant might be employed in combination with or before chemotherapeutic drug treatment to evade the related side effects. Results increase improved sperm parameters, testicular histology architecture and antioxidant enzymatic activities. Conclusively, *R. graveolens* has protective potential against cisplatin damag.

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لعشبة الروتا جرافولينز كمضاد للأكسدة علي تلف الخصيتين في التأثير الوقائي فئران الألبينو في المحدث من السيسبلاتين

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الملخص العربى

تم اجراء هذه الدراسة لمعرفة قدرة عشبة روتا جبرولين علي ضعف الخصية المحدث من السبلاتين في فئران التجارب. استخدم في هذه الدراسة عدد ٣٠ فأرا تم تقسيمهم عشوائيا الي ست مجموعات (A–F) "كل مجموعة تحتوى علي ٥ فئران" . المجموعة A تم تغذيتها علي غذاء اساسي وتم امدادها بالمياه. تم حقن المجموعة B بجرعة ١٠ملجم سسبلاتين /كجم وزن داخل الغشاء البروتونى واستخدمت هذه المجموعة كمجموعة ضابطة موجبة "مصابة". تم اعطاء المجموعتين C & D (٥٠ و ١٠٠ ملجم من مستخلص الروتا لمدة ٦ أسابيع ثم تم حقن فئران هذه المجموعات بالسسبلاتين بجرعة ١٠ملجم سسبلاتين /كجم وزن داخل الغشاء البروتونى. تم حقن فئران المجموعتين E & F بالسسبلاتين بجرعة ١٠ملجم سسبلاتين /كجم وزن داخل الغشاء البروتونى ثم تم بعد ذلك اعطائهم (٥٠ و ١٠٠ ملجم من مستخلص الروتا لمدة ٦ أسابيع). أظهرت النتائج أن فئران المجموعة B التى تم حقنها بالسسبلاتين انخفاضا في خصائص الحيوانات المنوية ، وزيادة في التشوهات المورفولوجية للحيوانات المنوية، والبنيةالنسيجية المشوهة للأنابيب المنوية، وانخفاض نشاط مستويات الجلوتاثيون في الخصيتين. في حين أظهرت نتائج المجموعتين C & D والتى تلقت مستخلص عشبة روتا جيرولين قبل حقنها بمادة السسبلاتين عدم وجود اختلاف ملحوظ بينهم وبين المجموعة الضابطة السالبة. بينما أظهرت نتائج الفئران في المجموعتين F & F تحسنا ملحوظا في تقديرات الحيوانات المنوية، وبنية الخصية وانشطة الانزيمات المضادة للأكسدة.

الكلمات المفتاحية: سسبلاتين ، روتا جبرولينز ، الخصية ، فئران