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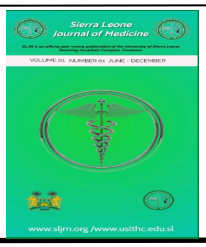

Therapeutic Effects of Ginseng and Doxorubicin on DMBA-Induced Ovarian Cancer in Wistar Rats

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ABSTRACT

Background: Ovarian cancer can be attributed to various external factors, such as tobacco use, exposure to chemicals and radiation, and infections. Internal factors, including inherited mutations, hormonal factors, immune conditions, and random mutations, also play a role in its development. Exposure to carcinogen such as 7,12 Dimethyl Benz Anthracene can induce ovarian cancer. The aim of the study is to investigate the effect of Ginseng and Doxorubicin on Ovotoxicity induced by DMBA in Wistar rat. s

Methods: A total number of twenty-five females (25) wistar rats which average weight was 135g were used and the animals were randomly split into five groups (A, B, C, D, E) with each group comprising of five rats. Group A (served as the control) given physiological saline only, Group B were induced with 7,12 Dimethyl Benz Anthracene and post treated with Ginseng (50 mg/kg) (GIN). Group C were induced with 7,12 DMBA and post treated with Doxorubicin (25mg/kg). Group D were induced with 7,12 DMBA and post treated with Doxorubicin (25 mg/kg) and Ginseng (50 mg/kg). Group E were induced with 7,12

Dimethyl Benz (a) Anthracene (DMBA) (50mg/kg). Drug administration was done orally using oral cannula and intramuscularly using syringe and needle.

Results: Ovary histoarchitecture for control group A, B (GIN group), and D (DOX+GIN group) revealed intact organization and structure of the ovary. In these groups, no observable pathological changes were seen as the ovaries were characterized with the presence of numerous follicular cells with a normal and well-defined cellular density. For C (DOX group), the histoarchitecture showed a localized collection of blood outside the blood vessels, typically resulting from a ruptured blood vessel (hematoma of blood vessels) and slight degenerative changes in the ovary. For E (DMBA group), showed atrophied and atretic ovarian cells, necrotic oocyte, severe degenerative changes were also observed.

For Hormonal analysis, there was a significant decrease in Serum FSH & LH concentration in DMBA treated group compared to the Ginseng and control groups.

Conclusions: DMBA evidently induced ovarian toxicity, and its effects were efficiently attenuated by the use of Ginseng and Doxorubicin.

Key words: Ovotoxicity, Ginseng, Dimethyl Benz Anthracene, Doxorubicin, Therapeutic

1. INTRODUCTION

Cancer is a collection of diseases marked by the uncontrolled proliferation and dissemination of abnormal cells. Its development is influenced by a variety of external factors, such as tobacco use, exposure to chemicals and radiation, and infections, as well as internal factors like inherited mutations, hormonal influences, immune conditions, and random mutations[1]. Several factors, including dietary choices, specific infections, sedentary lifestyle, obesity, and environmental toxins, are known to elevate cancer risk[1]. These elements can collaboratively trigger or accelerate the process of carcinogenesis in human body and in Wistar rat [1], thus cancer is a leading cause of death.

The World Health Organization (WHO) recently provided updated data on the global epidemiology of cancer. Cancer is among the most prevalent diseases worldwide, with approximately 14 million new cases annually and more than 8.8 million deaths recorded globally[16]. In Nigeria, around 100,000 new cancer cases are reported each year, with a high case fatality ratio[2]. About 20% of Africa's population, slightly over half of West Africa's population, resides in Nigeria[2]. In 2008, Nigeria accounted for 15% of the estimated 681,000 new cancer cases reported in Africa[3].

Ovarian cancer is a fatal disease that kills 150,000 women globally each year and it is regarded as the seventh most type of common cancer in women[4].

7,12-dimethylbenz[a]anthracene appears as yellow to greenish-yellow crystals or a yellow solid, Odorless, Maximum fluorescence at 440 nm, Bluish-violet fluorescence in UV light.7,12-Dimethylbenz[a]anthracene (DMBA) is an immunosuppressor and a powerful organ-specific laboratory carcinogen[5]. DMBA serves as a tumor inducer. 7, 12-dimethylbenz[a]anthracene (DMBA), a polycyclic aromatic hydrocarbon (PAH), is produced from the burning of organic material [6], thus cigarette smoke, charred foods and car exhaust fumes, is an exposure source. DMBA depletes all ovarian follicles in mice. Doxorubicin was originally made from the bacterium Streptomyces peucetius[7]. Doxorubicin is an antibiotic derived from the bacterium known as Streptomyces peucetius. Doxorubicin is utilized in the treatment of soft tissue[8] bone sarcomas as well as cancers affecting the breast, ovary, bladder, and thyroid. It is also used to treat acute lymphoblastic leukemia and small cell lung cancer because of its antioxidative and potential neuromodulating effects. It has become a popular supplement in neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and brain ischemia. Additional claimed uses are for its antihypertensive, cardioprotective, and anticancer effects. A diversified group of steroidal saponins called ginsenosides are the major active components. Tumor growth is mainly inhibited by blocking the cell cycle, particularly targeting cyclin-dependent kinases and cyclins in the G0/G1 phase. Additionally, it removes reactive oxygen species and suppresses the formation of new blood vessels in tumor cells[7]. Ginseng enhances the maturation of mouse preantral follicles and increases the production of steroids and proliferating cell nuclear antigen (PCNA)[9]. Studies indicate that ginseng extract, owing to its potent antioxidant properties, boosts the quantity of ovarian follicles, thereby elevating sex hormone levels, while simultaneously decreasing the number of antral follicles[10].

From different literature reviews, DMBA is a well-known ovotoxic agent that can induce significant damage to ovarian tissues, potentially leading to infertility or reduced reproductive capacity[17] while various therapeutic approaches have been explored, the effectiveness of ginseng and doxorubicin in mitigating DMBA-induced ovotoxicity remains largely unexplored. Ginseng, a popular herbal remedy with antioxidant and anti-inflammatory properties, and doxorubicin, a chemotherapy drug with known protective effects on ovarian function, hold promise as potential therapeutic agents. This study seeks to investigate the therapeutic role of ginseng and doxorubicin in ameliorating DMBA-induced ovotoxicity in Wistar rats. By elucidating the mechanisms underlying their protective effects, this research aims to provide valuable insights into novel strategies for preserving ovarian function and fertility in individuals exposed to ovotoxic agents.

2. METHOD

2.1 Compounds Procurement and Animals Procurement

All compounds used (7,12 DMBA, Doxorubicin) were pure compounds procured from TMJ Chemical Co. Ltd China and verified at Pharmacology Department, Osun State University, Osogbo. Experimental animals used for this research were procured from the Animal Holdings, College of Medicine, Ladoke Akintola University Ogbomoso, Oyo State. The animals were allowed access to food and ad libitum. They were given two weeks to get used to the lab condition before the study started. The study followed the rules set by the Health Research Ethics Committee at the College of Health Sciences, Osun State University, Osogbo, Nigeria, and complied with the National Institute of Health guidelines for caring for and using lab animals.

2.2 Ginseng Procurement and Extraction

Ginseng roots were procured from Hefei TDJ Chemical Co.Ltd China and authenticated by the Department of Biological Sciences, Osun State University, Osogbo, Nigeria. Ginseng roots were air dried and the dried pieces were then pulverized using an electric blender (Blender/Miller III, model MS-223, Taiwan, China) and the extraction procedure was done as described by Adeleke et al[11].

2.3 Experimental Design

Twenty-five female (25) Wistar rats which average weight was 135g were used and the animals were randomly split into five groups (A, B, C, D and E), each with five rats. Group B-E rats were induced with the carcinogenic compound (DMBA) twice in a period of one week and then left for two weeks to observe the effect of DMBA.

Group A (served as the control) given physiological saline at 1.2ml per grams of the body weight of the animal and feed only, Group B rats were exposed to 50 mg/kg of DMBA and post-treated with 50 mg/kg of Ginseng (GIN) for two weeks, Group C rats were exposed to 50 mg/kg of 7,12 Dimethyl Benz (a) Anthracene (DMBA) and post-treated with 25 mg/kg of Doxorubicin (DOX) for two weeks, Group D rats were exposed to 50 mg/kg of 7,12 Dimethyl Benz (a) Anthracene (DMBA) and post-treated with concomitant administration of Doxorubicin (25 mg/kg) and Ginseng (50 mg/kg) for two weeks. Group E rats (DMBA group) were administered with 50 mg/kg of 7,12 Dimethyl Benz (a) Anthracene (DMBA) only.

2.4 Sacrifice of Experimental Animals, Sample Collection and Hormonal Assay

Blood was withdrawn from the apex of the heart (left ventricle) of the twenty-five adult rats, which were first anesthetized with 80 mg/kg of ketamine hydrochloride, 12 hours after the last administration just according to Saha et al., (2005)[19]. The blood was then dispensed into red-topped tubes for hormonal analysis. The ovary was excised following an abdominal incision, and they were fixed in Neutral buffer Formalin for histological analysis. It was then dehydrated progressively in stronger alcohols, cleared in Xylene and infiltrated in paraffin wax, before being embedded in molten paraffin wax. A rotary microtome was then used to slice the paraffin block containing the tissue into 4 µm thick sections. The sections were then transferred to a glass slide, floated in a water bath set at 40 degrees Celsius, and stained with hematoxylin and eosin dyes.

2.5 Hormonal Assay

Serum samples were assayed for FSH, LH in batches with the control sera at both physiological and pathological levels by the standard Quantitative Enzyme-Linked Immunosorbent Assay (ELISA) technique with microwell kit which was manufactured by Syngenemed. The manufacturer instructions that accompanied the assay kits were strictly adhered to.

2.6 Statistical Analysis

The mean and standard error of mean (S.E.M) of all data's were calculated. Comparison of means was made by one way analysis of variance (ANOVA) using GraphPad Prism 5. Tukey's test was used to adjust for multiple comparisons. P value < 0.05 was considered to be statistically significant

3. RESULTS

Histological Observation of the Ovary

Photomicrograph showing the general cytoarchitecture of the ovaries of rats across the various experimental groups using H&E stain (magnification: x100) is displayed in Figure 1.

The cytoarchitecture of the ovary revealed the different parts of the ovary; the cortex, medulla, hilum, tunica albuginea, oocyte, primordial follicle, primary follicle, secondary follicle, germinal epithelium, zona pellucida, and follicular cells.

The photomicrographs revealed intact organization and structure of the ovary in groups A (Control), B (DMBA+GIN) and D (DMBA+DOX+GIN). In these groups, no observable pathological changes was seen as the ovaries were characterized with the presence of numerous follicular cells with a normal and well-defined cellular density.

In group C (DMBA+DOX), the cytoarchitecture of the ovary showed the presence of hematoma of blood vessels and slight degenerative changes.

Rats in group E (DMBA only) showed atrophied and atretic ovarian cells, highly disorganized follicles, severe degenerative changes were also observed in the surrounding cells with wasted and

atretic follicles. Furthermore, necrotic ovarian cells (N), and the presence of hematoma (H) were observed (black arrows).

Biochemical Results

From Table 1, post hoc comparisons using Tukey's HSD test indicated that the mean score for Group A (M = 0.5500, SD = 0.012) was significantly different from Group E (M = 0.2800, SD = 0.012), Group C (M = 0.3700, SD = 0.017), and Group D (M = 0.4200, SD = 0.017). Additionally, Group A showed a significant difference compared to Group B (M = 0.4800, SD = 0.012). Group B showed a significant difference compared to Group E (M = 0.2800, SD = 0.011), Group C, and Group D (M = 0.4200, SD = 0.017). Group C showed a significant difference from Group E but no significant difference from Group D. Group D showed a significant difference from Group E. As shown in Table 2, Post-hoc comparisons using Tukey's HSD test indicated that the mean score for Group A (M = 1.867, SD = 0.1453) showed a significant difference from Group E (M = 1.300, SD = 0.06). However, Group A showed no significant difference from Group B (M = 1.867, SD = 0.088), Group C (M = 1.467, SD = 0.1202), and Group D (M = 1.600, SD = 0.1155). Group B showed a significant difference when compared to Group E, but showed no significant difference from Group C and Group D. Group C showed no significant difference when compared to Group D and Group E, and Group D showed no significant difference from Group E.

Group A (M = 1.900, SD = 0.1155) had significantly different mean scores compared to Group C (M = 1.300, SD = 0.1155) and Group E (M = 1.300, SD = 0.06), but no significant difference from Group B (M = 1.867, SD = 0.088) or Group D (M = 1.733, SD = 0.1453) (Table 3). Group B showed a significant difference from Group C and Group E but not from Group D. Group C showed no significant difference from Group D or Group E, and Group D also showed no significant difference from Group E.

4. DISCUSSION

The photomicrographs A (Control), B (DMBA+GIN) and D (DMBA+DOX+GIN) revealed intact organization and structure of the ovary. In these groups, no observable pathological changes were seen as the ovaries were characterized with the existence of numerous follicular cells with a normal and well-defined cellular density. The findings of this study for B (DMBA+GIN) group corroborate with the work of Seghinsara et al.,2018 where they reported that Ginseng enhances the maturation of mouse pre-antral follicles. Additionally, ginseng extract, known for its potent antioxidant properties, augments the ovarian follicle count[16]. Ginseng has the ability to regulate cellular activity and function through genomic mechanisms and non genomic signaling. Tumor growth inhibition is primarily via cell cycle inhibition.

The simultaneous use of DOX with another drug, like ginsenoside

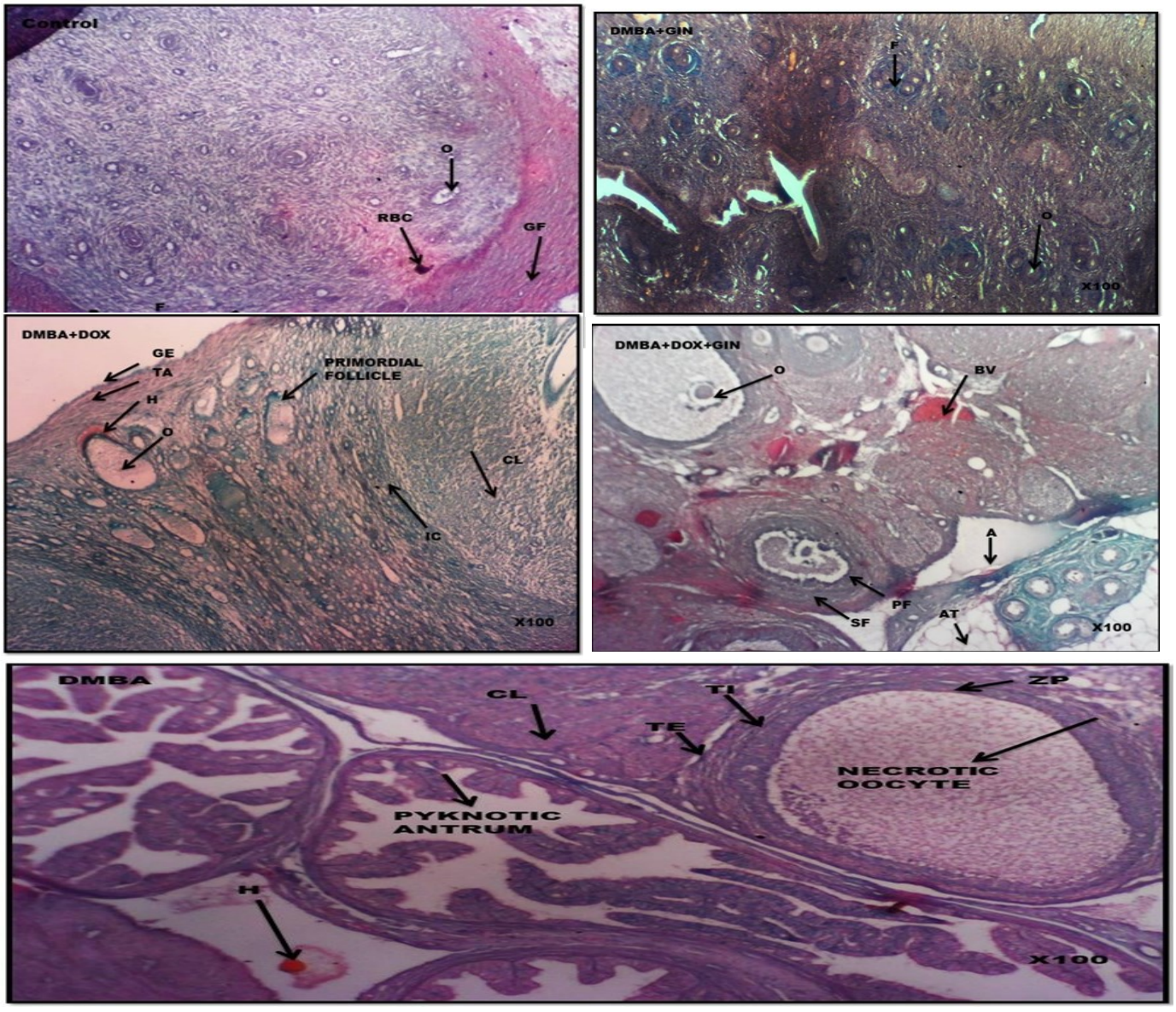

Figure 1: Photomicrograph of the Histological Section of the Ovary Stained with Hematoxylin and Eosin x100, done and arranged together using PowerPoint. A= Control; B= DMBA+Ginseng; C= DMBA+DOX; D= DMBA+ DOX+GIN; E= DMBA only.

Key: (BV) Blood Vessel, (F) Follicle, (IC) Interstitial Cell, (CL) Corpus luteum,(H) Hematoma,(N) Necrosis, (TI) Theca Interna, (TE) Theca Externa, (Fc) Follicular Cells, (ZP) Zona Pellucida, (GE) Germinal Epithelium, (O) Oocyte, Tunica Albuginea, (PF) Early-Stage Follicle, (SF) Developing Follicle, (A) Antrum, (AT) Adipose Tissue, (GF) Graafian Follicle.

Table 1: Serum Follicle Stimulating Hormone Concentration Among the Study Groups. n= 5.

Comparison	Mean Difference	Standard Error	P-value
Group A vs B	0.07	0.01	0.0128
Group A vs C	0.18	0.02	0.0010
Group A vs D	0.1300	0.02	0.0034
Group A vs E	0.2700	0.02	0.0001
Group B vs C	0.11	0.20	0.0062
Group B vs D	0.0600	0.02	0.0449
Group B vs E	0.2000	0.02	0.0003
Group C vs D	-0.05	0.02	0.1108
Group C vs E	0.0900	0.02	0.0124
Group D vs E	0.1400	0.02	0.0025

Rh2, a promising compound, can either enhance the antitumor effects or regulate different physiological responses (such as immune, nervous, and hormonal functions) as reported by Razina et al., (2010)[18] support my findings that the microarchitecture of D (DOX+GIN) group also revealed a normal structure. A better understanding of Rh2's biological effects was achieved through various cell-based molecular techniques: (a) Rh2's mild pro-oxidant impact on tumor (Ehrlich's adenocarcinoma) and immune (splenocytes) cells was verified using a cell-permeable fluorescent ROS indicator, and (b) the stabilization of Nrf2 transcription factor, which serves as the primary regulator of genetic antioxidant mechanisms response, by micro molar Rh2[13].

In group C (DOX+DMBA), the cytoarchitecture of the ovary showed the existence of blood vessel hematoma and slight degenerative changes of follicles. This findings corroborate with the work of Doroshow et al., 1986 who documented that Doxorubicin binds to DNA by intercalating between base pairs, and it hinders the topoisomerase II complex, impeding the relegation step of the ligation–relegation reaction that topoisomerase II facilitates. Essentially, doxorubicin undergoes oxidation to form semiquinone, which is then converted back to doxorubicin, releasing reactive oxygen species in the process. These reactive oxygen species can induce lipid peroxidation and membrane impairment, DNA damage, oxidative stress, and activate apoptotic pathways leading to cell death.

The previous work of Gewirtz et al.,1999 documented that the mechanism of action of doxorubicin involves the production of free radicals that cause damage to cellular membranes, DNA, and proteins can cause hematoma and slight degenerative alterations in the ovary.

Furthermore, rats in group E (DMBA only) showed atrophied and atretic ovarian cells which agrees with previous work of Borman et al., 2000 that approximately 99% of ovarian follicles die by a process known as atresia, highly disorganized follicles, severe degenerative changes was also observed (Pollard, 1967). Furthermore, necrotic ovarian cells (N), and the existence of blood vessel hematoma were observed. Previous reports of Igawa et al., 2009 are in alliance with this findings. This findings are supported by previous report that DMBA is mediated through an apoptosis-like mechanism[14]. Previous report was found that DMBA suppress both humoral and cell-mediated immune (T and B cell) responses in

Table 2: Post-Hoc Comparison of Luteinizing Hormone Concentration Among the Study Groups n=5.

Comparison	Mean Difference	Standard Error	P-Value
Group A vs B	0.0	0.17	1.0000
Group A vs C	0.40	0.18	0.1012
Group A vs D	0.2667	0.18	0.2241
Group A vs E	0.5667	0.15	0.0223
Group B vs C	0.40	0.14	0.0550
Group B vs D	0.2667	0.12	0.1404
Group B vs E	0.5667	0.11	0.0058
Group C vs D	-0.5960	0.33	0.4685
Group C vs E	0.1667	0.13	0.2794
Group D vs E	0.3000	0.13	0.0808

Table 3: Superoxide Dismutase Concentration Among the Experimental Groups. n=5

Comparison	Mean Difference	Standard Error	P-Value
Group A vs B	0.0	0.19	1.0000
Group A vs C	0.6000	0.16	0.0213
Group A vs D	-0.3485	0.68	0.4199
Group A vs E	0.6000	0.13	0.0097
Group B vs C	0.6000	0.19	0.0351
Group B vs D	0.1667	0.21	0.4734
Group B vs E	0.6000	0.16	0.0213
Group C vs D	-0.9485	0.08	0.0798
Group C vs E	0.0	0.1291	1.0000
Group D vs E	0.0	0.87	0.0502

spleen and cultured splenocytes[15]. The hydroxylation of DMBA at 7 -methyl group is a crucial step towards its carcinogenesis (Wong et al., 1983).

For Hormonal analysis of the Ovary in this research, comparison of DMBA treated group with Ginseng treated group like Group B which is (DMBA+GIN), Group D which is (DMBA+DOX+GIN) showed that the roots of ginseng herb elevation in sex hormone concentrations as it have a stimulatory effect on sex hormones synthesis. This finding agrees with the report of Pak et al., 2009 that the herb contains active ingredients such as saponin and glycosides, both have a stimulatory impact on the anterior lobe of the pituitary gland, resulting in elevated levels of FSH and LH hormones secretion for members of this group.

Korean red ginseng attenuated the impact of DMBA by augmenting the quantity of ovarian follicles, and subsequently increasing sex hormones, this findings corroborate with previous work of Chen et al., 2008 that ginseng is estrogenic and an anticancer drug. The mechanism is that ginseng can modulate cellular activity and function through genomic and non genomic signaling. In addition, some ginseng ginsenosidic acids have a similar basic structure to estrogen hormones.

DOX treated group showed significant decrease in FSH and LH Concentration when compared with the control group as this findings agrees with the work of Zhang et al., 2017 that injection of doxorubicin in mice has toxic effects to the ovaries and decreases the concentration of Serum FSH and LH. DOX showed significant decrease in FSH and LH Concentration in comparison with GIN group and this agrees with previous work of Gewirtz et al.,1999.

Decrease in Serum FSH and LH Concentration in DMBA treated group when compared to GIN group, DMBA is reported to induce mutations by making DNA adducts as documented. DMBA interferes with various crucial elements of the female rats' Hypothalamic-Pituitary-Gonadal (HPG) axis, leading to a reduction in the expression and secretion of GnRH by the hypothalamus, which, in part, contributes to the decreased levels of LH and FSH due to decreased pituitary GnRH-R expression concentration. The DMBA exposure induced impairment of steroidogenic mechanisms might have resulted in a reduction in the serum level of FSH and LH in DMBA treated group. The impact of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are mediated by their receptors LHR and FSHR. This finding is in alliance with the previous work of Banu et al., 2008 that DMBA induce deleterious effects on female ovary. Superoxide dismutase (SOD) is a primary defense mechanism against oxygen toxicity, regulating levels of reactive oxygen species (ROS) by converting superoxide radicals into hydrogen peroxide and oxygen. Excessive ROS can overwhelm antioxidant defenses, leading to oxidative stress and cell death. However, the activities of intracellular antioxidant enzymes, including SOD, which scavenge ROS and hydrogen peroxide to reduce oxidative stress, were significantly reduced compared to the control group. Parameters on body defense mechanism investigated in this research SOD revealed a notable reduction in DMBA and Doxorubicin treated groups which aligns with Wijeratne et al., 2005 who reported decrease in SOD activity within DMBA induced ovarian

cancer.

4.1 Conclusion

DMBA evidently induced ovarian toxicity and its effects were attenuated by the use of Ginseng and Doxorubicin.

4.2 Recommendation

In the chemotherapeutic treatment of cancer Doxorubicin is encouraged to be use with Ginseng in other to avoid ovotoxicity that can be caused by Doxorubicin. If Doxorubicin will be used, it should be administered with another medication such as ginseng as these two drugs have anti tumor effect. Ginseng has proven as a potent herbal medicine in the treatment of ovarian toxicity.

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Conflicts of Interest

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this paper.

Contributor Roles Taxonomy Statement

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