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Effects of Graded Dose of Sodium Benzoate on Ovaries of Adult Female Albino Wistar Rats

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Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [3]analysis, or interpretation of data for the work,[6]Active participation in active methodology, [5,6]Drafting the work or revising it critically for important intellectual content

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ABSTRACT

Objective: To determine the gross effects of graded dose dependent affects Sodium Benzoate on ovaries in adult female albino Wistar rats.

Methodology: This quasi-experimental study was conducted from October to March 2021 at the Animal House of Sindh Agriculture University, Tando Jam, using 30 adult female albino Wistar rats (150–200g), randomly divided into three groups: A (control), B, and C. Group A received a regular lab chow diet, while Groups B and C were fed chow mixed with sodium benzoate at doses of 300 mg/kg and 600 mg/kg body weight, respectively. Initial and final body weights were recorded. After the experiment, rats were anesthetized with chloroform and sacrificed using cervical dislocation. Ovaries were extracted, weighed, and preserved in 10% formalin for histological analysis using Hematoxylin and Eosin staining. Data were analyzed using SPSS version 26.0.

Results: Ovarian weight was higher in the control group (0.065g) compared to group B (0.039g) and group C, ($p > 0.05$). Though, group C showed a significantly higher incidence of blood congestion (66.7%) than group B (25.0%) and the control group (8.3%) ($p < 0.004$). Cellular hypertrophy rat was significantly higher in group C (70.0%) compared to group B (30.0%) and the control group (0%) ($p < 0.001$). Oocyte degeneration was also significantly more common in group C (69.2%) than in group B (23.1%) and the control (7.7%) ($p < 0.001$). Additionally, vacuolation was observed in 61.5% of group C, 30.8% of group B, and only 7.7% of the control group ($p < 0.001$).

Conclusion: Histological analysis indicated that sodium benzoate may have contributed to increased blood congestion, cellular hypertrophy, and vacuole formation within the ovarian tissue specifically at higher dose.

Keywords: Cataract, Female Rats, Ovaries, Sodium Benzoate, Histological alterations.

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Introduction

The ovaries are integral components of the female reproductive system, located beside the lateral walls of the uterus. Their primary function is the production of ova and the secretion of essential reproductive hormones such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are crucial for menstrual cycle regulation and fertility.[1] Histologically, the ovary is covered by a germinal epithelium and surrounded by a connective tissue capsule called the tunica albuginea.[2] Internally, it is divided into two main regions: the cortex, which houses developing follicles and the corpus luteum, and the medulla, which contains blood vessels and connective tissue.

Follicular development begins with flat epithelial cells that transform into cuboidal granulosa cells, proliferate, and form stratified layers. Oocyte maturation occurs within fluid-filled follicles, and typically, only one oocyte fully matures and is released during ovulation. The process remains triggered by a surge in LH, leading to follicular rupture and release of the oocytes. The ruptured follicle then becomes the corpus luteum, which secretes progesterone to prepare the uterus for the implantation.[3] In addition progesterone; the ovaries also produce estrogen, testosterone, and inhibin. Such hormones contribute to secondary sexual characteristics, reproductive organ development, and overall health of the reproduction.[4]

Safety of the food has long been a global concern, particularly with regard to chemical preservatives used to extend the shelf life of perishable things. Particularly preservative is sodium benzoate (E211), widely used for its antimicrobial properties in acidic foods like carbonated beverages, salad dressings, fruit juices, pickles and the jams.[5,6] Its also commonly found in pharmaceuticals and cosmetic products, leading to widespread exposure to human.

In spite of its usefulness in food preservation, sodium benzoate has been associated with potential risks for the health.[7] Once ingested, it is metabolized in the liver, where it binds with glycine to form hippuric acid, which is then excreted through urine. The liver plays a key role in detoxifying this compound via hepatocyte-mediated biochemical pathways. However, evidence suggests that sodium benzoate may interact with DNA, cause genetic alterations, disrupt normal cell division, and impair mitochondrial function.[6,8,9]

This compound is also increasingly recognized as a potential endocrine-disrupting chemical (EDC**)**. According to the World Health Organization (WHO), EDCs are external substances that interfere with the endocrine system, potentially causing adverse effects in the organism, its offspring, or populations. Sodium benzoate's widespread use in food and cosmetics raises concerns about cumulative exposure and its long-term effects on reproductive health.[10-12] Numerous studies link EDCs to a range of disorders including infertility, altered gametogenesis, and structural abnormalities of reproductive organs such as endometriosis and hypospadias and they may also disrupt the normal timing of puberty and related developmental processes.[8,13,14] Given these concerns, it is essential to evaluate the possible histological and functional changes in reproductive organs such as the ovaries following exposure to sodium benzoate. Hence an effort is being made through this study to assess the different doses effects of the NaB on the ovaries of adult female albino Wistar rats. The findings may helpful to bridge a significant research gap, raise awareness about possible endocrine-disrupting effects, and contribute to establishing safer consumption limits for sodium benzoate.

Methodology

This quasi-experimental study was conducted over duration of six months, from October to March 2021, at Isra University IRB no IU/RR-10/BASR-46/2020/1449 in collaboration with the Animal House, Department of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University, Tandojam. A total of 30 adult female albino Wistar rats were used in the study.[7] The rats were provided with a standard lab chow diet and had free access to water throughout the experiment. The animals were randomly divided into three groups: Group A (n=10) served as the control group and received only the standard lab diet and water; Group B (n=10) was the low-dose experimental group, receiving 300 mg/kg body weight of sodium benzoate mixed in their chow diet; and Group C (n=10) was the high-dose experimental group, receiving 600 mg/kg body weight of sodium benzoate mixed in their chow diet. Initial body weights were measured and recorded prior to the intervention. Non-probability convenience sampling was used for animal selection. The animals were chosen based on clear inclusion and exclusion criteria. Adult female albino Wistar rats weighing between 150–200 grams were studied. Comprised sick or moribund rats, male rats, and any rat weighing less than 150 grams or more than 200 grams were excluded.

All procedures followed ethical guidelines and were approved by the Ethics Committee of Sindh Agriculture University. Animals were housed in stainless steel cages lined with sawdust bedding and equipped with appropriate feeding and drinking containers. The environment was kept clean, well-ventilated, and maintained under a regulated 12-hour light/dark cycle using a diurnal switch to mimic natural conditions. The rats were handled according to the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals.

At the end of the experimental period, the final body weights of rats from all groups were recorded. The

animals were anesthetized using chloroform swabs in an inverted glass jar and euthanized by cervical dislocation using a hemostat placed at the base of the skull [24]. Following dissection, the ovaries were removed, weighed, and observed for any gross morphological changes. The tissues were preserved in 10% formalin for histological analysis. For slide preparation, the ovaries were processed through graded alcohol solutions (70%, 80%, 95%, and 100%) followed by xylene. The tissues were then embedded in paraffin wax, sectioned at 5-micron thickness using a microtome, and mounted on slides. After placement on a warm water bath, the slides were stained using Hematoxylin and Eosin for microscopic evaluation. Data were analyzed using SPSS version 22.0. Continuous variables were assessed using

Analysis of Variance (ANOVA), while categorical data were evaluated using the Chi-square test. A p-value of ≤ 0.05 was considered statistically significant.

Results

All groups had almost similar initial body weights with no significant difference (p = 0.1434). However, by the end of the experiment, rats exposed to sodium benzoate (Groups B and C) showed a significant decrease in final body weight compared to the control group (p = 0.001), suggesting a dose-dependent adverse effect on weight gain as shown in Table I.

The comparison of ovarian weights across the study groups showed a statistically significant reduction in ovarian weight in sodium benzoate-treated groups. Group C had the lowest mean ovarian weight, followed by Group B, compared to the control Group A. All comparisons (A vs B, A vs C, and B vs C) showed significant differences (p < 0.05). (Table II)

Histopathological analysis revealed significant differences across the study groups. Blood congestion, cellular hypertrophy, oocyte degeneration, and vacuolation were markedly more frequent in the high-dose sodium benzoate group (Group C), with incidences of 66.7%, 70.0%, 69.2%, and 61.5% respectively. In contrast, the control group (A) showed minimal changes, and the low-dose group (B) exhibited moderate effects. All observed changes were statistically significant (p < 0.05). (Table III)

Table I: Different study groups of the rats comparison according to initial and final body weight. (n=30)

Groups		Mean ± SD Grams	F-value	p-value
Initial Body wright	Group A	189.74 ± 1.63	2.0887	0.1434
	Group B	188.53 ± 1.52		
	Group C	189.62 ± 1.19		
Final Body weight	Group A	190.45 ± 1.98	165.06	0.001
	Group B	180.79 ± 1.77		
	Group C	176.38 ± 1.44		

Table II: Ovaries wright comparison across the study groups.

Groups	Mean ± SD		F-value	p-value
A vs B	0.0383±0.001	0.0292±0.001	2210.909	0.009
A vs C	0.0383±0.001	0.0201±0.001	2210.909	0.018
B vs C	0.024 ±0.006	0.0201±0.001	2210.909	0.009

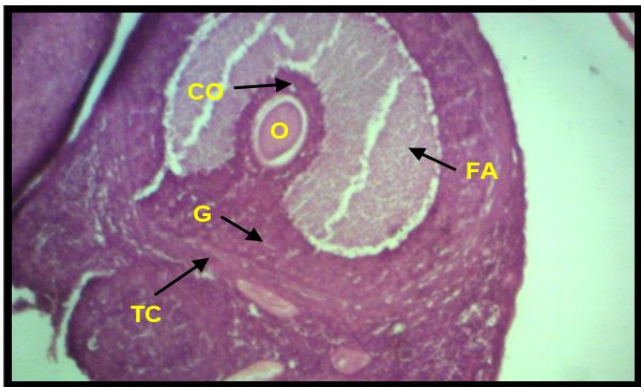

Figure 1. Photomicrograph showing histological section of ovarian parenchyma of control group A rat with normal architecture of ovarian follicle with Cumulus oophorus (CO) Follicular antrum (FA) Oocyte (O) Granulosa cells (G) Theca cells (TC) (H&E) x 400

Table III: Histopathological changes comparison across the study groups

Groups	Blood congestions			Cellular hypertrophy			Oocyte degeneration			Vacuolation		
	Yes	**No**	**Total**	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
Control group A	1	9	10	0	10	10	1	9	10	1	9	10
	8.3%	50.0%	33.3%	0.0%	50.0%	33.3%	7.7%	52.9%	33.3%	7.7%	52.9%	33.3%
Experimental group B	3	7	10	3	7	10	3	7	10	4	6	10
	25.0%	38.9%	33.3%	30.0%	35.0%	33.3%	23.1%	41.2%	33.3%	30.8%	35.3%	33.3%
Experimental group C	8	2	10	7	3	10	9	1	10	8	2	10
	66.7%	11.1%	33.3%	70.0%	15.0%	33.3%	69.2%	5.9%	33.3%	61.5%	11.8%	33.3%
Chi-value		**10.83**			**11.10**			**14.11**			**10.04**	
p-value		**0.004**			**0.003**			**0.001**			**0.007**	

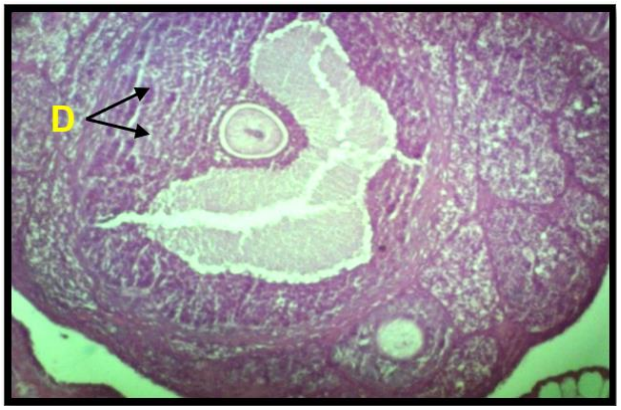

Fig-2. Photomicrograph showing histological section of ovarian parenchyma of experimental group B rat with (D) Degeneration of oocyte (H&E) x 400.

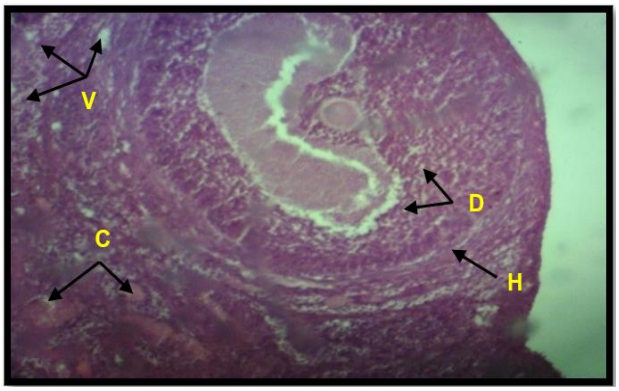

Figure 3. Photomicrograph showing histological section of ovarian parenchyma of experimental group B rat with (D) Degeneration of oocyte; (V) Vacuolations; (C) Congestion; (H) Cellular hypertrophy. (H&E) x 400

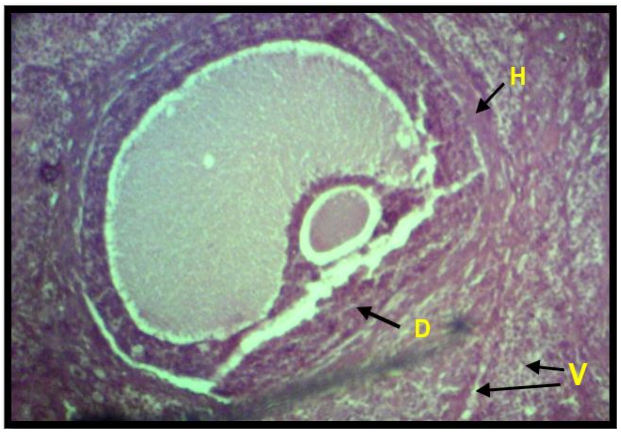

Fig-4. Photomicrograph showing histological section of ovarian parenchyma of experimental group C rat with (D) Degeneration of oocyte; (V) Vacuolations; (H) Cellular hypertrophy. (H&E) x 400

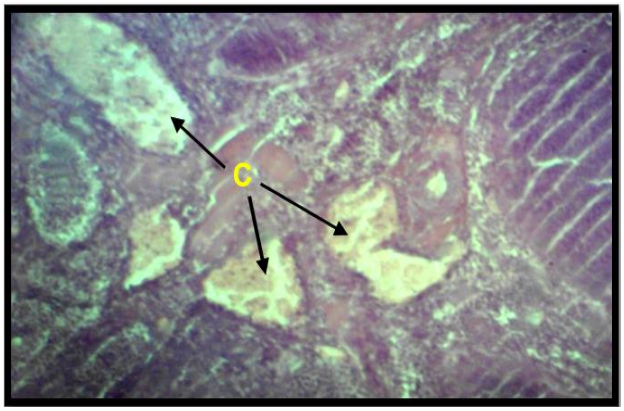

Figure 5. Photomicrograph showing histological section of ovarian parenchyma of experimental group C rat with (C) Congestion (H&E). x 400

Discussion

Sodium Benzoate is primarily used to extend the shelf life of food items and prevent microbial spoilage. The effects of Sodium Benzoate on reproductive health in females, specifically in relation to fertility and the reproductive system, are an area of ongoing scientific research. While there is limited direct evidence specifically focused on Sodium Benzoate's impact on female reproductive health, some studies have examined related areas that might provide insights. In this study, the average ovarian weight in the control group was 0.065 grams, which was higher compared to group B (0.039 grams) and group C. However, these differences were not statistically significant ($p>0.05$). The post hoc ANOVA analysis also revealed that ovarian weight more decreased in group C while findings were statistically insignificant ($p>0.05$). In a consistent study by Sohrabi et al[15] it was reported that NaB, when administered at a concentration of 560 mg/kg, resulted in a reduction in ovarian weight, as well as a decrease in the levels of FSH and LH hormones compared to the control group. Additionally, at a concentration of 280 mg, sodium benzoate led to a decrease in progesterone levels when compared to the control group. In a study conducted by Al-Gnami SA et al[14] the effects of NaB on ovarian function were investigated. The results revealed that in the T1 group, there was a noticeable inhibition of follicular development, alongside congestion in the ovarian stroma, when compared to the control group. In another study, significant reduction of heart weight was observed by Al-Ameen SA et al[16]. Inconsistently, Awad FM et al[18] reported that there was no significant reduction in the weight of testes in male rats of experimental group. These findings suggest that NaB may negatively affect ovarian

structure and function, leading to impaired follicular maturation and disruption of the ovarian tissue.

Based on the histological analysis, there was a significant increase in blood congestion observed in group C (66.7%) compared to group B (25.0%) and the control group (8.3%) ($p<0.004$). This suggests that Sodium Benzoate may disrupt normal blood flow and vascular integrity in the ovarian tissue. Altered blood circulation can have implications for the delivery of nutrients, oxygen, and hormonal signals to the ovaries, potentially affecting their normal functioning. In comparison to this study, a study examined the effects of NaB on ovarian histology in female rats. It reported that sodium benzoate exposure led to an increase in blood congestion within ovarian tissue. This finding aligns with the observations of Al-Gnami SA et al[14], who also reported blood congestion in experimental groups exposed to NaB. Similarly, Akter D et al[18] and C. Jyothi et al[19] observed congestion in the liver and kidneys of mice and in the medullary part of ovaries and myometrium of the uterus in rats, respectively, further supporting the findings of the current study.

According to this study, a significant increase in cellular hypertrophy was observed in Group C (70.0%) compared to Group B (30.0%) and the control group (0%) $p = 0.001$. However the limited literature exists on the effects of sodium benzoate on tissues of the ovaries. In the study by Suljević et al[20] reported marked cellular hypertrophy in the hepatocytes of rats, which aligns with the results of the present study. On other hand, Zeghib et al[21] observed massive glomerular atrophy in the kidneys of rats, demonstrating inconsistent effects in different tissues in animals. The alterations in cell size may adversely affect the normal development and maturation of ovarian cells, potentially impairing fertility and function of the ovaries.

Increased oocyte degeneration findings in this study are consistent with the study done by Al-Gnami SA et al[14], where reported the raised oocyte degeneration in the rats treated by the sodium benzoate. Consistently, Sohrabi D et al[15] found oocyte degeneration associated to the sodium benzoate exposure. Additionally, El-Shennawy L et al[12] demonstrated that the sodium benzoate adversely affected male reproductive health, causing the decreases in sperm count and disrupting the structure of seminiferous tubules in the testes of the Rats. The findings highlighting that the sodium benzoate may potential to impair the reproductive organs in female and males. Furthermore, degenerative changes in multiple organs, including the Lungs, heart, liver, spleen, and the testes, were found by Dinca V et al[22], aligning with the degenerative trends observed in the present report. The Oocytes are integral to reproductive success, as their quality and viability are essential for successful fertilization and the proper development of the embryo. Increases in the oocyte degeneration underscored the potential detrimental effects of sodium benzoate on reproductive health, justifying the further experimental research into its toxicological mechanisms and the broader reproductive consequences.

According to the findings of this study, a significant increase in vacuolation was observed in group C (61.5%) compared to group B (30.8%) and the control group (7.7%), which were align with the study by Moghimi et al[23], which also reported similar effects of sodium benzoate exposure. Our findings were also consistent with Mondal et al[24], where they observed vacuolation in the ovarian stroma of experimental groups and cellular damage. Consistently Imoni et al[25] observed the vacuoles as predominant histopathological findings in the testes of male rats, highlighting the sodium benzoate NaB potential to induce vacuolation across different tissues. Few other studies also reported that the NaB has also been shown to cause comparable histological alterations in the brain and testicular tissues.[17,26] Though, Khan LS et al[27] did not reported the vacuolation in their animal study, which contrasts with the present study. Presence of vacuolation underscores NaB potential to disrupt normal cellular function and the structure, emphasizing the need for further research on its histopathological effects across various tissues. It's essential to note that the available evidence is limited and further research is needed to establish a comprehensive understanding the effects of NaB on ovarian health. Additional studies with larger sample sizes, dose-dependent analyses, and longer exposure durations would provide more conclusive evidence regarding the specific mechanisms and implications of NaB on the tissues of the ovaries.

Conclusion

Study revealed that (NaB) induces moderate to significant morphometric and histopathological alterations in the ovaries of adult female albino Wistar rats, with the severity of effects increasing in a dose-dependent manner. These findings provide anatomical and histological evidence of NaB's toxicity to the reproductive system, emphasizing the need for strict monitoring and regulation of its use in food and consumer products to protect ovarian health. Proper

regulation of NaB levels in food, along with public awareness initiatives, can help educate consumers about its potential risks. However, further research involving larger sample sizes, detailed dose-dependent analysis, and long-term exposure studies is necessary to validate these results and gain a deeper understanding of NaB's effects on the ovaries, including the underlying mechanisms involved.

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