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The impacts of domperidone and nanoparticals on hormones and tissues of rabbit female reproductive system

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ABSTRACT

The study aimed at the effect of gold nanoparticles and the drug Domperidone on the reproductive system of local female rabbits. In this study, female rabbits whose weight ranged between (1500-1700 gm) were divided into four treatments. Each transaction includes five transactions. The first group includes (control group) and was given water and food only, and the second group was dosed orally the drug Domperidone in the form of a syrup at a dose of (0.3) mg / kg at a rate of three times a day with water and food, and the third group was dosed with a gold nano solution at a dose of 0.05 mg / kg and a concentration of mg 3.271 * 10-7 and the diameter of the gold particle is 60 nm and it was given orally to rabbits at a rate of once a day for two days only per week with water, and the fifth group (the drug group + gold nanoparticles) where they were dosed Domperidone at a dose of 0.3 mg / kg orally and a solution of gold nanoparticles was dosed at a dose of 0.05 mg / kg, a concentration of 3.271 mg * 10-7, and a gold particle diameter of 60 nm, and it is given once a day for two days only in a week, and also with water and food. It was dosed to all groups for a period of (50) days. The dose of the first gold nanoparticles solution and the drug Domperidone in the rabbits resulted in a decrease in the concentration of the LH hormone compared with the control group and a decrease in the concentration of the LH hormone when they were dosed with the drug + gold nanoparticles group. One of the main histological effects observed in our study was the lysis of the primary follicle in the ovary of the Domperidone group.

تأثير الدومبيريدون والجسيمات النانوية على الهرمونات وأنسجة الجهاز التناسلي الأنثوي للأرانب

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الخلاصة

هدفت الدراسة تاثير جزيئات الذهب النانوية والدومبريدون على الجهاز التكاثري اناث الارانب المحلية في هذه الدراسة تم تقسيم اناث الارانب الذي تراوحت اوزانهم بين (1500 – 1700 غم) الى اربعة معاملات . تضم كل معاملة خمسة معاملات المجموعة الاولى تضم (مجموعة السيطرة) وتم اعطاؤها ماء وغذاء فقط والمجموعة الثانية تم تجريعها فمويا عقار الدومبيريدون على شكل شراب جرعة (0.3 mg / kg) بمعدل ثلاث أوقات يومياً مع الماء والغذاء والمجموعة الثالثة تم تجريعها محلول الذهب النانوي بجرعة 0.05 mg / kg وتركيز 7-10 * 3.271 mgوقطر جسيمه الذهب 60 nm واعطاؤها فمويا للأرانب بمعدل مره واحدة باليوم ليومين فقط بالأسبوع مع الماء ,والمجموعة الخامسة (مجموعة العقار + الذهب النانوي) حيث تم تجريعها عقار الدومبيريدون بجرعة 0.3 mg / kg فمويا وتجرع محلول جسيمات الذهب النانوي بجرعة 0.05 mg / kg وتركيز 7-10 * 3.271 mg وقطر جسيمه الذهب 60 nm وتعطى مرة واحدة باليوم ليومين فقط بالأسبوع وأيضاً مع الماء والغذاء وتم التجريع لكل المجاميع لمدة (50) يوم . وادى تجريع الارانب تجريعها محلول الذهب النانوية وعقارالدومبريدون الى انخفاض في تركيز هرمون LH مقارنة مع مجموعة السيطرة وانخفاض في تركيز هرمون LH عند تجريعها مجموعة العقار + الذهب النانوية ومن التاثيرات النسيجية الرئيسة التي تم ملاحظتها في دراستنا تحلل الجريب الاولي في مبيض في مجموعة عقار الديمبريدون.

الكلمات الافتتاحية: الجسيمات النانونية وظائف الاعضاء والجهاز التناسلي الانثوي.

INTRODUCTION

Gold nanoparticles are a special type of fine gold particles whose dimensions are of the order of nanometers (one billionth of a meter). The size of GNPs has given researchers the advantage of using nanotechnology to discover facts inside cells where they can easily penetrate the cell envelope and monitor them where they can be used in drugs, genes, or disease detection and treatment (Kumari *et al*,2020). Gold is (safe), chemically inert, and one of the rarest metals on earth. Since the Middle Ages, there has been a great deal of interest in it up to the present time, as it is not only used in the jewelry industry, but also in the fields of medicine, environment, and technology. The gold nanoparticles used in the drug delivery process are often coated with a thin layer of molecules that help in adjusting the chemical properties. Some of these molecules or bonds are negatively charged and water-loving, while others are hydrophobic. The researchers found that the ability of the particles to enter the cell depends on Interaction of hydrophobic bonds with lipids in the cell membrane. (Connor and Broome. ,2018; muhamad *et al*,2019).

Pharmaceutical drugs contain different functional groups within the chemical composition that determines their solubility, stability, pharmacological activity and properties, as well as nanoparticles contain multi-component systems that contain surface-determining factors and recognition molecules, as GNPs contain the basic substance (gold) and its binding materials on the surface And showed that the absorption of GNP after oral administration depends on the particle size, and it was found that the small sizes cross the wall of the digestive tract after oral administration more easily than the large sizes. As absorption and distribution are inversely related to particle size (Rónavári *et al*, 2021)), and GNP is different from pharmaceutical drugs in that the second is eliminated in the body through metabolism or subtraction, while the first is nanoparticles that are resistant to elimination methods such as

metabolism and renal excretion. Nanoparticles are not excreted in the urine, but are found in the blood by the mediation of the reticuloendothelial system and subsequently accumulate in the liver and spleen. (Mikhailova, 2021).

Domperidone is a drug that increases the movement and contractions of the stomach and intestines, and is usually used to treat nausea and vomiting caused by taking certain medications, such as those used in the treatment of Parkinson's disease. For vomiting and a feeling of fullness of the stomach because it increases gastric emptying (Shen *et al*, 2021). Domperidone does not usually cross the blood-brain barrier, and its anti-emetic effect is due to a group of effects, as it acts on dopamine receptors in the chemoreceptor stimulation zone (CTZ) where It is located outside the physiological blood-blood barrier, and acts on (D2) receptors at the esophageal-gastric junction, thus blocking the action of dopamine associated with nausea from any cause (Suain and Mahmud, 2022). Domperidone may inhibit the activity of choline esterase (Doggrell and Hancox, 2014). Domperidone is a peripherally selective dopamine D2 and D3 receptor antagonist that has no clinical interaction with D1 receptors (Yedla and Sharmila, 2022) The drug provides relief from nausea by blocking D2 receptors in the chemoreceptor triggering zone (a site in the nervous system that mediates nausea) in the floor of the fourth ventricle (a location near the brain), as domperidone increases the motility of the upper gastrointestinal tract to a moderate degree and increases the decrease in pressure of the lower esophageal sphincter by blocking dopamine receptors in the membrane of the stomach and duodenum (Sharma *et al*, 2022) it prevents receptors dopamine in the anterior pituitary gland, which leads to increased secretion of prolactin, domperidone may be more beneficial in some patients and cause harm in others due to genetics (Krutsch and Datta, 2023).

MATERIALS AND METHODS

Preparation of animals

Female white rabbits with weights ranging between (1500-1700 g) were used. The experiment was carried out in a room with a temperature ranging between (20 ± 22 ℃) and the photo cycle was 12 hours of light, and 12 hours of darkness. The experiment was conducted in Samarra Pharmaceutical Laboratory. Preparation of laboratory animals. Female rabbits of the white type, weighing between (1500-1700 g), were used. The experiment was conducted in a room with a temperature ranging between (20 ± 22 m0) and the photoperiod was 12 hours of light and 12 hours of darkness. The female rabbits were placed in special metal cages for raising rabbits with a size of (70 X 100 cm) with a tray at the bottom of the cage and wood shavings were placed at the base of the cage, taking into account cleaning the tray and the cage completely every 48 hours and sterilizing them. The animals were left for (10) days for the purpose of acclimatization and adaptation before starting the dose and ensuring that they were not infected with diseases. The rabbits were fed with a special, ready-made feed purchased from local markets. The animals were given water and food in appropriate quantities in the form of two meals per day throughout the experiment period.

The animal care guidelines recommended by the Animal Ethics Committee of the College of Health and Medical Techniques/Al-Dour, Northern Technical University were followed (7/27/1579).

Experience Design

Gold nanoparticles prepared by Sigma-Aldrich USA in the form of a solution with a particle size of 60 nm, a dose of 0.05 mg/kg, a concentration of 3.271 mg, a surface area of 1.13E+04nm, a pH of 7, and a wavelength of 585 nm were used. Motilium (domperidone) from Janssen Pharmaceuticals/Belgium was used in the form of a syrup with a dose of 0.3 mg/kg, where each 1 ml of the syrup contains 1 mg of domperidone. The ages of the rabbits in the experiment ranged from 4-6 months. In this study, (32) female rabbits were used and divided into four groups, with each group having (8) rabbits. Consideration was taken of the equal weights of each group as much as possible before starting the study. The experiment was designed as follows:

First group, G1: (control group), was given food and water only for a period of (50) days

Second group, G2: (the drug group), was dosed orally with domperidone in the form of a syrup, at a dose of (0.3) mg/kg at a rate of three times a day with food and water for a period of (50) days.

Third group, G3: (the gold nanoparticles), was dosed with a gold nanoparticle solution at a dose of 0.05 mg / kg, a concentration of 3.271 mg * 10^{-7}, and a gold particle diameter of 60 nm, and it was given orally to rabbits at a rate of once a day for two days only per week, with water and food for (50) days.

Fourth group, **G4:** (drug group + gold nanoparticles), where they were dosed with Domperidone at a dose of 0.3 mg / kg orally, and a solution of gold nanoparticles was dosed at a dose of 0.05 mg / kg, with a concentration of 3.271 mg * 10^{-7}, and a gold particle diameter of 60 nm, and it was given once a day for only two days a week. And also with water and food for a period of (50 days).

Collection of samples

Blood samples were collected directly through the Cardiac heart puncture, where the volume of the sample taken was (5 ml) for each rabbit, and it was placed in a (Gel tube) for the purpose of separating it with a centrifuge at 5000 revolutions / min for a period of (15) minutes and keeping the samples At a temperature of (-20) degrees Celsius in Eppendorf tubes until hormonal analyzes are performed. Estimation of serum luteinizing hormone concentration (LH) and follicle-stimulating hormone (FSH) concentrations. The hormone FSH , LH was estimated by following the steps included with the ready-made analysis kit and according to the manufacturer's instructions for the ELISA technique (Vitt *et al*., 1998).

Tissue Sample Preparation

After dissecting the animals, extracting the ovaries and washing them with Phosphate solution, they were placed in a 10% neutral formalin buffer for an hour. The samples were then washed with tap water for half an hour to remove excess fixative solution. A series of procedures were then performed on them based on the method. (Bankroft and Stevens,1982) These are fixation, washing, drying, decantation, infiltration, burial, and staining of histological slides.

The histological slides were examined

Using a Novo-USA light microscope at magnifications of 40X–10X to determine the changes in the histological composition of each of the treated experimental groups compared to the control group.

Histological sectioning

The tissues were photographed using a color digital camera, a Novo microscope, and a Canon 2900 digital camera connected to an HP P4 computer. Images were printed using a printer.

Statistical Analysis

Data were analyzed by the ANOVA analysis, using the general linear model of the Statically Analysis System (SAS Institute, 2001). Significant treatment differences were evaluated using Duncan's multiple-range test (Duncan, 1955). All statements of significance are based on the 0.5 level of probability.

RESULTS AND DISCUSSION

The results shown in Figure (1) showed that there were no significant differences in FSH in all treatments compared to the control group. The results shown in figure (2) showed a significant increase in the LH hormone in the group treated with the first nanogold group and the drug group compared to the control group at (P≤0.05), and a significant decrease in the second nanogold group and the drug + nanogold group compared to the control group at (P≤0.05).

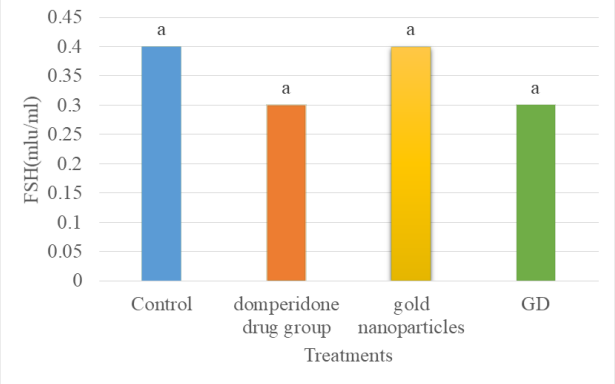

Fig-1: Effect domperidone and gold nanoparticles FSH concentrations (mlu/ml)

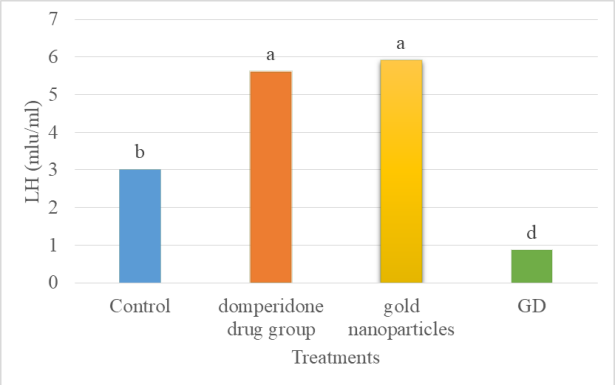

Fig-2: Effect domperidone and gold nanoparticles LH concentrations (mlu/ml)

The LH hormone works to promote ovulation and the explosion of the adult follicle in the middle of the menstrual cycle, and then the formation of the corpus luteum from the remains of the follicle. The concentration of the LH hormone begins to rise in the blood serum from the two days before the middle of the menstrual cycle, and there is a sudden rise and It is secreted rapidly 24 hours before ovulation, and it is believed that this sudden increase causes the explosion of the adult follicle and then ovulation (Scoullar *et al*, 2021). The LH hormone also has an important role in stimulating the white body after its formation to secrete estrogen and progesterone. The researcher indicated The LH hormone has an important role in the process of maturation of the egg and the occurrence of ovulation, and its level remains high for approximately 36 hours. Ovulation occurs 36 hours after the level of the LH hormone reaches its highest peak. Measuring the LH hormone is necessary to detect the ovulation process. The ovarian sex hormones estrogen and progesterone affect the secretion of the hormone. Gonadotropins (FSH, LH) are mediated by the anterior lobe of the pituitary gland through positive and negative feedback depending on their concentration in the plasma. Therefore, an increase in the level of estrogen reduces the secretion of FSH (negative feedback) and enhances the secretion of LH in abundant quantities (positive feedback) and vice versa (Guyton and Hall, 2020). The

level of LH increases in women in menopause or due to the cessation of the menstrual cycle due to primary failure of the ovaries as well as polycystic ovary syndrome. The level of the LH hormone decreases in cases of estrogen therapy, in ovarian or adrenal tumors that secrete estrogen or progesterone, and in menopause due to failure of the pituitary gland.

The FSH hormone plays a very important role in the growth of ovarian follicles, as it stimulates their growth and development from a primary follicle to a mature follicle, a kraph's follicle, ready to burst and release the egg with the help of the ovulation hormone LH in the middle of the menstrual cycle (luteinic phase) (Howard, 2021). The levels of sex hormones and steroid hormones in the blood are considered one of the most important factors that play a role in regulating the secretion of this hormone through a negative feedback mechanism in the hypothalamus and pituitary. (Zhao *et al*,2023) and through positive feedback in the ovary and pituitary gland, as a decrease in the level of progesterone concentration leads to an increase in the level of FSH concentration and vice versa (Chen *et al*, 2023).

Gold nanoparticles are also used in detecting and diagnosing cancer, as they have many advantages in cellular imaging, as gold nanoparticles have the ability to scatter light more intensely and brighter than other chemicals such as fluorine. Through this characteristic, cancerous tumors can be detected and diagnosed (Kumar *et al*, 2020) Gold nanoparticles are considered an effective system for delivering either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) to obtain a gene. Therefore, through this characteristic, gold nanoparticles can also be used for therapeutic purposes. Gold nanoparticles have been widely used in the medical field due to their manufacturing ability. In the form of a colloidal solution, it does not interact with biological tissue and is not oxidized, so it does not produce toxic effects in the tissue. Gold nanoparticles have been used in the treatment of brain cancer when gold nanoparticles interact with high-energy gamma ray photons. This interaction does not affect brain cells, and it also prevents the recurrence of the disease after treatment (Yücel *et al*, 2020) Gold nanoparticles are also used in the treatment of ovarian cancer, as the use of gold nanoparticles causes damage to cancerous ovarian cells, as the results of studies have shown an improvement in the treatment of the ovary using gold nanoparticles with no or minimal damage to the normal cells surrounding the cancerous cells that form them. For a cancerous tumor, when gold nanoparticles are injected into the site of the cancerous tumor with a radiation source, this leads to the generation of free radicals, which in turn cause significant damage to the cancer cells (Yang *et al*., 2022). There are side effects to the use of diclofenac, the effect of the drug on pregnancy, as studies and research indicate that the use of diclofenac during pregnancy increases the risk of miscarriage and the appearance of birth defects (Eliot, 2022).

The study showed (Silva *et al* ,2021) domperidone drug can cause dysfunctions in male reproduction, as its use causes an excessive increase in prolactin (PRL) levels, observed in 50% of cases. PRL modulates the FSH and LH receptors in Sértoli and Leydig cells, and is involved in germ cell meiosis, regulating various functions of the testicles. The increase in PRL levels interrupts the pulsatile secretion of gonadotropin-releasing hormone, inhibits the release of LH, FSH, and directly reduces gonadal steroidogenesis, causing significant effects on spermatogenesis, as well as clinical effects such as acquired hypogonadotrophic hypogonadism and even infertility. Giventhe above, it can be considered that domperidone is a possible inducer of reproductive dysfunctions in men, due to its potential to cause deregulation in the hormone that regulates male gonads.

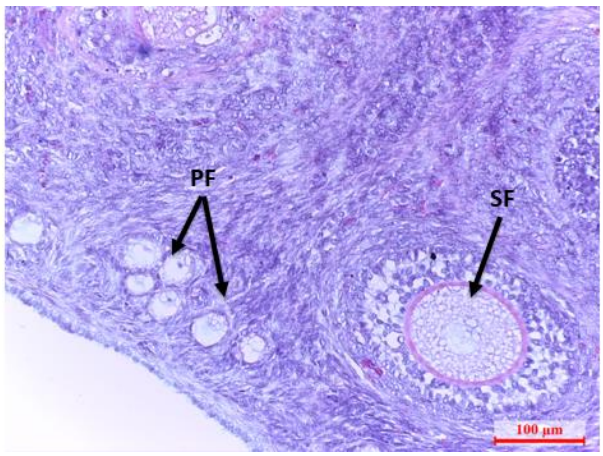

Figure 3: control group ovary show normal development of follicles, Secondary Follicle (SF), Primary Follicle (PF) (H&E. 20x).

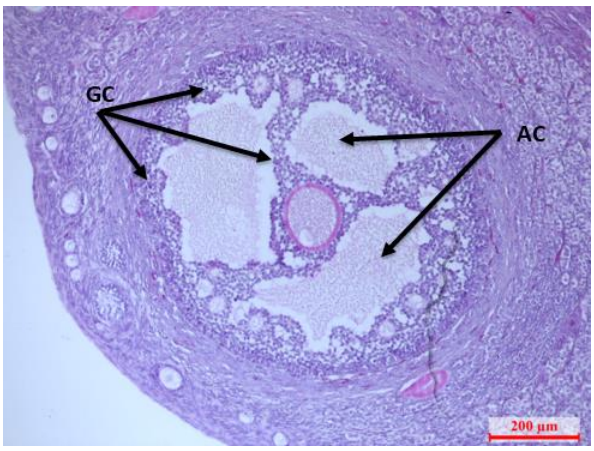

Figure 4: Graffian Follicle shows the antral cavities with numerous and large in size and the granulosa cells (GC) increased and fill the spaces between the antral cavities (AC). (H&E. 10x).

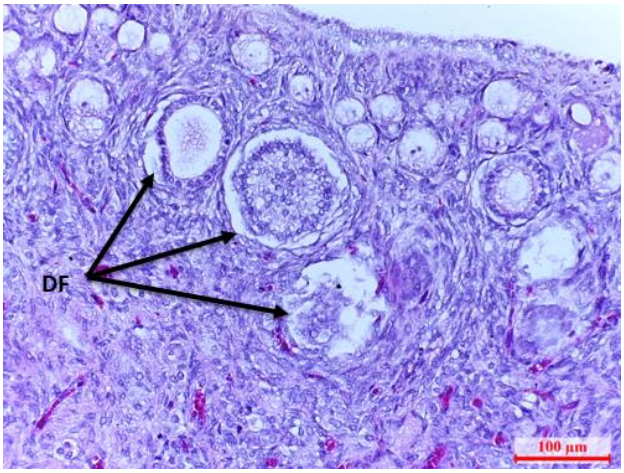

Figure 5 It shows Decomposition of the primary follicle (DF) within the stroma.(H&E. 40x).

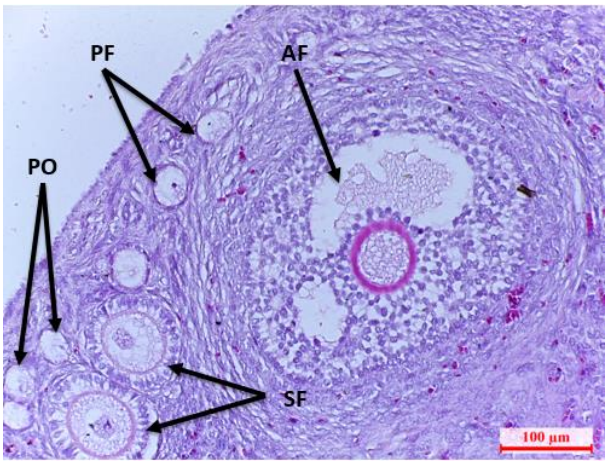

Figure 6: The parenchyma appears as it includes the different stages of the follicles and properly Pre-Ovulatory (PO), Primary Follicle (PF), Secondary Follicle (SF), Antral Follicle (AF) (H&E. 40x)

The histological sections of the ovary in the Gold particles group are shown in Figure 3. Graffian Follicle shows the antral cavities with numerous and large in size and the granulosa cells (GC) increased and fill the spaces between the antral cavities (AC). and in the domperidone drug group are shown in Figure 3.It shows Decomposition of the primary follicle (DF) within the stroma and Gold particles and Domperidone group shown Figure 4 The parenchyma appears as it includes the different stages of the follicles and properly Pre-Ovulatory (PO), Primary Follicle (PF), Secondary Follicle (SF), Antral Follicle (AF) Fig. (4,5 and 6). It is known that oocyte growth and maturation are sensitive to microenvironmental changes, especially extracellular chemical compounds. Recent studies have demonstrated the new phenomenon that mammalian oocytes show different toxic responses to gold and silver. The results (2017) Hou *et al* of (2017) showed that both silver and gold accumulate mostly in the cell layers and eggs, as well as the study of Hou *et al* (2017).the study showed (kumar ,*et al* 2023) the exciting potential of LHRH conjugated AuNPs to target ovarian cancer and also as a potential contrast agent for novel SPCCT imaging technology.

LHRH conjugated gold nanoparticles assisted efficient ovarian cancer targeting evaluated via spectral photon-counting CT.

One of the main effects observed in our study is the degeneration of the primary follicle in the ovary in the Domperidone group, the occurrence of some histological pathological conditions in the ovaries, which may occur as a result of degeneration of ovarian cells, in addition to the occurrence of disturbances in hormonal regulation, which is important in ovarian productivity and thus affects its histology. The ovaries, the surface, and the resulting negative effects on the function of the blood in gas exchange in a way that leads to the accumulation of carbon dioxide gas in them and the phenotypic and metabolic pathological effects that this causes, and this is what many studies agree on. Study showed Ghattas and Derbala, (2017).

CONCLUSION

In conclusion, treatment with the drug domperidone results in an increase in the hormone LH over a period of 50 days; however, this treatment negatively impacts ovarian tissue. Conversely, the application of gold nanoparticles also leads to an increase in the hormone LH for the same duration and has a positive effect on Graafian follicle ovarian tissue.

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