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## Original Article

## Resveratrol prevents cisplatin-induced lipid peroxidation in the non-gravid uterus of Sprague-Dawley rats

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## ABSTRACT

**Background:** Several studies have demonstrated Cisplatin-induced toxicity on the ovary. However, there is a dearth of literature on the effect of Cisplatin on the non-gravid uterus.

**Objective:** This study investigated the effect of cisplatin and supplementation with Resveratrol on the oxidant status and histoarchitecture of the uterus in Sprague-Dawley rats.

**Materials and methods:** Forty-five female Sprague-Dawley rats with average weight of 160 g divided into 9 groups (n = 5) were used in this study. Group 1 served as control and received distilled water. Groups 2 and 9 received cisplatin only. Groups 3, 4 and 5 received different doses (5, 10 and 20 mg/kg respectively) of Resveratrol after a single dose of cisplatin. Groups 6, 7 and 8 received different doses (5, 10 and 20 mg/kg respectively) of Resveratrol before cisplatin. At sacrifice, the uterus was analysed for relative organ weight, histopathology and oxidation parameters.

**Result:** No significant difference was observed in Glutathione (GSH), Superoxide dismutase (SOD) and Catalase (CAT) levels of rats treated with cisplatin and/or Resveratrol when compared to the control group ( $p < .05$ ). Compared with the control group, Cisplatin treated groups showed a significant increase in Malondialdehyde (MDA) levels ( $p = .007$  and  $.012$ ) while groups treated with 20 mg/kg Resveratrol before cisplatin showed a significant decrease ( $p = .003$ ) in their MDA levels. Cisplatin and Resveratrol treated groups showed normal histoarchitecture of the uterus.

**Conclusion:** This study showed that cisplatin-induced oxidative stress can be prevented by supplementation with Resveratrol in the uterus of Sprague-Dawley rats.

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## 1. Introduction

Cisplatin is a platinum-containing anticancer drug which reacts in the body by binding to the DNA and causing its strands to cross-link thereby triggering cells to die in a programmed way [1]. Hence, it is a common drug used for different types of cancer and solid malignancies [2]. Cisplatin's use over the years has been shown to have attending side effects ranging from visual perception, hearing disorder [3], hemolytic anemia [4], liver damage [5], kidney damage [6,7], testicular toxicity [8] to female infertility [9].

Several studies have assessed the reproductive successes after cancer and following anticancer treatments. The childhood cancer survivor study found that female survivors were substantially less likely to have live births compared to their siblings [9]. A study found an increase in the use of Assisted Reproductive Technologies (ARTs) with both male and female cancer patients and a significant

decrease in first-time parental probability in female patients compared with the general population [10]. This finding supported the result of yet two Scandinavian studies which found the relative probability of a cancer survivor having a child to have reduced by about 50% for women [11,12]. These findings may be reflective of the reproductive damages observed during chemotherapy even as seen with cisplatin. Studies have opined anticancer treatment effects in the hypothalamic-pituitary-gonadal axis leads to subfertility or infertility [13]. This impact has been largely observed in the way either on its histoarchitecture or the germ cell [14,15]. However, there is no evidence for chemotherapy-induced uterine toxicity [16].

Resveratrol, a natural phenol and phytoalexin has been shown to be well tolerated and non-toxic to the reproductive function in male or female rats [17]. Resveratrol supplementation has significantly increased uterine artery blood flow velocity and fetal weight in mice [18]. Due to its role in reducing the oxidative stress damage in the ovary, Resveratrol has been suggested to be an effective option in protecting ovarian tissue [19] and may be relevant to the development of novel treatment for Polycystic Ovarian Syndrome [20].

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Two recent studies [19,21] on the effect of the co-administration of Resveratrol and cisplatin have shown Resveratrol to be effective in protecting the ovary against damage during chemotherapy. Hence, this study has investigated some uterine indices following the co-administration of Cisplatin and Resveratrol.

## 2. Materials and method

### 2.1. Ethical approval

Ethical approval was gotten from the College of Medicine of the University of Lagos Health Research Ethics Committee (CMULHREC) with HREC ID number CMULHREC/09/16/025.

### 2.2. Animal care and handling

Forty-five adult female Sprague–Dawley rats with average weight of 160 g were procured from the Animal House, College of Medicine of the University of Lagos. They were acclimatised for two weeks to exclude any intercurrent infection under standard housing of  $24 \pm 2^\circ\text{C}$  and 12/12 h light/dark cycle. The rats were fed with standard rat chow and water *ad-libitum*. All procedures were carried out in accordance with the National Academy of Science's Guide for Care and Use of laboratory Animals [22].

### 2.3. Experimental drugs

Resveratrol with brand name 'Restorlyf', manufactured by Nature's Way U.S.A., was procured from Alliance in Motion Global Ltd., Ikeja, Lagos, Nigeria. 325 mg of Resveratrol was diluted immediately before each use in 20 ml of distilled water and doses of 5, 10 and 20 mg/kg/b.wt. were administered orally using the oral cannula. The remaining formulation was discarded after each use. The drug dosages and formulations were chosen on the basis of previously published studies on Resveratrol [23–26]. Cisplatin (Zuplatin, 50 mg/50 ml) injection manufactured by Taj pharmaceuticals Limited India was procured from Bayston Pharmacy, Mushin, Lagos, Nigeria. The injection was given intraperitoneally according to body weight in a single dose of 5 mg/kg. The drug dosage were chosen on the basis of previously published studies on Cisplatin [27,28].

### 2.4. Experimental design

Forty-five adult female Sprague–Dawley rats with average weight of 160 g were randomly divided into 9 groups ( $n = 5$ ) in this study. Group 1 received 1 ml distilled water and served as control. Groups 2–9 received a single dose (5 mg/kg/b.wt.) intraperitoneal injection of cisplatin. Groups 3–5 received resveratrol daily for 7 days at doses of 5, 10 and 20 mg/kg/b.wt, 24 h after cisplatin. While groups 6–8, received resveratrol daily at doses of 5, 10 and 20 mg/kg/b.wt 14 days before and 7 days after cisplatin administration. Groups 2 and 9 received cisplatin only and were monitored for 7 and 21 days respectively before sacrifice.

### 2.5. Animal sacrifice and sample collection

At the end of the study, the animals were fasted overnight and sacrificed by cervical dislocation. The uterus were excised, trimmed of fat and weighed immediately before rinsing in cold saline. The right uterine horn of each rat was immediately stored in the refrigerator at a temperature of  $-20^\circ\text{C}$  for oxidative stress assay while the left uterine horns were fixed in 10% formal saline for histological preparation.

### 2.6. Tissue processing

Seventy two hours after fixation, the tissues were dehydrated by passed through ascending grades of alcohol. After dehydration, uterine tissues were cleared in xylene and then embedded in molten paraffin wax at a temperature of  $60^\circ\text{C}$ . The issues were then sectioned at  $5\ \mu\text{m}$  and stained with heamatoxyline and eosin. Photomicrographs of these sections were obtained using the DM 750 Leica digital photomicroscope.

### 2.7. Biochemical analysis of oxidation

The uterine tissue was homogenized in a Teflon-glass homogenizer with a buffer containing 1.5% potassium chloride to obtain 1:10 (w/v) whole homogenate. Malondialdehyde (MDA) was measured using the thiobarbituric acid test to determine the concentrations of ovarian MDA level. The reduced glutathione (GSH) and Catalase (CAT) levels in the uterine tissue were estimated as described by Rukkumani and colleagues [29]. Total Superoxide dismutase's (SOD) activity was measured by the method described by Sun and his co-workers [30].

### 3.7. Statistical analysis

The results were analysed using the Statistical Package for the Social Sciences version 21.0 (SPSS, Chicago, IL, USA). Data was reported as mean  $\pm$  SD Differences between mean and the main effects of treatment group were determined by the one way analysis of variance (ANOVA) and multiple comparisons was done using the LSD post-hoc tests. The mean difference is significant at the 0.05 level ( $P < .05$ ).

## 4. Results

### 4.1. Uterine weight

### 4.2. Oxidative status

### 4.3. Histological observation

Figs. 1–9 shows the photomicrographs of the uterine tissues of the different treatment groups in this study. Treatment with cisplatin alone (Figs. 2 and 9) shows a normal histoarchitecture of a rat uterus comparable to the control group (Fig. 1). Also, the co-

**Table 1**

The effect of Cisplatin and supplementation with Resveratrol on the absolute and relative uterine weights in Sprague–Dawley rats.

Groups	Relative uterine weights ( $\times 10^{-3}$ )	Absolute uterine weights (g)
Group 1	$4.10 \pm 0.03^{bc}$	$0.62 \pm 0.08^c$
Group 2	$2.10 \pm 0.03^{ac}$	$0.44 \pm 0.07$
Group 3	$2.90 \pm 0.03^{abc}$	$0.46 \pm 0.08$
Group 4	$2.18 \pm 0.04^{ac}$	$0.27 \pm 0.26^a$
Group 5	$2.00 \pm 0.03^{abc}$	$0.25 \pm 0.05^a$
Group 6	$3.10 \pm 0.03^{abc}$	$0.52 \pm 0.09$
Group 7	$4.50 \pm 0.03^{abc}$	$0.64 \pm 0.09^c$
Group 8	$4.10 \pm 0.03^{bc}$	$0.58 \pm 0.09$
Group 9	$2.60 \pm 0.03^{ab}$	$0.40 \pm 0.07^a$

Values are expressed as mean  $\pm$  Standard Error of Mean (SEM).

CIS = cisplatin; RES = Resveratrol; MED = Medium. Group 1 = normal control; Group 2 = Cisplatin 7; Group 3 = CIS + RES LOW; Group 4 = CIS + RES MED; Group 5 = CIS + RES HIGH; Group 6 = RES LOW + CIS + RES LOW; Group 7 = RES MED + CIS + RES MED; Group 8 = RES HIGH + CIS + RES HIGH; Group 9 = Cisplatin 21.

<sup>a</sup>  $p < .05$  significant compared to control group.

<sup>b</sup>  $p < .05$  significant compared to group 2.

<sup>c</sup>  $p < .05$  significant compared to group 9.

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