Rutin Ameliorates Docetaxel-Induced Testicular and Reproductive Dysfunction

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ABSTRACT

Docetaxel, an antineoplastic alkylating agent used to treat different types of cancer, exhibits adverse effects on testis and sperm cells. This study aimed at investigating possible protective roles of rutin against testicular and reproductive impairment caused by treatment with docetaxel in Wistar albino rats. Thirty-five male rats randomly divided into five groups (n = 7), received the following per kg body weight for 14 days: Control (physiological saline – 1 ml/kg), single dose docetaxel (30 mg/kg), rutin (100 mg/kg), low-dose rutin (50 mg/kg) + docetaxel (30 mg/kg) and high-dose rutin (100 mg/kg) + docetaxel (30 ng/kg). Body and testis weight, sperm count, motility and viability, and serum levels of sex hormones were evaluated in treated rats. Docetaxel significantly decreased final body weights of rats and percentage sperm count and motility, while increasing abnormal sperm cells. Testosterone and luteinizing hormone levels were also affected by docetaxel treatment. Pre-treatment with rutin restored percentage sperm count, motility and preserved the morphological integrity of sperm cells. Rutin also positively modulated the compromised serum hormone levels observed in docetaxel-treated rats in a dose dependent manner. In conclusion, rutin holds potential to preserve testicular function and sperm parameters negatively affected in patients undergoing chemo-therapy with docetaxel.

Keywords: Docetaxel, Rutin, Testis, Sperm Cell, Sex hormones.

Introduction

The taxane group chemotherapeutic agents are anti-microtubule agents that have been mostly used for treatment of several cancer types including lung, kidney and prostate cancer (Chen, 2023; Assunção, *et al.,* 2025). Docetaxel (DTX), a member of this group of chemotherapeutics, is a more potent semi-synthetic analogue of paclitaxel, which was first produced from 10-deacetyl baccatinIII, extracted from the needles of the European yew tree (*Taxus baccata* L) in 1986. It was first approved for the treatment of locally advanced or metastatic breast cancer by the US Food and Drug Administration in 1996 (Kenmotsu & Tanigawara, 2015; Sati *et al*., 2024). It is a taxoid cytotoxic agent that promotes tubulin assembly into microtubules, stabilizes microtubules and inhibits their depolymerization, thereby causing mitotic arrest in the G2/M phase of the cell cycle and, subsequently, cell death (van Vuuren *et al*., 2015; Baş & Nazıroğlu, 2019). DTX has been used in cancer treatments for several decades and still remains an approved primary treatment for metastatic prostate cancer, and is a standard adjunct agent in breast cancer treatment (Farha & Kasi, 2022) because of its potent and broad antineoplastic properties and favorable effects on patients' survival (da Costa *et al*., 2020; Gupta *et al*., 2023). However, despite its positive potential to systematically address certain types of cancer, its use is fast becoming limiting as a result of its attendant significant side effect. DTX chemotherapy has been reported to elicit adverse effects in normal tissues, including the testis through excessive production of reactive oxygen species (Baş & Nazıroğlu, 2019). The oxidative stress induced by this cytotoxic agent can lead to sperm DNA damage and death which ultimately compromises the reproductive function of the testis, impairing male fertility (Altintas, 2015; Ashour *et al.,* 2025).

Flavonoids are potent antioxidants that inhibit lipid peroxidation and platelet aggregation. It protects tissues from free radicals by direct scavenging reactive oxygen species (ROS), reactive nitrogen species (RNS), and activating antioxidant enzymes (Satari *et al*., 2021). Rutin belongs to the flavanol class of flavonoids and is composed of the flavonol quercetin and disaccharide rutinose. It is naturally obtained from various plant species and is also found in apple, green tea, Betula pendula leaves, and other sources. Buckwheat is a known source of natural rutin. (Narayana, 2008; Negahdari *et al*., 2021). Rutin is a strong antioxidant and has many pharmacological benefits including anti-cancer, anti-mutagenic, anti-inflammatory, myocardial protecting activities e.t.c. (Imani *et al*., 2020; Negahdari *et al*., 2021). Several studies have suggested the protective effects of rutin against reproductive toxicity as a result of its antioxidant, anti-inflammatory, anti-apoptotic and sex hormone modulating potential. These studies report that rutin detoxify reactive oxygen and nitrogen species produced in the body during the metabolism of various drugs and chemicals (Osawe & Farombi, 2018; Kandemir *et al*., 2020; Abarikwu *et al.,* 2022; AbdElrazek *et al*., 2024).

While several information exists on the male reproductive toxicity of the class of antineoplastics such as the alkylating agents, topoisomerase inhibitors, antitumor antibiotics and some selected mitotic inhibitors (Jahan *et al*., 2018; Abarikwu *et al.,* 2022; AbdElrazek *et al*., 2024), there is paucity of data on the mechanism of DTX-induced impairment in reproductive function of the testis. Furthermore, keeping in view the protective effects of rutin, this study was designed to evaluate if rutin can protect against docetaxel-induced interference with reproductive indices and testes function in rats.

Materials and methods

Drug and Chemicals

Docetaxel (Zuvitere-80; 80mg/2ml) was purchased from Tonik Pharmacy (Ibadan, Nigeria). Rutin hydrate (> 94% HPLC #207671-50-9), Enzyme linked immunosorbent assay (ELISA) kits for hormone analysis were procured from Cusabio Biotechnology, Germany. All other chemicals used were of analytical grade and were obtained from registered sales outlets.

Experimental Animals and Design

Thirty-five male albino Wistar rats (100 - 120 kg), purchased from the Department of Veterinary Medicine, University of Ibadan and maintained in plastic cages, were used for this study. The animals received humane care in accordance with the updated Guide for the Care and Use of Laboratory Animals by the National Research Council published by the National Institute of Health (NIH Publication No: 85 – 23) and approved by the Benson Idahosa University Ethics Committee (BIUREC/2026/060). Rats with similar weights were assigned to five groups (n = 7) and administered the following for 14 days, based on average weight of rats per group:

Group 1: Normal control (1ml/kg physiological saline)

Group 2: Docetaxel only (30mg/kg single dose, i.p)

Group 3: Rutin only (100mg/kg)

Group 4: Rutin (50mg/kg) + docetaxel (30mg/kg single dose, i.p)

Group 5: Rutin 100mg/kg + docetaxel (30mg/kg single dose, i.p)

50mg/kg and 100mg/kg of rutin was administered orally from day 1-14, while 30mg/kg single dose of docetaxel was given intraperitoneally on day 8.

Body weights of all experimental rats were taken on day 15 after an overnight fast. They were thereafter euthanized by cervical dislocation 24 hours after last treatments. The testis and caudal epididymis were harvested, cleared of adhering tissues and weighed. Semen was quickly collected for sperm analysis.

Semen Analysis

Examination of Epididymal Sperm Motility and Count: Sperm motility was assessed by the method described by Zemjanis (1970) and was evaluated microscopically within 2-4 minutes of collection from the caudal epididymis and later expressed as percentage. Observation was done at X 100 magnification. Epididymal sperm was counted with the aid of a hemocytometer using the improved Neubauer chamber (Deep 1/10m; LABART, Munich, Germany) as described by Pant & Srivastava (2003).

Determination of Sperm Morphology and Percentage Viability (live-dead ratio): An aliquot of semen obtained from an incision made into the lumen of the caudal part of the epididymis was mixed with 2-4 drops of 2.9% buffered sodium citrate (diluent). Sperm suspension was stained with Wells and Awa stain for morphological examination and 1% eosin B and 5% nigrosine in 3% sodium citrate dehydrate solution for live-dead ratio (Wells & Awa, 1970).

Analysis of Male Sex Hormones: Plasma testosterone was determined by RIA matched assay reagent using WHO protocol as described by Niswender *et al*. (1968). Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) were measured ELISA according to the manufacturer's (Cusabio Biotechnology, Germany) instructions.

Statistical Analysis

Statistical analyses were performed using Student T-test. Data were expressed as mean ± standard deviation (SD). A 95% confidence interval was used to determine statistically significant differences between treated and control groups. The significance level was set at $p < 0.05$.

Results

Effects of Rutin on Body and Testis Weight of treated rats

The body and testis weight of rats in each treated group are presented in Table 1. The final body and testis weight of the DTX-treated rats were significantly ($p < 0.05$) lower in comparison with the control group. There also was a significant ($p < 0.05$) reduction in percentage change in body weight of rats treated with only DTX after 14 days. Body weight reduction in DTX treated rats was significantly prevented on pre-treatment with both 50 mg/kg and 100mg/kg of rutin significantly.

Table 1: Effect of rutin on body weight and testis weight of docetaxel-treated rats.

Weights (g)	Control	DTX	RT (100)	RT(50) + DTX	RT(100) + DTX
Initial body wt.	200.00 ± 0.01	278.57 ± 5.56	165.00± 15.55	182.86 ± 8.59	177.14 ± 2.67
Final body wt.	220.71 ± 9.32	185.43± 13.20*	200.00 ± 0.01	190.00± 13.69	200.00 ± 0.01
% change in body weight	10.36	-33.43*	21.21	3.90	12.91
Testis weight	1.27 ± 0.05	1.15 ± 0.07*	1.18 ± 0.02*	1.21 ± 0.02**	1.24 ± 0.02**

DTX = Docetaxel, RT (50) = rutin (50 mg/kg); Data are expressed as mean ± SD, n = 7. *p < 0.05 compared with control, **p < 0.05 compared with Docetaxel.

Effects of Rutin on Serum Testosterone, LH and FSH levels of treated rats

The effects of rutin on serum testosterone, LH, and FSH of DTX-treated rat is illustrated below in Table 2. Serum luteinizing hormone and testosterone levels were significantly ($p < 0.05$) elevated in DTX-treated in comparison with levels of control group. Levels of these hormones were significantly ($p < 0.05$) reduced when rats were pre-treated with rutin at 50 mg/kg prior to DTX treatment compared with DTX-treated rats not pre-administered with rutin.

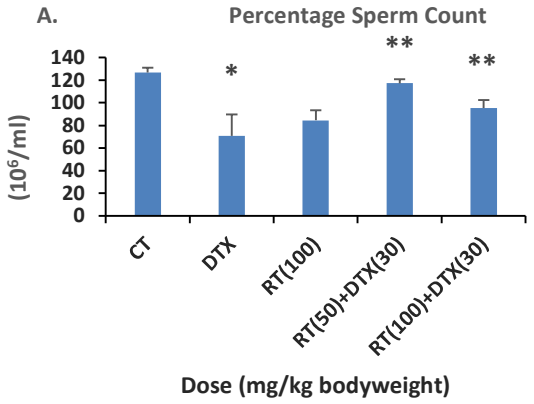
Table 2: Effect of rutin on Serum Testosterone, LH, and FSH in Docetaxel-treated rats

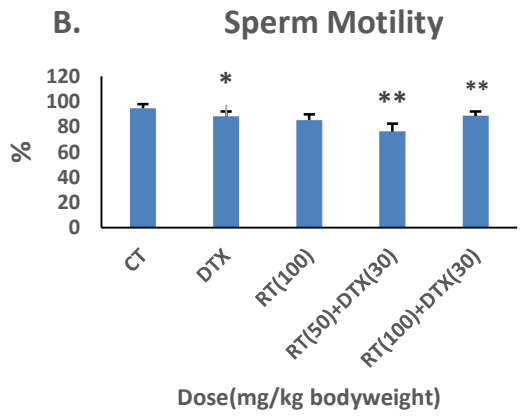
Hormones	Control	DTX	RT (100)	RT(50) + DTX	RT(100) + DTX
Testosterone (ng/mL)	6.65 ± 1.43	4.44± 0.86*	5.82 ± 2.20	2.70 ± 0.97**	6.03 ± 1.76
LH (mIU/ml)	1.18 ± 0.06	1.39± 0.14*	1.13 ± 0.30	1.16 ± 0.10**	1.15 ± 0.23
FSH (mIU/ml)	4.23 ± 0.09	4.29 ± 0.21	4.19 ± 0.99	4.31 ± 0.01	4.19 ± 0.06

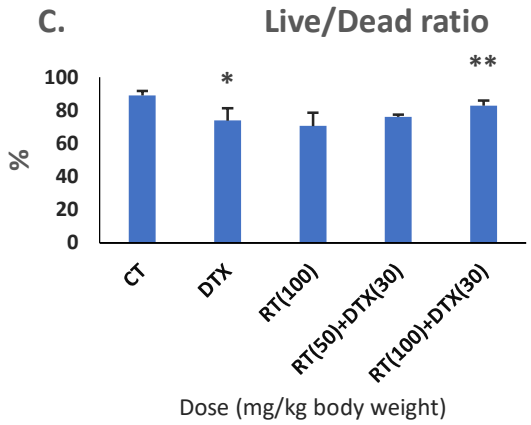
DTX = Docetaxel, RT (50) = rutin (50 mg/kg); Data are expressed as mean ± SD, n = 7. *p < 0.05 compared with control, **p < 0.05 compared with Docetaxel.

Effect of Rutin on Sperm Profile of Docetaxel-treated rats

The effects of rutin on sperm characteristics of DTX-treated rats is illustrated below in Figures 1A -D. There was a non-significant ($p > 0.05$) reduction in the percentage of motile and live sperm in DTX-treated rats when compared with the control group. However, the percentage count and motility of sperm in DTX-treated rats was significantly reduced ($p < 0.05$) in comparison with those of the control group, while there was a significant ($p < 0.05$) increase in the percentage number of abnormal sperm in DTX-treated rats compared with the control group. Pre-treatment with rutin at both 50 and 100 mg/kg body weight of rats significantly ($p < 0.05$) increased percentage sperm count and motility and decreased the number of abnormal sperm cells in the DTX-treated rats when compared with the group administered DTX alone.







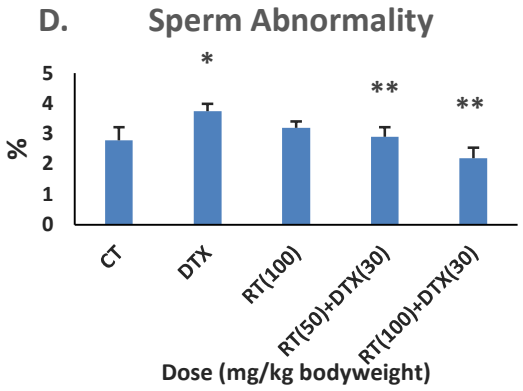


Figure 1 Effects of rutin on sperm characteristics of DTX-treated rats. DTX = Docetaxel, RT (50) = rutin (50 mg/kg); Data are expressed as mean ± SD, n = 7. *p < 0.05 compared with control, **p < 0.05 compared with Docetaxel.

Discussion

Docetaxel (DTX), though a preferred drug for treatment of different types of cancers, especially breast and prostate cancer, is reportedly toxic to the male reproductive system (Öztürk *et al.*, 2025; Ashour *et al*., 2025).

In our study, the body and testis weight of rats administered DTX alone were significantly ($p < 0.05$) reduced after 14 days of treatment. Reduction in body weight of patients undergoing chemotherapy has been consistently reported over the years (Halpen-Silveira *et al.* 2010; Takamoshi *et al.,* 2017; Doshi *et al*., 2023; Taoka *et al*., 2024). Also, our findings align with those of previous authors who report a reduction in body and reproductive organ weights, including the testis of experimental rats and mice administered chemotherapeutics as cyclophosphamide, busulfan, cisplatin (Mesbahzadeh *et al.,* 2021; Liu *et al*., 2021; Khamis *et al*., 2023), and earlier used taxanes as vincristine and vinblastine (Madhu *et al*., 2016; Veloso *et al.,* 2023). Sperm toxicity induced by DTX treatment evident in the reduced number (count) of mature sperm cells in the epididymis can also account for the reduced testis weight observed in our study. The testis is the organ for steroidogenesis and spermatogenesis; key reproductive processes regulated by the Leydig and Sertoli cells respectively. In the later stages of spermatogenesis, spermatozoa exit through the seminiferous tubule lumen of the testis through the rete testis and into the epididymis for maturation (Hess & Franca, 2015). It has been reported that DTX interferes with the development of spermatozoa. It destroys sperm membrane via lipid peroxidation caused by ROS generated during its metabolism (Baş *et al*., 2019; Ashour *et al*., 2025). DTX also prevents destabilization of microtubules, mitotic division and arrest of cell cycle in prostate cancer cells leading to apoptotic death (Baş & Nazıroğlu, 2019). Since the dynamics

of cell death in the use of chemotherapy is not limited to cancerous cells alone but affects healthy cells too, it could be possible that DTX also causes sperm death via this mechanism. This reduces the number of sperm cells in the lumen of the testis which possibly explains its reduced weight on DTX treatment. A reduced number of sperm hence migrate into the epididymis reducing epididymal sperm number (count). DTX can also cross the blood-testis barrier to exert its toxic effect directly on spermatogenesis leading to abnormal structure and death of sperm cells (Ashour *et al*., 2025). This can result in reduction in the number and count of viable (live-dead ratio) sperm while increasing abnormal features of sperm as was observed in our study. Our results are consistent with earlier reports that DTX damage sperm quality and inhibits spermatogenesis (Chatzidarellis *et al*., 2010; Altintas *et al*., 2015; Öztürk *et al.*, 2025). Hence our findings of decrease in testis weight and changed sperm characteristics potentiates a decreased reproductive capacity in males undergoing chemotherapy with DTX.

Pre-treatment with rutin both at (50 and 100) mg/kg caused a significant ($p < 0.05$) increase in sperm count, ratio of live to dead sperm and decreased the number of sperm abnormalities in comparison with DTX only treated group. Percentage of viable and motile sperm which was also significantly ($p < 0.05$) reduced on DTX treatment was only restored with 100 mg/kg rutin. The restoration of sperm function in rats pretreated with rutin confirms the protective effect of rutin against docetaxel–induced testicular dysfunction.

Furthermore, our results revealed that serum sex hormones were notably altered in rats administered with DTX alone, which is indicative of reproductive toxicity. There was a significant ($p < 0.05$) reduction in testosterone levels in rats-treated with DTX only compared with the control group, which suggests an impairment of Leydig cell steroidogenesis The gonadotoxic potential of taxanes, which generate reactive oxygen species (ROS), induce lipid peroxidation, and disrupt testicular steroidogenesis has been reported by various authors (Altintas *et al*., 2015; Baş *et al*., 2019; Veloso *et al.,* 2023). Interestingly, testosterone levels were restored to values close to those of the control group on pre-treatment with rutin (100 mg/kg). This highlights the antioxidant and steroidogenesis-preserving properties of rutin. In contrast, the lower dose of rutin (50 mg/kg) failed to prevent testosterone depletion suggesting a dose-dependent protective effect of rutin. Serum LH levels were significantly ($p < 0.05$) elevated in DTX-treated rats. This possibly reflects a negative feedback response to reduced testosterone levels. Our findings are consistent with those of earlier studies that report that chemotherapeutics such as DTX and other cytotoxics, disrupt Leydig cell steroidogenesis, reduce serum testosterone, and trigger compensatory increases in circulating LH due to altered hypothalamic–pituitary–gonadal axis feedback (Abarikwu *et al*., 2022; Ashour *et al*., 2025; Veloso *et al.,* 2023). Pre-treatment with rutin at either 50 or 100 mg/kg normalized LH levels indicating restoration of hypothalamic–pituitary–gonadal (HPG) axis function. No significant differences were observed in FSH values across all groups. Our results suggests that DTX toxicity and rutin protection were more pronounced on Leydig cell function (testosterone production) and its regulation via LH, while FSH, primarily regulated by Sertoli cells, was unaffected under these experimental conditions. Our observation that rutin interacts positively with male reproductive functioning to modulate sex hormones and preserve fertility agree with the studies of Jahan *et al.* (2018), Abarikwu *et al*. (2022) and AbdElrazek *et al*. (2024). They demonstrated that the potential of rutin to protect or modulate the adverse effects of cisplatin, busulfan, and cyclophosphamide induced male reproductive toxicity, can be

explained through its ability to act as an antioxidant, preserving sperm structure and integrity, augmenting its motility and hence function. Taken together the results from our study showed that DTX induces testicular toxicity and affects sperm negatively by interference with HPG axis functioning. Also, it was discovered that rutin can exert protective effects against DTX testicular dysfunction and male reproductive potential. Further research is recommended to investigate other possible mechanism of DTX- induced testis toxicity and the pharmacological effects of rutin in protecting sperm cells from the toxic effects of DTX.

Conclusion

Summarily, our overall findings demonstrate that DTX impairs testosterone synthesis, sperm characteristics and perturbs LH regulation in male rats, while rutin, particularly at 100 mg/kg, ameliorates these adverse effects. The ability of rutin to restore testosterone and normalize LH likely reflects its antioxidant, and hormone-modulating properties, thereby protecting the integrity of the HPG axis.

References

1. Abarikwu SO, Njoku RC, John IG, Amadi BA, Mgbudom-Okah CJ, Onuah CL: Antioxidant and anti-inflammatory protective effects of rutin and kolaviron against busulfan-induced testicular injuries in rats. Systems biology in reproductive medicine. 68 (2): 151 - 61. 2022.
2. AbdElrazek DA, Hassan NH, Ibrahim MA, Hassanen EI, Farroh KY, Abass HI: Ameliorative effects of rutin and rutin-loaded chitosan nanoparticles on testicular oxidative stress and histological damage induced by cyclophosphamide in male rats. Food and Chemical Toxicology. 184: 114436. 2024.
3. Altintas R, Ciftci, O, Aydin, M, Akpolat, N. Oguz, F, Beytur, A: Quercetin prevents docetaxel-induced testicular damage in rats. Andrologia, 47(3): 248 - 25. 2015.
4. Ashour MS, Hussein AA, Al-Shuwaili EHA, Hussin AM, Khalaf HH: Histomorphological evaluation of docetaxel effects on testes and epididymides in Wistar rats. Open Vet J. 15 (3):1140 - 1149. 2025.
5. Assunção HC, Silva PM., Bousbaa H., Cidade H: Recent Advances in Microtubule Targeting Agents for Cancer Therapy. Molecules, 30 (16): 3314. 2025.
6. Baş E, Bulut A, Kara A, Elmas L, Akbulut KG: Treatment with melatonin and selenium attenuates testicular damage of docetaxel via reducing oxidative stress, lipid peroxidation, apoptosis in rats. Andrologia. 51 (6): e13320. 2019.
7. Baş E, Nazıroğlu M: Treatment with melatonin and selenium attenuates docetaxel-induced apoptosis and oxidative injury in kidney and testes of mice. Andrologia 51(8): e13320. 2019.
8. Chatzidarellis E, Makrilia N, Giza L, Georgiadis E, Alamara C, Syrigos KN: Effects of taxane-based chemotherapy on inhibin B and gonadotropins as biomarkers of spermatogenesis. Fertility and sterility. 94 (2): 558 - 63. 2010.
9. Chen QH: Crosstalk between microtubule stabilizing agents and prostate cancer. Cancers. 15 (13): 3308. 2023.
10. da Costa R, Passos GF, Quintão NL, Fernandes ES, Maia JR, Campos MM, Calixto JB: Taxane-induced neurotoxicity: Pathophysiology and therapeutic perspectives. British journal of pharmacology. 177 (14): 3127 - 46. 2020.
11. Doshi S, Abad J, Wells A, Chawla A: Weight loss during neoadjuvant chemotherapy impacts perioperative outcomes in patients undergoing surgery for pancreatic cancer. Pancreatology. 23 (8): 1020 - 7. 2023.
12. Farha NG, Kasi A: Docetaxel. InStatPearls [Internet] StatPearls Publishing. 2024.
13. Gelmon K: The taxoids: paclitaxel and docetaxel. The Lancet. 344 (8932): 1267-1272. 1994.
14. Gupta R, Kadhim MM, Jalil AT, Alasheqi MQ, Alsaikhan F, Mukhamedova NK, Ramírez-Coronel AA, Jawhar ZH, Ramaiah P, Najafi M: The interactions of docetaxel with tumor microenvironment. International immunopharmacology. 119: 110214. 2023.
15. Halpern-Silveira D, Susin LR, Borges LR, Paiva SI, Assunção MC, Gonzalez MC: Body weight and fat-free mass changes in a cohort of patients receiving chemotherapy. Supportive care in cancer. 18 (5): 617 - 25. 2010.
16. Hess RA, de Franca LR: Spermatogenesis and cycle of the seminiferous epithelium. In: Plant TM, Zeleznik AJ, editors. Knobil and Neill's Physiology of Reproduction. 4th ed. Academic Press. p. 1140-1190. 2015.
17. Imani A, Maleki N, Bohlouli S, Kouhsoltani M, Sharifi S, Maleki Dizaj: Molecular mechanisms of anticancer effect of rutin. Phytotherapy Research. 35 (5): 2500 - 2513. 2021.

18. Jahan S, Munawar A, Razak S, Anam S, Qurat Ul Ain, Hizb Ullah, Afsar T, Abulmeaty M, Almajwal A: Ameliorative effects of rutin against cisplatin-induced reproductive toxicity in male rats. BMC Urology.18:107. 2018.
19. Kandemir FM, Caglayan C, Aksu EH, Yildirim S, Kucukler S, Gur C, Eser G: Protective effect of rutin on mercuric chloride-induced reproductive damage in male rats. Andrologia, 52 (3): e13524. 2020.
20. Kenmotsu H, Tanigawara Y: Pharmacokinetics, dynamics and toxicity of docetaxel: Why the Japanese dose differs from the Western dose. Cancer science. 106 (5): 497 - 504. 2015.
21. Khamis T, Hegazy AA, El-Fatah SS, Abdelfattah ER, Abdelfattah MM, Fericean LM, Arisha AH: Hesperidin mitigates cyclophosphamide-induced testicular dysfunction via altering the hypothalamic pituitary gonadal axis and testicular steroidogenesis, inflammation, and apoptosis in male rats. Pharmaceuticals. 16 (2): 301. 2023.
22. Liu W, Zhang L, Gao A, Khawar MB, Gao F, Li W: Food-derived high arginine peptides promote spermatogenesis recovery in busulfan treated mice. Frontiers in Cell and Developmental Biology. 9: 791471. 2021.
23. Madhu P, Reddy KP, Reddy PS: Role of melatonin in mitigating chemotherapy-induced testicular dysfunction in Wistar rats. Drug and chemical toxicology. 39 (2): 137 - 46. 2016.
24. Mesbahzadeh B, Hassanzadeh-Taheri M, Aliparast MS, Baniasadi P, Hosseini M: The protective effect of crocin on cisplatin-induced testicular impairment in rats. Bmc Urology. 21 (1): 117. 2021.
25. Negahdari R, Bohlouli S, Sharifi S, Maleki Dizaj S, Rahbar Saadat Y, Khezri K, Jafari S, Ahmadian E, Gorbani Jahandizi N, Raeesi S: Therapeutic benefits of rutin and its nano-formulations. Phytotherapy Research. 35 (4):1719 - 38. 2021.
26. Niswender GD, Midgley Jr AR, Monroe SE, Reichert Jr LE: Radioimmunoassay for rat luteinizing hormone with antiovine LH serum and ovine LH-131I. Proceedings of the Society for Experimental Biology and Medicine. 128 (3): 807 - 11. 1968.
27. Osawe SO, Farombi EO: Quercetin and rutin ameliorates sulphasalazine-induced spermiotoxicity, alterations in reproductive hormones and steroidogenic enzyme imbalance in rats. Andrologia. 50 (5): e12981. 2018.
28. Öztürk M, Bolat D, Yay A, Gürbüz P, Baran M: Evaluation of the protective and therapeutic effect of *Salvia officinalis* against testicular damage caused by docetaxel in rats. Cukurova Medical Journal. 50 (1): 137 - 144. 2025.
29. Pant N, Srivastava SP: Testicular and spermatotoxic effects of quinalphos in rats. Journal of Applied Toxicology: An International Journal. 3 (4): 271 - 274. 2003.
30. Pieniążek A, Czepas J, Piasecka-Zelga J, Gwoździński K, Koceva-Chyła A: Oxidative stress induced in rat liver by anticancer drugs doxorubicin, paclitaxel and docetaxel. Advances in Medical Sciences, 58 (1): 104 – 111. 2013.
31. Satari A, Ghasemi S, Habtemariam S, Asgharian S, Lorigooini Z: Rutin: a flavonoid as an effective sensitizer for anticancer therapy; insights into multifaceted mechanisms and applicability for combination therapy. Evidence-Based Complementary and Alternative Medicine. 2021(1):9913179. 2021.
32. Sati P, Sharma E, Dhyani P, Attri DC, Rana R, Kiyekbayeva L, Büsselberg D, Samuel SM, Sharifi-Rad J: Paclitaxel and its semi-synthetic derivatives: comprehensive insights into chemical structure, mechanisms of action, and anticancer properties. European journal of medical research. 29 (1): 90. 2024.
33. Takayoshi K, Uchino K, Nakano M, Ikejiri K, Baba E: Weight loss during initial chemotherapy predicts survival in patients with advanced gastric cancer. Nutrition and Cancer. 69 (3): 408 - 15. 2017.
34. Taoka M, Ichihara E, Yokoyama T, Inoue K, Tamura T, Sato A, Oda N, Kano H, Nakamura K, Kawai H, Inoue M, Ochi N, Fujimoto N, Ichikawa H, Ando C, Oze I, Kiura K, Maeda Y, Hotta: Frequency and significance of body weight loss during immunochemotherapy in patients with advanced non-small cell lung cancer. Cancers (Basel). 16 (23): 4089. 2024.
35. van Vuuren RJ, Visagie MH, Theron AE, Joubert AM: Antimitotic drugs in the treatment of cancer. Cancer chemotherapy and pharmacology. 76 (6): 1101 - 12. 2015.
36. Veloso EVL, Sales JES, Lucena WKB, Caldeira MEC, Araújo PPB, Silva RCM, Machado RAS, Menezes DJA: Cytoprotective effects of L-carnitine on testicular biometry and stereology of albino rats treated with vincristine sulfate in the prepubertal phase. Research, Society and Development. 11(3): e26121. 2023.
37. Wells ME, Awa OA: New technique for assessing acrosomal characteristics of spermatozoa. Journal of Dairy Science. 53 (2): 227 - 232.
38. Yang J, Guo J, Yuan J: In vitro antioxidant properties of rutin. LWT-Food Science and Technology. 41 (6): 1060 - 6. 2008.
39. Zemjanis R: Collection and evaluation of semen. Diagnostic and therapeutic technique in animal reproduction. 2: 467 - 523. 1970.
40. Zheng W, Zhang Y, Sun C, Ge S, Tan Y, Shen H, Yang P: A multi-omics study of human testis and epididymis. Molecules. 26 (11): 3345. 2021.