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Roles of Quercetin and Omeprazole in Ovotoxicity Induced by Indomethacin in Wistar Rats

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ABSTRACT

Background: Quercetin, a flavonoid in fruits and vegetables, offers health benefits like anti-carcinogenic, anti-inflammatory, and antioxidant effects. This work investigated role of quercetin against indomethacin-induced histological and functional changes in the ovaries of female Wistar rats.

Methods: 25 adult female Wistar rats with an average weight of 150 g (± 10 g) were used in the experiment, they were randomly assigned into 5 groups. All animals except those in control group (group A) were given a single oral dose of 30 mg/kg of indomethacin. Group B - induced with (30mg/kg) indomethacin only, in addition group C, D, E received, omeprazole, quercetin (50mg/kg), omeprazole (20mg/kg) and quercetin (50mg/kg) respectively. All administration were done orally for 30days.

Results: Reduced FSH serum levels were observed in the indomethacin and omeprazole treated group compared to other groups. There was a reduction of LH serum in the indomethacin and omeprazole treated group compared to the control group. Serum lipid peroxidase level concentration was significantly elevated in the indomethacin only treated group compared to the control and all other treated groups. Histological evaluation revealed pathological changes in the indomethacin only treated group.

Conclusions: Indomethacin negatively impacts ovarian function while quercetin confers a protective role. The triple combination of indomethacin, omeprazole, and quercetin shows observable positive effect of quercetin against indomethacin-induced ovotoxicity

Key words: Lipid Peroxidation, Anti-Inflammatory Agent, Follicle Stimulating Hormone, Luteinizing Hormone, Indomethacin.

1. INTRODUCTION

The female reproductive system is a sophisticated network of internal and external sex organs crucial for offspring production. The ovary, a pivotal organ in this system, not only produces eggs (ova) but also plays a vital role in hormonal regulation, influencing the menstrual cycle and fertility[1]. Disruption of the delicate balance within the female reproductive system by factors such as inflammation, oxidative stress, and hormonal imbalances can cause histo-pathological changes in the ovary and lead to fertility problems and other reproductive disorders[2].

Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), is commonly prescribed to alleviate symptoms of inflammation, including fever, pain, stiffness, swelling and also being used to induce gastric ulceration in rats[3]. Its mechanism of action involves the inhibition of prostaglandin production through the inhibition of cyclooxygenase, an enzyme catalyzing prostaglandin synthesis[4]. Indomethacin has demonstrated a consistent ability to impede ovulation[5]. Research has also suggested that the anti-ovulatory impact of indomethacin in rats is attributed to inducing several rupture sites on the basolateral or apical sides of the follicle therefore the luteinized follicles entrapped the oocyte rather than the direct inhibition of ovulation [6]. Athanasiou, et al [7] reported delayed follicular rupture in clinical trial study. Previous study by Tsubota, et al.,[8] on the toxicology effect of indomethacin, reported

follicular cyst, in the metestrus phase of animal treated with 4 mg/kg of indomethacin for 4 weeks[8].

Omeprazole, can be identify under the brand names Prilosec and Losec, belongs to the class of proton-pump inhibitors (PPIs). It is employed in the management of conditions such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger–Ellison syndrome. Its mechanism of action involves the inhibition of the proton pump located in the stomach lining, leading to a reduction in the secretion of stomach acid [9]. It inhibits the parietal cell H+ / K+ ATP pump, the final step of acid production. Omeprazole undergoes extensive metabolism primarily through the hepatic cytochrome P450 enzyme system, mainly involving CYP2C19 and CYP3A4 isozymes[10]. Omeprazole has been reported to elevate oxidative stress[11], potentially causing alterations in DNA, possibly by inducing an overproduction of reactive oxygen species (ROS) [12]. It was theorized by Akindele, et al [13] that long-term use of PPIs, especially at high doses, may increase the incidence of cancer especially in female animals. It was observed that female animals seem to be more affected by the adverse effects of long-term use of omeprazole than male animals.

Quercetin, a flavonoid found in fruits and vegetables, possesses diverse biological properties, including anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant activities. It also inhibits lipid peroxidation, platelet aggregation, and capillary permeability, while stimulating mitochondrial biogenesis[14]. Quercetin has been reported to regulate the phosphorylation of the PI3K/Akt/FoxO3a signaling pathway, inhibit oxidative stress, reduce ovarian tissue damage, improve the ovarian response and restore ovarian reserve function[15]. A study on effect of quercetin on letrozole (LETZ)-induced PCOS in female mice reported that quercetin decreases serum level of testosterone, FSH and LH [16].

From the literatures, it has been revealed that indomethacin and omeprazole induced damages in different anatomical structure while protective roles of quercetin against different toxicants are well established. To our knowledge, the protective effects of quercetin and omeprazole or the combination of the two compounds against indomethacin-induced histopathology and level of gonadotropins (FSH and LH) changes in the ovary of the Wistar rat remains relatively unexplored.

2. METHODOLOGY

2.1 Sourcing and Preparation of Compounds

Indomethacin and Omeprazole were procured from MedChemExpress (United Kingdom) while Quercetin was procured from Sigma Aldrich (USA). The compounds were authenticated at the Pharmacology Department, Osun State University, Osogbo. 50mg of each of these compounds were dissolved in 100ml of distilled water: i.e. 1ml of the solution contains 0.5 mg of the solvent (Stock solution). The solution was allowed to stand for some minutes with constant shaken for proper dissolution.

2.2 Experimental Design

Twenty-five (25) adults Female Wistar rats were randomly assigned into 5 groups designated as A, B, C, D and E with 5 rats (n=5) in each group. All animals except those in control group (group A) were induced with a single oral dose of 30 mg/kg of indomethacin. All administration were done orally for 30days. The groupings and dosage of treatments are as follows;

Group A - Control group (received only physiological saline and feed).

Group B - Induced with (30 mg/kg) indomethacin only.

Group C - Induced with (30 mg/kg) indomethacin and co-treated with omeprazole 20 mg/kg.

Group D - Induced with indomethacin (30 mg/kg) and co-treated with quercetin (50 mg/kg).

Group E - Induced with indomethacin (30 mg/kg) and co-treated with omeprazole (20 mg/kg) and quercetin (50 mg/kg).

All protocols and treatment procedures were done according to the Institutional Animal Care and Use Committee (IACUC) guidelines and as approved by the Faculty of Basic Medical Sciences Ethics Review Committee, Osun State University, Osogbo, Nigeria.

2.3 Animal Sacrifice and Samples Collection

Twenty-four hours after the last administration, the experimental rats were sacrificed by cervical dislocation, blood for biochemical assays were collected from the apex of the left ventricle and dispensed into the red-topped 10 ml bottles while the rat ovaries were harvested and fixed in Bouin's fluid.

2.4 Histological Examination

The ovaries were fixed in Bouin's solution, the volume of fixative was at least 10× the volume of the sample. For embedding, fixed ovarian samples were dehydrated in increasing concentrations of ethanol (70%, 80%, 95%, 100% ×3), cleared in xylene (×3) and immediately dipped in molten paraffin wax, and finally embedded in molten paraffin wax to make a paraffin block. The tissues were serially sectioned at 5 µm thickness from the paraffin block using the rotary microtome. The sections were transferred to a glass slide. Histological demonstration was carried out in paraffin wax embedded sections which was stained with hematoxylin and eosin for general cytoarchitectural demonstration after floating in a water bath at 40°C.

2.5 Analysis of Follicle Stimulating and Luteinizing Hormones

The blood samples collected into the red-topped sample bottles were centrifuged so as to separate the serum, which was then put in storage until it was needed. The Enzyme-linked- Immunosorbent Assay ELISA kits that were used were obtained from Sigma Aldrich (USA) and were built on the competitive inhibition enzyme immunoassay methodology. The kits' microtiter plate already has a specific protein pre-coated on it. An anti-LH, and anti-FSH, antibody biotin-conjugated was added to the appropriate microplate wells once the addition was made of standards or samples. The TMB substrate solution was then added to each microplate well, followed by the addition of an avidin-horseradish peroxidase (HRP) conjugate, which was then incubated for 45 minutes. The enzyme substrate reaction was stopped using the kits' stop solution, and the colour shift was detected using an ELISA reader that operates at a wavelength of 450 ± 10 nm.

2.6 Analysis of Lipid Peroxidation

Twenty microliters (20 µL) of serum were gently mixed with 500 µL of 42 mM sulfuric acid in a microcentrifuge tube. To this mixture, a volume of 125 µL of Phosphotungstic Acid Solution was added, and the contents were thoroughly mixed by vortexing. The samples were incubated at room temperature for a duration of 5 minutes. Subsequently, centrifugation was performed at 13,000 × g for 3 minutes. The supernatant was carefully removed, and the pellet was retained for further assay. The pellet, obtained from the previous centrifugation, was then resuspended on ice using the water/BHT solution. The volume was meticulously adjusted to 200 µL

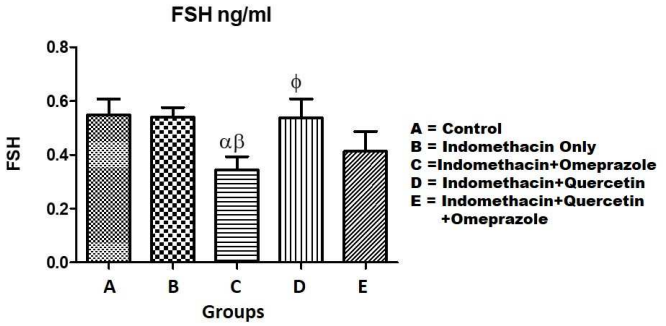


Figure 1: Effect of Quercetin, Omeprazole and Indomethacin Administration on Serum FSH in Female Wistar Rats. α Comparison with the Control Group. β Comparison with the Indomethacin. Φ Comparison with the Indomethacin Co-Administered with Omeprazole. p<0.005; n=5.

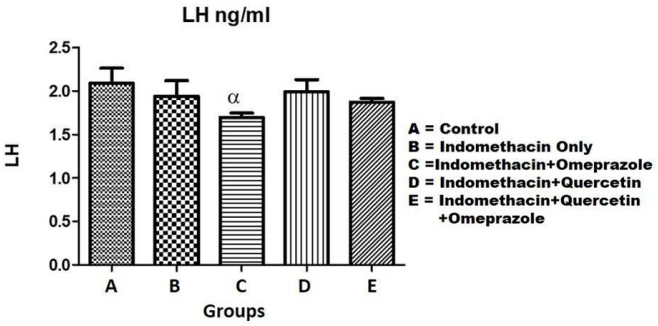


Figure 2: Effect of Quercetin, Omeprazole and Indomethacin Administration on Serum LH in Female Wistar Rats. α Comparison with the Control Group. p<0.005; n=5.

with water. Six hundred microliters (600 µL) of the TBA solution were added into the sample, then incubation at 95 °C for a duration of 60 minutes, were cooled to room temperature in an ice bath for 10 minutes.

Sample was mixed with 300 µL of 1-butanol and 100 µL of 5 M NaCl. The mixture was vigorously vortexed and subsequently centrifuged for 3 minutes at 16,000 × g at room temperature. The resulting 1-butanol layer (the top layer) was carefully transferred to a new centrifuge tube, and the 1-butanol was removed. This removal was achieved either heating on a hot block at 55 °C. The remaining material was resuspended in 200 µL of ultrapure water, thoroughly mixed, and then 200 µL of this solution were added into a 96-well plate, the absorbance (A) was measured at 532 nm using colorimeter.

2.7 Statistical Analysis

For all statistical studies, GraphPad Prism version 8.03 was utilized. All results were reported as Mean±SEM, with one-way ANOVA used to examine differences between groups. Multiple comparisons were adjusted using Tukey's test. Statistical significance was defined as a p value of less than 0.05.

2.8 Data Availability Statement

The data that support the findings of this study is available at https://doi.org/10.5281/zenodo.14846657

3. RESULT

3.1 Serum Follicle Stimulating Hormone Concentration was Decreased with the use of Indomethacin and Omeprazole

Figure 1 shows the mean value of serum FSH concentration after the administration of indomethacin, omeprazole and quercetin. A significant reduction in serum FSH concentration was observed in the group treated with indomethacin and omeprazole when compared with control, indomethacin only and indomethacin co-administered with quercetin treated groups. More also, slight decrease in serum FSH concentration was observed in indomethacin co-administered with omeprazole and quercetin (though not scientifically significant). No significant difference was seen in serum FSH concentration among the control, indomethacin only and indomethacin co-administered with quercetin treated groups.

3.2 Serum Luteinizing Hormone Concentration was Decreased with the Use of Indomethacin and Omeprazole

Figure 2 shows the mean value of serum LH concentration after the administration of indomethacin, omeprazole and quercetin. A significant reduction in serum LH concentration was observed in the group treated with indomethacin and omeprazole when compared with control group. Moreover, No significant difference was seen in serum LH concentration among the control, indomethacin only and indomethacin co-administered with quercetin treated groups.

3.3 Serum Lipid Peroxidase Concentration was Increased with the Use of Indomethacin and Omeprazole

Figure 3 shows the mean value of serum lipid peroxidase concentration after the administration of indomethacin, omeprazole and quercetin. High significant elevation of serum lipid peroxidase concentration was observed in the group treated with indomethacin alone when compared with the control and all other treated groups. Furthermore, no significant difference was seen in serum lipid concentration among the control, indomethacin co-administered with omeprazole, indomethacin co-administered with quercetin and indomethacin co-administered with omeprazole and quercetin treated groups.

3.4 Quercetin Attenuates Follicular Cell Degeneration Induced by Indomethacin and Omeprazole

Figure 4 shows the photomicrograph showing the general cytoarchitecture of the ovaries of rats across the various experimental groups using H&E stain (magnification: x100). 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 ovarian cells and follicles in the control group A, Indomethacin co-treated with Quercetin group D and Indomethacin co-treated with omeprazole and quercetin (Group E), no observable pathological changes were seen as the ovaries were characterized with the pres-

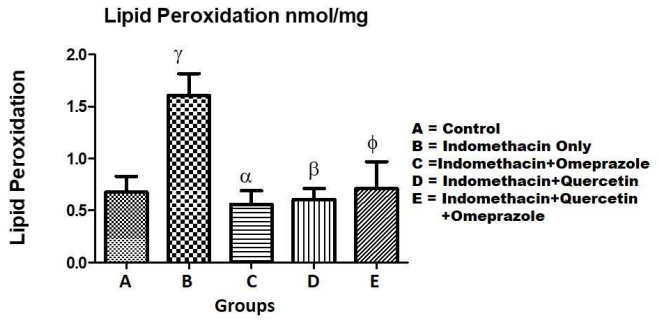
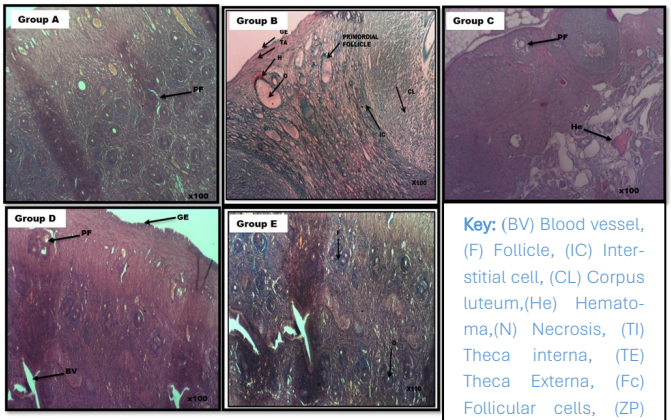


Figure 3: Effect of quercetin, Omeprazole and indomethacin administration on serum lipid peroxidase in female Wistar rats. p<0.005; p<0.001; n=5.

ence of numerous follicular cells with a normal and well-defined cellular density.

In group B (Indomethacin only treated group) the cytoarchitecture of the ovary showed slight degenerative follicular changes

Rats in group C (Indomethacin co-treated with omeprazole) the cytoarchitecture of the ovary showed the presence of hematoma of blood vessels and slight degenerative follicular cells changes, atrophied and atretic ovarian cells, highly disorganized follicles, and severe degenerative follicular cells changes were also observed. Degenerative changes were 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).



Key: (BV) Blood vessel, (F) Follicle, (IC) Interstitial cell, (CL) Corpus luteum,(He) Hematoma,(N) Necrosis, (TI) Theca interna, (TE) Theca Externa, (Fc) Follicular cells, (ZP) Zonapellucida, (GE) Germinal epithelium, (O) Oocyte, (TA) Tunica albuginea, (PF) Primary follicle, (SF) Secondary follicle, (A) Antrum, (AT) Adipose tissue, (GF) Graffian follicle.

Figure 4: Shows Photomicrograph of Histological Section of the Ovary Stained with Hematoxylin and Eosin (x100). A= Control; B= Indomethacin only; C= Indomethacin+Omeprazole; D= Indomethacin+Quercetin; E= Indomethacin+Quercetin+Omeprazole.

4. DISCUSSION

Toxicant, that causes histopahlogical changes in the ovary can cause damage to the oocyte contain in the ovarian follicle and also even the follicle, this can produce premature ovarian failure because this oocyte destroyed cannot be replaced [17]. Some medications may also affect reproductive functioning and thus may have an impact on fertility. Some have been implicated to serve as toxin to structures of the female reproductive system and induced wide range of changes on female reproductive system and causes reproductive hormonal imbalance. This study focus on investigating the possible roles of quercetin and omeprazole in suppression of histopathological changes induced by indomethacin in the ovary of female wistar rat.

4.1 Serum Hormone Concentrations

Indomethacin was used in this study as a toxicant while omeprazole was used as a treatment for indomethacin-induced ovarian damage. Quercetin was explored as a counter-effect to Indomethacin and Omeprazole to examine its potential role in the reversal or mitigation of ovarian damage and gonadotrophic hormone imbalance.

The findings from this study regarding the significant decrease in serum FSH concentration in the group treated with indomethacin and omeprazole align with previous research. Mokshagundam and Minocha [18] found that omeprazole, when administered alone, had no effect on FSH levels. Similarly, various studies have reported that indomethacin alone did not significantly affect FSH levels, consistent with reports such as Shirota et al.,[19]which stated that indomethacin-induced inhibition of prostaglandin synthesis does not impact the selective release of FSH during the peri-ovulatory period.

Furthermore, reports such as those by Athanasiou et al. [7], Hester et al., [20], and Duncan [21] indicated that indomethacin, when administered before ovulation, can prevent follicle rupture without affecting menstrual cycle length or FSH, LH, estradiol, and progesterone concentrations. These findings are in line with the overall level of FSH observed in the indomethacin-treated group in this study.

In contrast study conducted by Hiroshi, et al., [22] reported substantial reduction in the ovarian PGF2α levels and decreased in the basal serum level of inhibin, whereby serum FSH level significantly increased, 24hrs after indomethacin administration, this suggested the operation of negative feedback regulation between FSH and inhibin in these animal[22]. The results demonstrate the inhibitory effects of indomethacin on inhibin production, indicating a regulatory role of prostaglandins in the secretion of these hormones from the gonadotrophin-stimulated ovary, this was not observe in the present study in indomethacin only treated group, even though the level of inhibin was not measured in this study therefore the reduction in the serum FSH concentrated in indomethacin co-administered omeprazole group may be due to the synergistic effect of indomethacin and omeprazole, largely by the effect of omeprazole, because reduction in level of FSH was only observed in omeprazole co administered group although this study cannot conclusively claim this relationship, but it hints at a potential interaction. Lastly the effect of quercetin could be observed in indomethacin co-administered with omeprazole and quercetin treated group to regulate level of FSH even though it was reported that Quercetin elevated serum anti-Müllerian hormone, estradiol, and progesterone levels, decreased serum follicle-stimulating hormone and luteinizing hormone levels, and alleviated ovarian pathology in exposure to cyclophosphamide (CTX) [23]. Likewise Victor et al. observed that quercetin enhanced protection against cadmium chloride (CdCl2)-induced disruptions in reproductive hormones (E2, P, FSH, and LH) [24]

Result from this study revealed that co-administration of indomethacin and omeprazole led to a significant decrease in LH serum levels compared to the control group, while there were no significant differences in LH levels among the control, indomethacin alone, and indomethacin co-administered with quercetin groups. This result shows that quercetin have protective effect against toxin induced reproductive hormone disruption which was evidence in co-administration of indomethacin and omeprazole treated group, which quercetin protective effect was also observed by Victor et al., against cadmium chloride (CdCl2)-induced disruptions in reproductive hormones (E2, P, FSH, and LH) [24].

In a study by Kellis et al [25] it was reported that quercetin inhibits the conversion of androstenedione to estrone and testosterone to estradiol in human placental and ovarian microsomes [25]. Also findings from a study indicate that the levels of E2, P, FSH, and LH in menopausal rats treated with quercetin did not show significant differences compared to the control group [26]. A potential explanation for variation in observation could be the utilization of distinct animal models.

This study didn't observe any significant influence of indomethacin

on the serum level of LH, also the reduction of LH may be induced by omeprazole as its seen in FSH.

Therefore for what was observed in the data present in this study on effect of the administered drug on level of FSH and LH, it could be reported that Indomethacin and omeprazole co-treatment resulted in a significant decrease in serum FSH and LH concentrations, suggesting potential damage to ovarian function. However, quercetin co-administration showed protective effects, supporting previous studies on quercetin's positive impact on reproductive hormones.

4.2 Serum Lipid Peroxidase Concentration

Non-steroidal anti-inflammatory drugs (NSAIDs), commonly utilized for alleviating pain and inflammation, have been identified to trigger oxidative and endoplasmic reticulum (ER) stresses, leading to apoptosis in cancer cells [27], same group has previously documented that extended treatment (16 hours) of primary cultures of guinea-pig gastric mucosal cells with NSAIDs (1 mM for indomethacin) results in the induction of apoptosis [28].

Significant elevation of lipid peroxidation in the indomethacin only treated group compared to control and all other treated groups was observed in this study. Therefore, Indomethacin is observed to induced a significant increase in serum lipid peroxidase concentration, indicating oxidative damage to the ovaries. Omeprazole co -treatment reduced this elevation, and quercetin co-administration further attenuated lipid peroxidation, demonstrating the antioxidant properties of quercetin. This was in line with an observation reported that indomethacin increase the tissue levels of MDA and a significant decrease in the mean tissue levels of GSH, SOD, and NO also increase in lipid peroxidation where there is decrease in GSH, SOD and lipid peroxidation level in indomethacin –quercetin treated group [29]. Also levels of lipid peroxides in the gastric mucosa was reported to be elevated over time following the administration of indomethacin [30]. It was also stated in a report that the administration of indomethacin led to a reduction in the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-px). The decline in SOD and GSH-px activity within the gastric mucosa may exacerbate mucosal injury through the actions of free radicals and lipid peroxidation [31].

The combined findings from this investigation and other studies examining the impact of indomethacin and indomethacin+quercetin treatment on experimental animals indicate that quercetin plays a modulating role in the oxidative stress alterations induced by indomethacin. This modulation involves a reduction in the levels of proinflammatory markers and an increase in the levels of anti-inflammatory markers.

4.3 Quercetin Attenuates Follicular Cell Degeneration Induced by Indomethacin and Omeprazole

Series of studies as have reported gastric oxidative damaged induced by indomethacin, findings by Yoshikawa, et al [30] indicate that the development of gastric mucosal injury induced by indomethacin involves a significant role played by active oxygen species and lipid peroxidation. Furthermore, the exacerbated injury is attributed to the reduced activity of glutathione peroxidase, which accelerates the accumulation of hydrogen peroxide and lipid peroxides within the gastric mucosal cell. In this study only lipid peroxidation was quantify and the follicular cell degeneration induced by indomethacin was analyses for all group of experimental animal.

In which it was observed in this study through histological evaluation in Indomethacin only treated group, cytoarchitecture of the ovary showed slight degenerative follicular cells changes and Indomethacin co-treated with omeprazole, showed atrophied and atretic ovarian cells, highly disorganized follicles, presence of hematoma of blood vessel, and severe degenerative follicular cells changes. Degenerative changes were observed in the surrounding cells with wasted and atretic follicles. Furthermore, necrotic ovarian cells, and the presence of hematoma, were observed.

Histological evaluation confirmed the damaging effects of indomethacin on ovarian tissues. Omeprazole co-treatment intensify these effects, indicating it possible oxidative damaged effect .Quercetin co-administration showed no observable pathological changes, indicating its potential as a protective agent against indomethacin-induced ovarian damage.

This histo-pathological changes induced by indomethacin was also reported in an experiment conducted in the administration of indomethacin in increasing dosage manner, the histo-pathological examination of the ovaries of higher doses of IMC treated group reported include a reduced number of surviving follicles, including primary, secondary, and corpus lutea, a higher proportion of atretic follicles compared to the other groups. Vasoconstriction and inflammation were evident in the ovaries of all IMC treated groups, also reported an inflammatory response in the treated groups, the previous study also report infiltration of inflammatory cells, inflammatory changes and smooth muscle atrophy [32] , which indicate the follicular and ovarian degeneration indomethacin induced changes observed in this study in indomethacin treated group.

In contradiction to what was observed in omeprazole co administration of indomethacin group in this study, it was reported in an experimental study that Omeprazole has an antioxidant effect and it can have a protective function in the oxidative damage induced by ischemia-reperfusion, where it was found that omeprazole prevents oxidative damage due to ischemia-reperfusion injury in rat ovarian tissue [33]. OME (Omeprazole) has been documented to enhance in-vivo antioxidant levels and capacity [34].

Previous study reported that the ovarian tissues of female animals, given OME at all doses did not induce any histopathological abnormalities [13] in support of what was observed in this study. Akindele et al [13] also reported that OME elicited a significant reduction in blood levels of catalase and a non-significant reduction in other antioxidant parameters like GSH and SOD, alluding to the oxidative stress potential of OME. This is one of the mechanisms of the adverse effects of long-term use of OME [35].

It is reported that OME has been associated with causing liver damage, [36], displaying adverse effects on hepatic regeneration [37], and resulting in elevated levels of GPT and GOT liver enzymes, indicative of liver dysfunction [38]. Moreover, omeprazole has been shown to induce elevations in AST, ALT, and cholesterol levels, which subsequently decreased upon discontinuation of treatment [39].

Therefore studies have indicated that omeprazole is capable of inducing oxidative damage, as it was observed in this study where it intensify the oxidative damage induced by indomethacin.

Lastly Indomethacin co-treated with Quercetin group D and Indomethacin co-treated with omeprazole and quercetin (Group E), 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. According to Zheng et al. [15] it was stated that quercetin can restore ovarian function and inhibit oxidative stress by regulating the PI3K/Akt/FoxO3a signaling. The above results suggest that the protective effect of quercetin on indomethacin-induced may be related to its oestrogen-like effect. Quercetin can increase the number of follicles in the ovary and improve ovarian function, which is manifested in the increase in AMH protein and its receptor in ovarian tissue. Furthermore, quercetin can increase the expression of FSHR and LHR in ovarian tissue. FSH and LH interact in the ovary to promote follicular development. On the one hand, this phenomenon may be related to quercetin having an oestrogen-like effect, which can synergize with FSH to increase the content of FSHR in granulosa cells to increase the sensitivity of granulosa cells to FSH and promote follicular growth and development, which is consistent with existing studies [40].

4.1 Conclusion

Findings from this study showed that indomethacin administration causes decrease FSH and LH levels as well as increase in lipid peroxidation thereby leading to significant alteration in ovarian function. While on the other hand, quercetin ameliorates these deleterious effects of indomethacin thereby improving ovarian function. We therefore conclude that quercetin can protect against indomethacin-induced damages in the ovary of adult Wistar rats.

4.2 Acknowledgement

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Contributor Roles Taxonomy (CRediT) Statement

AOS: Conceptualization, Data curation, Formal analysis, review and editing , supervision
TB-U: Conceptualization, methodology, supervision, visualization, review and editing.
ATO: Data curation, Writing, review and editing
AOO: Conceptualization, methodology, review and editing
IB : Conceptualization, methodology, review and editing
BAF: Conceptualization, review and editing

Conflicts of Interest:

The authors declare that they have no conflict of interest.

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