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Original Research Article

# Effects of Aqueous Extract of *Crassocephalum rubens* (Juss. ex Jacq.) on the Histoarchitecture of the Testis following Cisplatin-Induced Toxicity in Adult Male Wistar Rats

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ABSTRACT

Researchers have demonstrated the therapeutic properties of natural products like *Crassocephalum rubens* against a range of clinical conditions that involve oxidative stress. In this study the effect of an aqueous extract of *Crassocephalum rubens* (AECR) leaves on the potential of testicular damage from cisplatin was investigated. Thirty adult male Wistar rats (150-240 g) were randomly assigned into 5 groups (n = 6) and used for the study. Group A was administered 2 ml/kg of distilled water as the normal control; groups B and C were administered 300 mg/kg and 450 mg/kg AECR, respectively, for 14 days; and cisplatin (5 mg/kg) was administered on days 7 and 14 to both groups. Groups D and E received 450 mg/kg AECR and 5 mg/kg of cisplatin, respectively, on days 7 and 14. Cisplatin and extract administration was done intraperitoneally and orally, respectively. Testicular tissue histology was assessed using Hematoxylin and eosin procedures. Statistical data were analysed using ANOVA and the tukey test. There was no statistically significant difference ($p = 0.3405$; $F = 1.193$) in the body weight change when all groups were compared to the control. Testicular weight showed a statistically significant difference in weight reduction ($p< 0.0001$; $F = 16.85$) in groups D and E Histological evaluation showed severe histoarchietctural derangement in testicular morphology, with no clearly distinguishable tubular lumen, in the cisplatin only group, while these were ameliorated in the extract treated groups. In conclusion, AECR at 300 and 450 mg/kg possesses protective effect against cisplatin-induced testicular toxicity.

***Keywords:*** Testes, Testicular damage, Wistar rats, *Crassocephalum rubens*, Cisplatin, histological assessment.

## Introduction

Cancer chemotherapy originated between the 1940s and 1950s, when mustine hydrochloride (mustard gas) was discovered to demonstrate anti-cancer effects.[1] By 1960, it was evident that alkylating drugs alone, even when taken over lengthy periods of time, would not cure cancer, and that compounds with distinct anti-tumour activities and therapeutic spectrum needed to be identified and tested.

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Inorganic metal-based compounds played a little role until Rosenberg and Van Camp discovered significant anti-cancer action in specific platinum coordination compounds in 1969. After some toxicological challenges the first platinum medicine, cisplatin, has shown to be an effective first-line treatment for a variety of tumours and has been licenced by both the governments of the UK and the US[1] Cisplatin is used in children to treat haematological tumors, and in adults to treat several solid tumours.[2,3] One of the most effective chemotherapy drugs available is cisplatin, and its introduction in the 1970s had a significant impact on the prognosis of various cancers.[4,5] Unfortunately, because this medicine is mainly unspecific, dosing frequently results in long-term tissue damage.[6] However, the use of naturally occurring plant-based antioxidants is being promoted to reduce the toxicity of cisplantin.[7,8] Oxidative and nitrosative stress are terms used to describe the detrimental and unfavourable effects of free radicals that can cause cellular damage.[9-11] Natural products such as Crassocephalum rubens have been shown to have therapeutic properties against a variety of clinical conditions involving oxidative stress. *Crassocephalum rubens*, commonly known as Yoruba bologi, is an erect, a little bit succulent annual herb that grows up to 180 cm tall.[12] Its leaves have been studied for antiheminthic,

antiinflammatory, and other medicinal activities.[13,14] *C. rubens* leaves contain biactive substances including tannins, coumarins, flavonoids, proanthocyanidin, mucilage, reducing chemicals, and steroids, according to a phytochemical analysis.[15] The aim of the current study is to evaluate the protective effect of an aqueous extract of *Crassocephalum rubens* on cisplatin-induced testicular injury in adult male Wistar rats.

## Materials and Methods

*Study location*
The study was carried out at the Animal House of the Anatomy Department, Ladoke Akintola University of Technology (LAUTECH), Ogbomoso, Oyo State.

*Chemicals and instruments*
Cisplatin, standard rat feeds and clean water, grinder, plastic cages with iron nettings, saw dust (litter), weighing balance, syringes, cannula and needles of various sizes, measuring cylinder and plastic specimen bottles, sample bottles, distilled water, water bowls and feeding plates, reflux apparatus, dissecting blades, dissecting board and hand gloves, bouin's fluid, 40% formaldehyde, cotton wool, tissue cassette, graded alcohol (50%, 70%, 90% and absolute alcohol), hot plate, water bath, xylene, paraffin wax, embedding mould and pot, DPX mountant, haematoxylin and eosin stain, Microscope (light), camera, rotatory microtome, and Freezer. Cisplatin was procured from AKOL Pharmaceutical Company, Ogbomoso, Oyo State.

*Plant material collection and classification*
Fresh leaves of *C. rubens* were collected from a cultivated farm in Ibokun, Osun State, Nigeria, on 1st April, 2021. The plant leaves were identified and authenticated by a taxonomist in the herbarium of the Department of Pure and Applied Biology, LAUTECH; and a specimen (voucher number LAU864) was deposited.

*Preparation of the aqueous extract*
The leaves were air-dried until they were completely dried. Dryness was ascertained when the leaves attained a constant weight. The dried leaves were pulverised into powder form by the use of a mechanical grinder. About 100 g of the powdered leaves was dissolved in 1L of distilled water inside a closed container for 72 hours. The mixture was then sieved using muslin cloth, and the filtrate was heated in a rotatory evaporator at a temperature of 50$^{o}$C which extracted the *Crasscephalum rubens* concentrate.

*Experimental animals*
Thirty male Wistar rats with weight ranging between (150-240 g) were procured from the animal house, Department of Anatomy, LAUTECH. They were kept in plastic cages and were allowed to acclimatize for a period of 1 week and allowed free access to air, water, and food. They were well handled in compliance with the rules of the Institutional Animal Care and Use Committee (IACUC). Administration of cisplatin and aqueous extract of *Crassocephalum rubens* was carried out through intraperitoneal and oral administration, respectively. Every process followed the guidelines established by the authorised institution, as well as the guidelines for animal care and use outlined in the European Council Directive (EU2010/63), which governs scientific procedures involving living animals.

*Experimental design*
A total of thirty (30) male Wistar rats were randomly allocated into five groups (A, B, C, D and E).
Group A (Control, n = 6) was administered 2 mL/kg of distilled water (orally ).
Group B (n = 6) was administered 300 mg/kg of AECR (orally) for 14 days, while they received 5 mg/kg of cisplatin (intraperitoneally) on days 7 and 14.
Group C (n = 6), was orally administered 450 mg/kg of AECR (orally) for 14 days, while they received 5 mg/kg of cisplatin (intraperitoneally) on days 7 and 14.
Group D (n = 6) was administered 450 mg/kg of AECR (orally) only for 14 days.
Group E (n = 6) was administered 5 mg/kg of cisplantin (intraperitoneally) only on days 7 and 14.
All animals were fed with standard feed and received distilled water *ad libitum.*

*Harvesting of organs*
The animals were sacrificed 24 hours after the last administration, using the cervical dislocation method. The testes were then carefully dissected out and fixed in Bouin's fluid for routine tissue processing by microscope.

*Histopathological analysis*
The excised testicles were processed as described by Baker *et al*.[16]

*Statistical analysis*
Statistical data was analysed using one-way analysis of variance (ANOVA) using a graph pad prism. The level of significance was set at $p<0.05$ by a multiple comparison test. The results were presented as the mean + S.E.M. (standard error of mean). The statistical package used was graph pad prism (version 5.0).

## Results and Discussion

Cisplatin, despite its chemotherapeutic efficacy, exhibits severe testicular toxicities when administered systemically. Cisplatin was reported to have an $LD_{50}$ in the range 8.2-8.6.[17] The $LD_{50}$ of *Crassocephalum rubens* leaves, at dosage levels up to 1000 mg/kg, is reported to be non-toxic.[18] In this current study that spanned three weeks, there was no observed decline in the food consumption and water intake of the rats across the groups. Also noticeable across the groups treated with cisplatin are the presence of wet fur around the hind limb and also the wetness of the bedding. It can be inferred that urinary incontinence is a side effect of cisplatin administration.

The result (Figure 1) obtained from the mean body weight of the rats showed no statistically significant difference ($p = 0.4590$; $F = 0.9391$) when groups B (224.5 ± 9.855), C (225.4 ± 8.629), D (246.3 ± 11.02), and E (220.7 ± 15.37) were compared to A (210.0 ± 11.64). Similarly, no significant difference was observed when groups C (225.4 ± 8.629), D (246.3 ± 11.02) and E (220.7 ± 15.37) were compared to B (224.5 ± 9.855). There was also no significant difference when groups D (246.3 ± 11.02) and E (220.7 ± 15.37) were compared to C (225.4 ± 8.629), and when group E (220.7 ± 15.37) was compared to D (246.3 ± 11.02). The result obtained from this study (Figure 2) on the testis weight shows a statistically significant increase ($p< 0.0001$; $F = 16.85$) when group D (CR 450 mg/kg only) (1.978 ± 0.03750) was compared to groups A (control group) (1.517 ± 0.06611), B (CR 300 mg/kg + Cis 5 mg/kg) (1.332 ± 0.05963) and C (CR 450 mg/kg + Cis 5 mg/kg) (1.396 ± 0.01965) and also when group D (CR 450 mg/kg only) (1.978 ± 0.03750) was compared to group E (Cis 5 mg/kg only) (1.416 ± 0.05826). However, there was no observable statistically significant difference between the other groups.

Histological assessment of the Haematoxylin and Eosin-stained testicular sections of the control group revealed intact histoarchitectural organisation of the testicular tissue with a normally appearing basement membrane, seminiferous tubules, spermatogonial stem cells, and supporting sertoli cells are also evident in the seminiferous tubules (Plate 1). Group B and C also showed preservation of testicular tissue histoarchitectural organisation but with mild to moderate cellular infiltration of the interstitial spaces adjoining the seminiferous tubules (Plates 2 and 3). In group D, there is also preservation of the histoarchitectural organisation of the testicular tissue with widened interstitial spaces (Plate 4). Group E administered cisplatin only showed severe derangement in the testicular tissue histoarchitectural organization with no clearly distinguishable tubular lumen.

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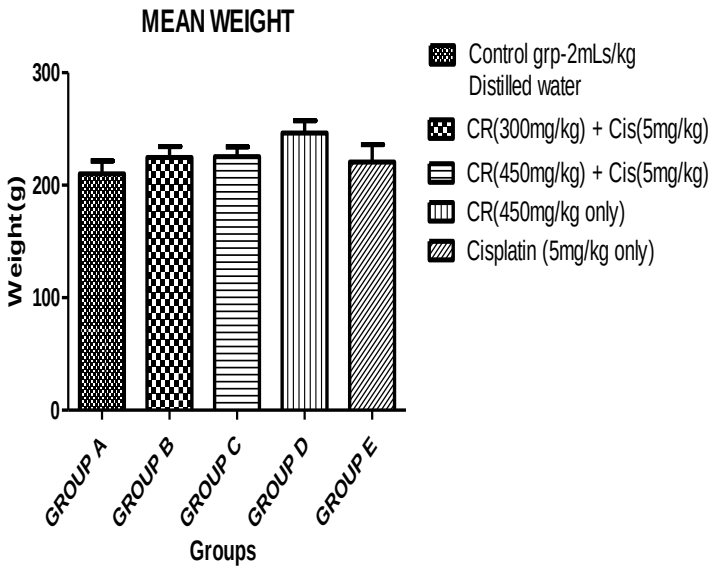


**Figure 1:** Bar chart showing the effect of cisplatin and *Crassocephalum rubens* (CR) on the mean body weight of Wistar rats across the groups (A-E).
Values are expressed as mean ± SEM. No statistical significance at ($p < 0.05$).

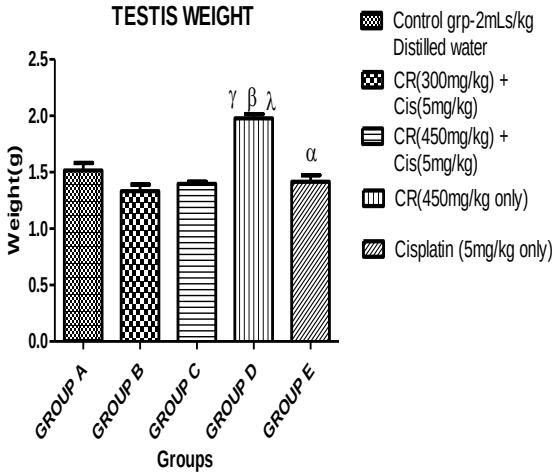


**Figure 2:** Bar chart showing the effect of cisplatin and Crassocephalum rubens on the weight of the testis of Wistar rats across the groups.
Values are expressed as mean ± SEM. Statistical significance at ($p < 0.05$). **α**- Statistical significant difference relative to group D, **β**- Statistical significant difference relative to group A, **γ**- Statistical significant difference relative to group B, **λ**- Statistical significant difference relative to group C.

There were also widened interstitial spaces and evidence of cellular debris infiltrating the seminiferous tubules, spermotogonial stem cells are not evidently suggestive of the deleterious effects following cisplatin administration (Plate 5). There are several mechanisms underlying cisplatin-induced testicular toxicity. One of these involves biochemical and pathological disturbances causing the generation of reactive oxygen species (ROS).[19-21] leading to oxidative damage.[13,22-25] It can be reasonably concluded that cisplatin caused the tissue histomorphological changes observed in this study, and aqueous extracts of *Crassocephalum rubens* substantially mitigate the effects of cisplatin, demonstrating the ability to protect against cisplatin-induced toxicity. In this study [Figure 1], observably there was no effect of cisplatin on the body weight across all groups. This is in consonance with the study of Levi *et al.*[26] in which there was also no significant effect on the body weight following cisplatin-induced toxicity. The study by Soni *et al.*,[23] counteracted the result obtained from this study as there was a decline in the body weight of rats treated with graded doses of cisplatin relative to the control group.

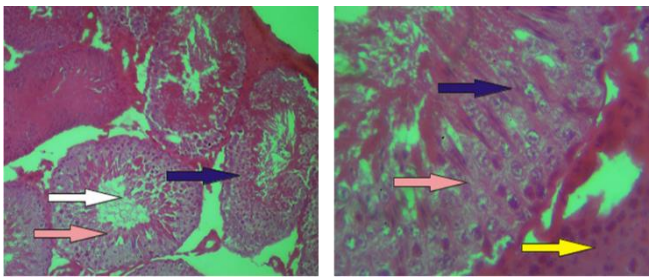

**Plate 1:** Representative light photomicrographs of the testis of the control group (A) stained in H and E showing normal testicular histoarchitectural appearance.
The seminiferous tubules appears normal (blue arrow), the interstitial spaces are well delineated, seminiferous tubular lumen are normal (white arrow) in appearance. The spermatids are also evident in the seminiferous tubules (pink arrow). Right and left panels (X 100 and X 400 magnifications respectively). Stain- Haematoxylin and Eosin.

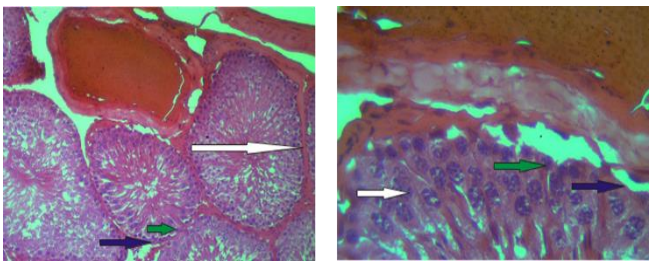

**Plate 2**: Representative light photomicrographs of the testis of the group B stained in H and E.
Sertoli cell - green arrow, basement membrane - blue arrow, seminiferous tubule and spermatocyte represented in white arrow. Right and left panels (X 100 and X 400 magnifications respectively). Stain- Haematoxylin and Eosin.

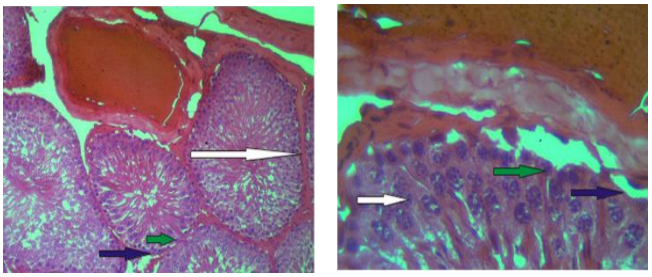

**Plate 3:** Representative light photomicrographs of the testis of the group C stained in H and E.
Orange arrow points to lumen, white arrow points to the basement membrane and black arrow points to seminiferous tubule pink arrow points to spermatids cell, green arrow points to seminiferous tubules and purple arrow points to the spermatocytes. Right and left panels (X 100 and X 400 magnifications respectively). Stain- Haematoxylin and Eosin.

Testicular weight was significantly decreased when compared to the control group in this study [Figure 2]. Since oxidative stress is one of the mechanisms by which cisplatin induces testicular toxicity, it is possible that this event might have resulted in testicular atrophy, suggestive of the decrease in the testicular weight as observed in this study. Decrease in testicular, epipidymal, and the weights of the accessory glands as a consequence of cisplatin administration in Wistar rats has also been documented.[27] Group D administered 450 mg/kg of the extract only showed an increase in testicular weight compared to the groups administered both cisplatin and extract and the cisplatin only group.

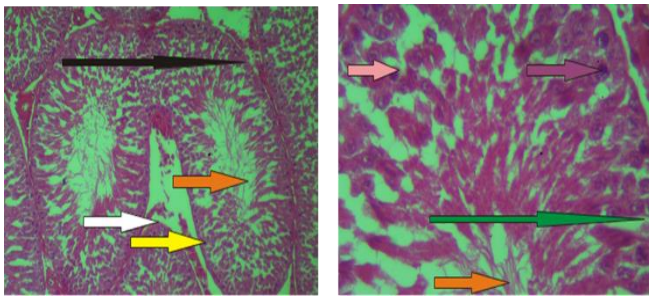

**Plate 4:** Representative light photomicrographs of the testis of the group D stained in H and E.
The lumen (orange arrow), the basement membrane (white arrow), the spermatid cell (yellow arrow) and the seminiferous tubules (black arrow); and spermatids cell (pink arrow), the seminiferous tubules (green arrow ), the lumen (orange arrow) and the spermatocytes (purple arrow). Right and left panels (X 100 and X 400 magnifications respectively). Stain- Haematoxylin and Eosin.

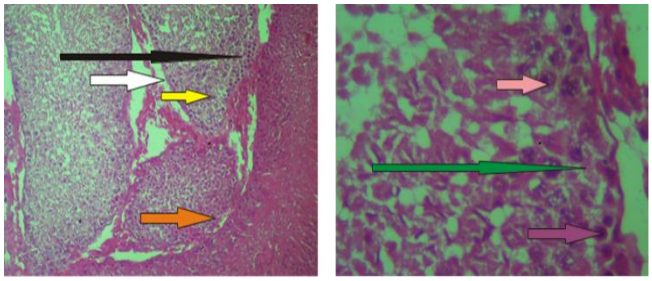

**Plate 5:** Representative light photomicrographs of the testis of the group E stained in H and E.
Spermatocyte (orange arrow), the basement membrane (white arrow), spermatid cell (yellow arrow) and the seminiferous tubules (black arrow); and the spermatids cell (pink arrow), the seminiferous tubules (green arrow), and the spermatocytes (purple arrow). Right and left panels (X 100 and X 400 magnifications respectively). Stain- Haematoxylin and Eosin.

This shows that the extract possesses some protective ability on the testis, which may be attributed to the presence of some important phytochemical compounds like tannins, coumarins, mucilage, flavonoids, and proanthocyanidin.[11] Results obtained from histological observation of group E administered with cisplatin only, using hematoxylin and eosin stain, showed severe derangement in the testicular tissue histoarchitectural organisation with no clearly distinguishable tubular lumen. There was also widened interstitial spaces and evidence of cellular debris infiltrating the seminiferous tubules, spermotogonial stem cells are not evident which is suggestive of cellular death, this shows the negative effect of cisplatin on the testis, and the mechanism by which cisplatin induced damage to the histoarchitecture of the testis could be by oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis.[20] Group B and C also showed preservation of testicular tissue histoarchitectural organization but with mild to moderate cellular infiltration of the interstitial spaces adjoining the seminiferous tubules suggestive of the protective effect of *Crassocephalum rubens* following cisplatin induction compared to the severe histoarchitectural distortion noted in Group E.

## Conclusion

*Crassocephalum rubens* leaves have consistently demonstrated significant medical benefits in many evaluations. This has inspired many researchers to conduct additional research on the plant. In this present study, cisplatin administration resulted in the impairment in testicular morphology, which was mitigated by the plant. Aqueous extracts of *Crassocephalum rubens* at doses (300 and 450 mg/kg) possess protective effects against cisplatin-induced testicular toxicity.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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