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Original Research Article

Ovatrine, a compound from plant extracts, used for female infertility treatment and increase the number of ovarian follicles

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ABSTRACT

Background: Recently natural products extracted from medical plants are very important in the field of alternative medicine. Glycosides, flavonoids and polyphenols are components of natural molecules have several health benefits such as anti-inflammatory, anti-oxidants, and have many ameliorative roles against male and female reproductive system intractable disorders. Objective of this study was to the compound of the plant extracts blend which is rich with glycosides, flavonoids and polyphenols was named as Ovatrine. The safety as well as the efficacy of some medical plants extracts on the fertility of the female mice was investigated using Ovatrine.

Methods: Firstly, the safety of Ovatrine was evaluated using some mice and the levels of the follicle stimulating hormone in the serum of the treated animals with Ovatrine was evaluated using biochemical tests. Also, the effects of the Ovatrine on the histological parameters of the treated ovary and uterus were evaluated using histological analysis.

Results: The animals treated with Ovatrine were healthy and did not show any signs of mortality, toxicities and there were no blood contents changes. Additionally, follicle stimulating hormone level in the serum increased after administration with Ovatrine twice a day for 30 days as compared with the non-treated animals. Furthermore, the histological structures of the ovary and uterus improved in the mice treated with Ovatrine compared with that in the non-treated mice.

Conclusions: In general glycosides, flavonoids and polyphenols, which were found in the Ovatrine in a higher concentration, have important health benefits such as antioxidant, anti-inflammatory and improve the fertility in the female mice. In the future this study will be very important for drug development which composed mainly from safe natural products and used for infertility and intractable diseases treatment.

Keywords: Flavonoids, Fertility, Follicle stimulating hormone, Glycosides, Ovatrine, Ovary, Polyphenols, Safety, Uterus

INTRODUCTION

Nowadays, many couples are suffering from infertility disorders. Usually, infertility results from female are over than those results from males. There are huge factors affecting the female fertility. Generally female infertility is caused by ovulation disorders, hypothalamic dysfunction, premature ovarian failure or too much prolactin. Additionally, other diseases include illnesses, injuries, chronic health problems, lifestyle choices and other factors can play an important role to produce

female infertility. Plant natural product extracts consider as main sources for many diseases' treatment, due to many reasons. Interestingly, plant natural products are safe and have no lower toxicities. From this point of view, previously many investigations revealed that glycosides, flavonoids, terpenoids and polyphenols can improve many tissue inflammation, especially testicular and ovarian tissue.¹⁻³ Furthermore, few studies were achieved for treatment of severe diseases using plant extracts containing antioxidant glycosides for treatment of the inflammation produced in the ovary or uterus.⁴

Additionally, tea polyphenols are the major constituents of tea leaves extracts and have shown many potential health benefits including increase in the follicular number in the ovary.⁵ In general, some plant extracts not only improve the histology of the ovary but also testis in the same time. Concerning the testicular tissue, Hussein ME, 2020 recently reported that flavonoids and polyphenols, which were found in the Manfort diet in a large amount, have a vital role as antioxidant, anti-inflammatory supplement. Additionally, Manfort supplementation could improve the fertility in the male mice by improving the testis histology and elevate the level of testosterone hormone. These data might be very important to develop a drug composed from safe plant extracts for infertility and intractable diseases treatment.⁶ Also, previously flavonoids extracted from *Cymbopogon citratus* reduced the activity and growth of PC-3 and HCT-116 carcinoma cells. Additionally, the whole extract ameliorates testicular dysfunction and prevent the testicular fail induced by anti-tumor drug such doxorubicin.⁷

Concerning the serum sex hormones, the testosterone and follicle stimulating hormone will be changed when diet rich with polyphenols or glycosides or flavonoids can be administrated daily for some time. For example the long-term exposure to tea polyphenols increased the follicle stimulating hormone and this associated with improved reproduction in hens and thus improved egg production.⁸ Total flavonoids in the taro flour (*Colocasia esculenta*) elevated the serum testosterone levels in the treated experimental animals.⁹ Furthermore, the isoprenylated flavonoids glycosides from *E. brevicornum* may induce beneficial health effects by promotion of estrogen biosynthesis.¹⁰

Follicle stimulating hormone is a glycoprotein polypeptide hormone. Follicle stimulating hormone is one of the hormones essential in development and the function of female's ovaries. This hormone stimulates the growth of ovarian follicles in the ovary before the release of an egg from one follicle at ovulation. Flavonoid, polyphenols and glycosides may improve the induction of the follicle stimulating hormone during ovulation. For example, quercetin, a polyphenolic flavonoid has many biological activities including anti-inflammatory and antiviral, inhibits lipid peroxidation, prevents oxidative injury and cell death. Quercetin improved productive activity, and its mechanism may be due to the oestrogen-like action of quercetin.¹¹ Several follicle stimulating hormone preparations have been used to treat secondary hypogonadism in males. These preparations have been reasonably successful at inducing spermatogenesis and achieving paternity. Additionally, girls with Turner syndrome (45, XO) have an elevation of FSH up to 6 years old due to lack of negative feedback from non-functional ovaries, while girls with (45, X/46, XX) have a much lower follicle stimulating hormone elevation due to partial ovarian function.¹²⁻¹⁴ Interestingly, glycosides can control and regulate the female serum sex hormone such as follicle stimulating hormone.¹⁵

Many medicinal plants have been shown to regulate ovarian function and improve the uterine blood flow and changes of the endometrium.¹⁶ Therefore, here in this study, I prepared a blend from medical plant extracts with precise ratios, by which the follicle stimulating hormone increased and the histological structure of the female ovary and uterus improved. Due to induction and improvement of the fertility parameters of this compound it was named Ovatrine. This study will provide some evidences about the safety as well as the effective role of Ovatrine on the female mice fertility including the following: Morphological and toxic signs were observed after the administration of Ovatrine. The ovary morphometric analysis was performed. Furthermore, follicle stimulating hormone level was investigated in control and treated mice with Ovatrine. The vitale role of Ovatrine on female mouse fertility was investigated using biochemical analysis and histological tests. Further detailed studies are needed to confirm the role of the Ovatrine in the treatment of the infertility. This report is the first and novel study which showed the improvement of the fertility parameters such as follicle stimulating hormone level and histological structure of the ovarian and uterine tissue using the Ovatrine supplementation. The data collected from this report showed that Ovatrine can help in the treatment of female's infertility.

METHODS

Materials

Paraffin, xylene, ethyl alcohol, DPX, hematoxylin stain, and eosin stain were purchased from Sigma-Aldrich Chemical Co., UK. The targeted medical plants were collected from Sohag and El-wady El-Gadid governorates.

Preparation and characterization of Ovatrine

Preparation of Ovatrine

After collection the plants, they were completely dried in draying ovum and grinded separately in a blender to get the fine powder. The grinded plants then were mixed together with targeted ratios with honey bee to make a paste like compound. The prepared Ovatrine was used to the check the smell, color, and morphological appearance.

Characterization of Ovatrine chemically

Part of Ovatrine was used for chemical analysis using IR spectra to detect the main and reactive groups and constituents. According to standard methods in 70% ethyl alcohol and water, the compound of Ovatrine was analyzed for the presence of some effective chemicals such as alkaloids, glycoside, saponins, tannins, steroids, coumarins, carbohydrates, terpenoids and flavonoids. Then, the compound of Ovatrine was divided to three parts; the first part is dissolved in hexane, the second

portion is dissolved in ethyl acetate and the last part in aqueous solution. Here after, phytochemical screening for these extracts was investigated. Additionally, the presence of glycosides, flavonoids and polyphenols were confirmed by standard chemical methods. Additionally, the activity of sample as antioxidant using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical method was investigated.

Animal eligibility criteria

Adult male mice (*Mus musculus*), (14 weeks, age) around weight 30 gm, were used for this study. Animal experiments are performed according to the guidelines and ethics for the care and use of animals approved by animal experiments committee in Center of Embryo Bank and Genetic Resources Conservation, National Research Centre. Mice were kept in metal cages in the animal room under the controlled conditions of a 12:12-h light/dark cycle, 25°C room temperature and free access to food and water for two weeks before starting time of the experiment. The normal mice with the same weight (around 30 gm), and with no symptoms of diseases or signs of inflammation were included for this experiment. But the animals with lower or higher weight than 30 gm and with symptoms of diseases were canceled from this experiment.

Methods and experimental animals

The total mice used in this experiment was thirty-two mice, were sorted into 2 groups. The group no. 1 contained 16 mice was left as control left without any treatment. The group no. 2 contained 16 mice, and was orally administrated with 100 mg/mice, twice a day, for 30 days consequently using disposable mouse gavage.

Safety of Ovatrine

Around 5 mice from control group and treated group with Ovatrine were used for monitoring the toxic signs or mortalities through the experimental period.

Biochemical analysis

To investigate the biochemical analysis of blood parameters, blood was drained from 5 mice from control animals and treated animals with Ovatrine. The target biochemical analysis were complete blood picture with differential count of the white blood cells, and follicle stimulating hormone level in the serum. To investigate the complete blood picture, blood was drained from 3 mice from control and treated groups in Lavender-Top Tube - EDTA to prevent blood coagulation and kept in refrigerator (4°C). For the follicle stimulating hormone level in the serum, blood was drained from 3 mice from control and treated animals in Lavender-Top Tube without EDTA and kept for 1 hour at 25°C for 1 hour. After blood coagulation, the blood serum was collected by centrifugation of the blood by centrifuge (14000

rpm/10 min). Then blood serum was kept in the -20°C for follicle stimulating hormone analysis using.

Morphometric analysis test

The body weight and the obtained ovaries from both control and treated animals with Ovatrine were weighted and recorded.

Efficacy of Ovatrine on the ovary and uterus histology

The ovary and uterus of 3 mice from control and treated mice with Ovatrine was collected and kept in the fixative, Carnoy solution for 1 hour or Bouin's solution for 24 hours. Then the fixative ovary and uterus were washed and dehydrated in ascending series of alcohol, and incubated in methyl benzoate for 24 hours, and then it incubated again in toluene for 30 mins. To prepare paraffin sections, ovary and uterus tissues were infiltrated in the melted paraffin and kept for 6 hours in the oven under 59°C. For light microscope imaging, paraffin sections (7 µm) of non-treated and treated ovary and uterus was sectioned from the paraffin blocks and affixed to glass slides. To stain the sections, some sections then paraffin was removed using xylene and hydrated through descending concentrations of ethanol and washed in distilled water. Then sections were stained with the general staining (Hematoxylin and Eosin stains), dehydrated again in ascending concentrations of ethanol, cleared in the xylene for 10 mins, mounted in DPX, and investigated under (Axio Scope.A1, Carl ZEISS, Germany) equipped with AxioCamERc5s camera.

RESULTS

Ovatrine preparation and characterization

Morphological characterization

The Ovatrine is a blend from grinded medical plants and mixed with honey bee to form compound like a paste. This blend is acceptable to eat and characterized with brown color and acceptable smell.

Chemical analysis

Based on the IR spectrum analysis Ovatrine composed chemically from flavonoids, carbohydrates, coumarins, steroids, terpenoids, glycosides and polyphenols. The phytochemical screening is showing that, Ovatrine has higher ratio from flavonoids, polyphenols and glycosides. These three constituents are the most dominant components in the Ovatrine blend. The exact percentage of some targeted chemicals was determined by the standard chemical method, and the concentration of flavonoids was 6 mg/gm and polyphenols were 12 mg/gm (Table 1).

Furthermore, the antioxidant activity of the Ovatrine blend calculated using 2,2-diphenyl-1-picrylhydrazyl

method. The inhibition percentage using Ovatrine increased by increasing the concentration. That is to say, the inhibition percentage of Ovatrine at concentration 2.7 mg/ml was about 76 %. The activity of the Ovatrine as

antioxidant showed that, the IC50 was found to be 1.2 mg/ml compared with ascorbic acid as standard antioxidant (0.7 mg /ml) (Table 2).

Table 1: The preliminary phytochemical screening.

Components	Hexane extract	Aqueous extract	Ethyl acetate extract	Ethyl alcohol 70% (v/v)
Flavonoids	-	++	++	
Carbohydrates	-	+++	-	
Alkaloids	-	-	-	+
Coumarins	-	-	++	
Steroids	++	-	-	
Tannins	-	-	-	++
Saponins	-	-	-	
Terpenoids	++	-	-	
Glycosides		+++		
Polyphenols				+++

+++ : Strong intensity reaction, ++ : Medium intensity reaction, + : Weak intensity reaction, - : Non detected.

Table 2: The activity of sample as antioxidant using 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical method.

Concentration mg/ml	Inhibition percentage
0.65	32.15
1.3	54.85
2.6	75.94

Ovatrine. During all the experiment time, the treated mice with Ovatrine were actively living. There was no change in the appetite of the treated mice with Ovatrine during the experimental time. The blood picture analysis showed that, there was not significant change in the blood parameters between treated and non-treated animals. The white blood cells in the non-treated mice were 3×10^3 and it was 3.2×10^3 for the Ovatrine treated mice. Furthermore, red blood corpuscles, platelets, lymphocytes and monocytes didn't change after administration of the Ovatrine compared with the non-treated animals. Fortunately, hemoglobin slightly increased in the administrated group with Ovatrine (12.2 g/dl) as compared with the control (11.5 g/dl) (Table 3), however there was no signal for the toxicity of Ovatrine.

Safety of Ovatrine

The mice were administrated by Ovatrine for two times/day with a dose of 100 mg/mice for 30 days. It was remarked that, there was no abnormalities such as toxicity or mortalities in the administrated mice with

Table 3: The mean values of the mice blood contents for control and Ovatrine treated samples n = 3.

Group	RBCs	WBCs	Hb	Plat.	lymphocytes	Monocytes
Control	5×10^3	3×10^3	11.5 g/dl	239.4×10^9	2.1×10^3	0.4×10^3
Ovatrine	5.6×10^3	3.2×10^3	12.2 g/dl	247.2×10^9	2.1×10^3	0.6×10^3

Morphometric analysis

Body weights of the administrated mice with Ovatrine slightly increased (about 11%) compared with the non-treated mice (Figure 1A). Additionally, the ovary weight increased in the treated mice with Ovatrine (about 13%) compared with the non-treated mice (Figure 1B).

Follicle stimulating hormone

The follicle stimulating hormone levels increased by 52% in the mice administrated with 100 mg/mouse dose (twice

a day for 30 days) compared with the non-administrated mice (Figure 1D).

Histological improvement of the ovary and uterus

As shown in Figure 2 and 3, administration of Ovatrine to mice for 30 days consequently showed many positive signs for Ovatrine efficacy on the fertility such as, follicle stimulating hormone level, and ovarian follicle number and histological improvement of ovary and uterus. In general, the ovarian stroma forms the body of the ovary and is composed of spindle-shaped, fibroblast-like cells

and delicate collagen fibers admixed with ground substance. The cortex of mature mice contains different follicles at various stages of development. Additionally, the mice uterus compassed mainly from the muscular layer followed by the uterine stroma which contained uterine glands. The inner layer of the uterus is the uterine epithelium.

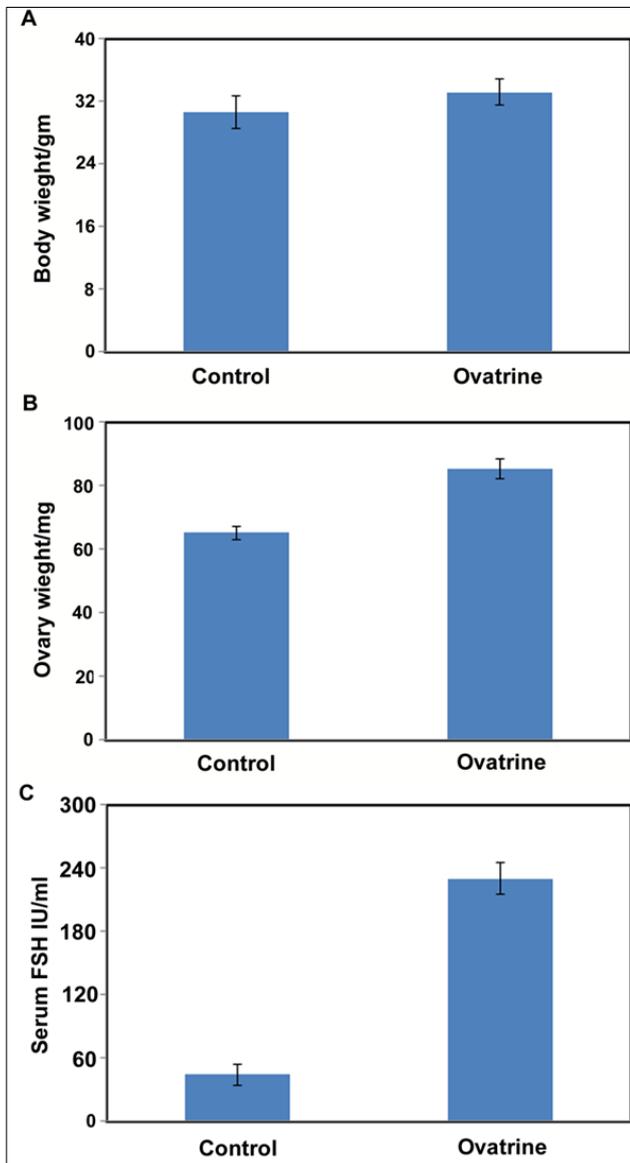


Figure 1: (A) the body weight of treated mice with Ovatrine and non-treated mice (control) (B) the ovary weight of treated mice with Ovatrine and non-treated mice and (C) the serum follicle stimulating hormone in treated mice with Ovatrine and non-treated mice. SD = 3 mice.

The histological findings showed many positive findings after administration with the Ovatrine. For example, in the case of the ovary the number of the follicles in the ovary treated with Ovatrine increased compared with that of the non-treated ovary. Additionally, the blood supply in the ovary treated with Ovatrine increased as compared

with the non-treated ovary. Also, the mature ova and the follicles cells in the treated ovary were intact with no inflammation or lymphocytes infiltration (Figure 2).

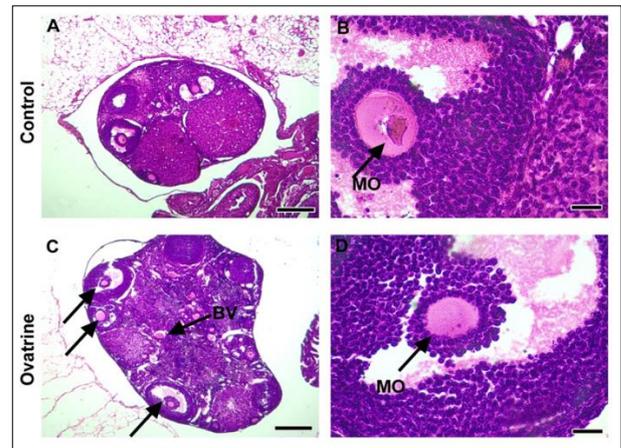


Figure 2: Light microscope images (A) Ovary of control mice showed low number of mature follicles and blood vessels (BV) (B) Mature follicles (MO) with non-intact cells. (C) Ovary of treated mice with Ovatrine with large number of mature follicles with mature ova and many blood vessels (D) mature ova with intact cells. Scale bar = 10 µm.

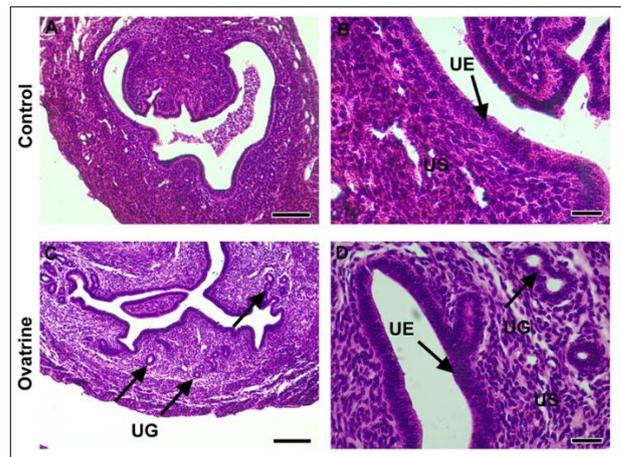


Figure 3: Light microscope images (A) Uterus of control mice showed low number of uterine glands (UG) (B) degenerated uterine stroma (US) and uterine epithelium. (C) Treated uterus with Ovatrine with increased number of uterine glands (UG) (D) Intact uterine epithelium (UE) and uterine glands (UG). Scale bar = 10 µm.

Furthermore, the histological structure of the uterus in the mice administrated with Ovatrine improved in many regions compared with the non-administrated mice. For example, the number of the uterine glands increased in the treated mice with Ovatrine as compared with the control. The uterine epithelium of the treated mice with Ovatrine was intact compared with the non-treated mice.

Additionally, there was no inflammation or lymphocytes infiltration was found in the uterine stroma (Figure 3).

DISCUSSION

Recently I reported that, flavonoids and polyphenols concentrated in Manfort blend in a higher concentration, flavonoids were 1.98 mg/gm and polyphenols was 3.43 mg/gm. These two compounds have many positive effects on the fertility and testicular histology of the male mice.⁶ In this report the concentration of the glycosides, flavonoids and polyphenols in the Ovatrine compound is higher than other components even “Manfort” published previously. Additionally, the previous studies showed that the glycosides and polyphenols included in the ingested diets have protective role, antioxidants effects and anti-inflammatory properties and improved the ovarian histology.¹⁻³ Therefore I will discuss the role of glycosides and polyphenols to improve the ovarian follicles number and improvement of the ovarian and uterine histology. In chemistry, glycosides are a molecule in which sugars are bound to another functional group via a glycoside bond. Furthermore, glycosides play numerous important roles to improve cell functions. Also, many plants store chemicals in the form of inactive glycosides, these natural glycosides are used as a source in alternative medicine for treatment of many diseases. Additionally, glycosides are increasingly being used as diet by many populations. There are many healthy beneficial properties have been attributed to glycosides dietary compounds. These properties include anti-inflammatory, anti-oxidant, and anti-carcinogenic effects.^{17,18} Ovatrine in this study contains 6 mg/gm of flavonoids and higher concentration from glycosides. Therefore, Ovatrine in this study can improve the histology of the ovary and increase the follicles number through the beneficial properties of the flavonoids and glycosides in the administered diet. Ovatrine contains many reactive groups came from the different types of plant extracts. For example, Ovatrine contains 12 mg/gm from polyphenols, which additionally can improve the histology and increase the follicle stimulating hormone levels in the serum.¹¹ Previously, total flavonoids of Epimedium are the main active composition of Epimedium which is truly important to treat reproductive problems including sex hormones.¹⁹

Many studies revealed previously that there was a relationship between flavonoids and glycosides and sex hormone metabolism.^{1,2,5} Furthermore, diet including polyphenols and glycosides can protect ovarian tissue from damage and improve the function and uterine function by increasing the reproduction.³ Follicle stimulating hormone is very important for ovulation and ovarian follicles production.²⁰ The higher concentration of the polyphenols and glycosides in the Ovatrine might regulate the level of the follicle stimulating hormone level in the serum after oral administration of 100 mg/mouse for 30 consecutive days. The increase in the level of the follicle stimulating hormone

might promote the follicle production and keep the function of the ovary and uterus.

CONCLUSION

Most of the studies done before, about the beneficiary of the medical plants extract such as flavonoids, polyphenols and glycosides to improve the function of the reproductive systems in the females are in consistent with this data including the efficacy of Ovatrine for the infertility treatment. As conclusion, Ovatrine can improve fertility of female mice and it can be used for treatment of female infertility after further studies to confirm this data.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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