RESEARCH ARTICLE

Effect of Dostenix and *Origanum majorana* L. Leaf Extract in Regulating the Prolactin and Sex Hormones in Females Rats Chlorpromazine-induced Hyperprolactinemia

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ABSTRACT

Hyperprolactinemia is associated with many changes in weight and sex, and ovarian hormones. Sixty adult females rats were allotted to six groups consisting of 10 rats each, Group C: control, orally administered Normal Saline 1 mL) for 30 days, Group A1: orally administered aqueous extract of *Origanum majorana* L leaves at a dose of 540 mg/kg for 30 days, Group A2: orally administered Dostinex 0.5 mg/kg for 30 days). Group R: orally administered chlorpromazine 30 mg/ kg for 30 days, which induced hyperprolactinemia. Group R1: hyperprolactinemia was induced and synergistically orally administered aqueous extract of *O. majorana* L. 540 mg/kg leaves for 30 days. Group R2: Hyperprolactinemia was induced, and Dostinex was orally administered d 0.5 mg/kg for 30 days). The results showed a significant decrease in the weight in the group treated with aqueous *O. majorana* L. leaf extract (OM) and the group treated with Dostinex from the treatment.

In contrast, a significant increase occurred in the group induced to hyperprolactinemia with chlorpromazine (CPZ), while the body weight decreased from (OM) and the group treated with Dostinex. As for the average weights of the uterus and ovaries, there was a significant decrease in the weight of the uterus and the left and right ovaries when treated with OM, and the group treated with Dostinex, and when induction with CPZ, a significant increase in the weight of the uterus and left and right ovaries compared with the control group, while we noticed the return to the normal weight of the uterus and ovaries. When rats induced to hyperprolactinemia were treated with OM and the group treated with Dostinex. a significant decrease in prolactin in the group treated with OM and the group treated with Dostinex from the treatment, with a significant increase in the levels of LH, FSH, Progesterone, Estrogen. The group inducing hyperprolactinemia with CPZ recorded a significant increase in prolactin, with a decrease in FSH, LH, and progesterone hormones compared to the control group.

Keywords: Chlorpromazine, Dostinex, FSH, Hyperprolactinemia, LH, *Origanum majorana*, Progesterone Estrogen.

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INTRODUCTION

Hyperprolactinemia is an increase in the level of prolactin in the blood, and this increase leads to a defect in the ovulation process and a disorder in the hypothalamus-pituitary gland. Thus, the direct effect is to reduce the hormones estrogen and progesterone, which leads to an imbalance in the menstrual cycle, irregularity, and lack of ovulation.[1] Hyperprolactinemia may be pathological, such as the appearance of a prolactinoma in the pituitary gland. It is considered a benign non-cancerous tumor or the presence of a tumor in the pituitary gland or hypothyroidism, as well as chronic liver disease, kidney disease, or physiology where it rises due to pregnancy or medication By some drugs that affect receptors in the hypothalamus or dopamine receptors in the pituitary gland.[2]

Dostinex (Caprigoline), a powerful agonist that acts on dopamine D2 receptors, directly affects lactotroph cells located in the pituitary gland (prolactin). Dostinex reduces the level of prolactin in the blood. Dostinex has a low binding capacity to dopamine D1 receptors, and α1-adrenergic receptors are α2-adrenergic receptors.[3]

Medicinal plants have many properties that enable them to modify the levels of female sex hormones by the action of the biologically active substances possessed by *Origanum majorana* L. Marjoram belongs to the Lamiaceae family, a medicinal plant family that includes about 236 genera and

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more than 6000 species. *O. majorana* L. contains biologically active substances such as (tannins, phenols, flavonoids, alkaloids, carbohydrates, terpenes, glycosides, essential oils, and phytoestrogens such as {biochanin A, daidzein, genistein, formononetin}). It has a role in reducing hyperandrogenism, insulin resistance, ovarian weight, and thus the return of natural hormones to their normal levels and ovulation.[4]

The study aimed to evaluate the effect of Dostinex and *O. majorana* L. extract on reducing hyperprolactinemia and improving sex hormones in chlorpromazine-induced hyperprolactinemia laboratory animal rats.

MATERIALS AND METHODS

Experimental Animals

Sixty adult female rats (*Rattus norvegicus*), weighing about (200–250 g) were used for this research work. They were purchased from the animal house of the Department of the Biology, College of Science; the animals were housed under the standard condition with 12 hours light and 12 hours dark cycle throughout the duration of the experiment. Food and water were provided ad libitum. The experiment was conducted in accordance with the Guidelines of the US National Institute of Health (NIH) on the care and use of laboratory animals.

Experimental Protocol

The sixty adult females rats were allotted to six groups consisting of ten rats each,

Group C: orally administered Normal Saline 1 mL) for 30 days

Group A1: orally administered aqueous extract of *O. majorana* L leaves at a dose of 540 mg/kg for 30 days

Group A2: orally administered Dostinex 0.5 mg/kg for 30 days)

Group R: 30 orally administered chlorpromazine 30 mg/ kg for 30 days of which hyperprolactinemia was induced –

Group R1: Hyperprolactinemia was induced and synergistically orally administered aqueous extract of *O. majorana* L. 540 mg/kg leaves for 30 days.

Group R2: Hyperprolactinemia was induced, and Dostinex was orally administered d 0.5 mg/kg for 30 days).

Plants Collection

The dried *O. majorana* L leaves were purchased from the local markets in Babylon city. The leaves were ground using an electric mixer, and the powder was kept in plastic cans. The extract was done by the Soxhlet Apparatus device, according to the method of.[5]

Chlorpromazine Treatment. CPZ (Sigma-Aldrich Co., Germany) was used at dose 30 mg/kg/body weight to induce hyperprolactinemia according to[6] and then dissolved in water.[7] The administration of the drug to the female rats was carried out by oral gavage for 30 consecutive days.

Dostinex treatment tablets at a dose of 0.5 mg/kg/body weight were used only to reduce hyperprolactinemia levels.[8] An oral gavage carried out the administration of the drug to the female rats for 30 consecutive days.

Serum Collection and Blood Storage

Samples were collected by heart puncture, and serum samples were separated by centrifugation and kept frozen at (-2°C) temperature until used. Prolactin, sex and ovarian hormones were determined by an automated hormone analyzer using the (VIDAS®) test from a French company (BioMérieux Marcy) using only blood serum.[9]

Statistical Analysis

The data were analyzed according to (mean ± SD), and the value of the least significant difference LSD was used with the use of one-way ANOVA according to the level of probability ($p < 0.05$).

RESULTS

Results showed that there was a significant increase in body weight in the control group when comparing the initial weight to the final weight. For groups: (A2) that administered Dostinex, (R2) group that Hyperprolactinemia induced and group (R2) that hyperprolactinemia induced and synergistically orally administered aqueous extract of *O. majorana* L., there was an insignificant increase in the body when comparing initial to final weight (Table 1).

(A1) group that administrated aqueous extract of *O. majorana* L. leaves. and (R) group induced to

Table 1: Effects of the aqueous extract of *Origanum majorana* L. leaves and Dostinex on body weight of Experimental Animal.

Treatment	*Weight before treatment in g/kg (Meam ± SD)*	*Weight after treatment in g/kg (Meam ± SD)*	*LSD (0.05)*	*p-value*
C	225.0 ± 2.45	229.01 ± 1.83	2.038	0.0003
A1	218.50 ± 28.48	208.30 ± 18.97	22.74	0.179 p >
A2	223.50 ± 30.74	196.0 ± 17.61	23.53	0.011 p <
R	223.60 ± 22.53	254.10 ± 32.81	26.44	0.013 p <
R1	246.0 ± 21.71	207.60 ± 9.78	15.82	p < 0.00003
R2	245.6 ± 19.43	214.30 ± 19.46	15.80	p < 0.0003
LSD (0.05)	21.087	18.15		

A1: Group of female laboratory animals treated with aqueous extract of *O. majorana* L. leaves.
A2: Group of female laboratory animals treated with Dostinex.
R: Group of female laboratory animals induced to hyperprolactinemia for chlorpromazine.
R1: Group of female laboratory animals treated with chlorpromazine and aqueous extract of *O. Majorana* L. leaves.
R2: Group of female laboratory animals treated with chlorpromazine and Dostinex.
All data are presented as Mean ± SEM, n=10.

hyperprolactinemia with chlorpromazine showed a significant decrease ($p > 0.05$) in weight when comparing the initial weight to the final weight. The results of showed there is a significant improvement ($p < 0.05$) in group R1 compared with the all group, and (R2) group compared with (R) group.

Weight of the Uterus and Ovaries

The results of Table 2, which show the weights of the female genital organs of white female rats orally administrated aqueous extract and Dostinex when suffering from hyperprolactinemia, indicated the least significant hyperprolactinemia and according to the LSD value. With group (C) 175.01 ± 3.82 mg/100 g, while (A2) group recorded 161.62 ± 3.1 mg /100g. (R) group 191.76 ± 2.76 mg/100 g recorded a significant increase compared with (C) group 175.01 ± 3.82 mg/100 g, while we note that (R1) group 176.83 ± 2.85 mg/100 g - (R) 191.76 ± 2.76 mg / 100 g, and the weight of the female white rats of the (R2) group recorded a significant decrease - (R) 175.80 ± 2.10 mg/100 g.

The results of Table 2 showed that the weight of the right ovary recorded some significant differences, where a significant decrease was recorded for (A1) group 13.995 ± 1.787 mg/100 g compared with (C) group 16.23 ± 1.36 mg/100 g. In comparison (C) group recorded 16.23 ± 1.36 mg/100 g. A2) 13.38 ± 2.03 mg/100 gm compared with (C) group; also (R) group recorded a significant increase of 20.39 ±1.69 mg/100 gm compared with (C) group. The (R1) group recorded a significant decrease of 16.41 ± 2.69 - (R) 16.23 ± 1.36 mg/100 g, as well as the (R2) group 15.15 ± 1.19 mg/100 g, which recorded a significant decrease in comparison with the (R) group.

As for the left ovary, we notice that there are significant differences between the treatment groups, according to the value of the least significant difference LSD, and the weight of the left ovary for (A1) group recorded a significant decrease of 13.21 ± 0.97 mg/100 g compared to (C) group 15.38 ± 0.78 mg/100g. While (A2) group recorded 12.91 ± 1.58 mg/100 g compared with (C), (R) group also recorded a significant increase of 19.61 ± 0.66 mg/100 g compared with (C) group. While the (R1) group recorded a significant decrease of 14.63 ± 1.86 mg/100 g compared with the group (R) 19.61 ± 0.66 mg/100 g, as well as the group (R2) 14.54 ± 1.28 mg/100 g, which recorded a significant decrease in comparison with the (R) group.

The statistical analysis as shown in Table 2 showed a significant decrease ($p < 0.05$) in the level of prolactin hormone in the serum of treated laboratory animals (A1) group 0.022 ± 0.002 µIU/mL of blood, as well as (A2) group 0.024 ± 0.004 µIU/mL of blood when compared with a group (C) 0.051 ± 0.005 IU/mL of blood. Treatment (R) led to the induction of hyperprolactinemia and a significant increase in the hormone 0.098 ± 0.006 µIU/mL of blood compared with (C) group. The results of the Table when treatment (R1) showed a significant decrease of 0.060 ± 0.004 µIU/ml of blood Compared with (R) and (C) groups.

Through the results of the Table, the Luteinizing Hormone (LH) showed that there were no significant differences ($p > 0.05$) between the groups, and the two groups (A1, A2) showed a significant improvement, as they recorded 0.070±0.003, 0.073 ± 0.005 µIU/mL of blood, respectively. Compared with the control group (C), the two groups (R1, R2) recorded a significant improvement 0.051 ± 0.005-0.066 ± 0.004 µIU/mL of blood compared to the (R) group. Induced hyperprolactinemia 0.048 ± 0.008 µIU/mL of blood.

As for the level of follicle-stimulating hormone (FSH), significant differences ($p < 0.05$) were evident between the groups, which indicated a significant increase ($P < 0.05$) for the (A1, A2) group was 0.07 ± 0.004 0.06±0.006 µIU/mL of blood in comparison. With (C) group 0.04±0.005 µIU/mL of blood, while the Table showed a significant decrease.

It was clear in the FSH hormone in the serum of laboratory animals induced by chlorpromazine (R) in comparison with (C) group of blood, respectively, compared to (R) group.

As for the white body hormone progesterone, its concentrations were significant ($p < 0.05$) between groups, and the serum of laboratory animals group for (R1) group 15.20 ± 1.86 µIU/mL of blood (R2) 16.99 ± 1.82 µIU/mL of blood showed a significant increase compared with the induced (R) group 8.56 ± 1.81 µIU/mL of blood and compared with the control (C) group 8.48 ± 1.86 µIU/mL of blood.

Estrogen levels showed significant differences between groups ($p < 0.05$).

Where we notice in the results of the Table a significant increase in the concentration of the hormone when treating the (R1) group 34.25 ± 2.87 µIU/mL of blood and a significant increase in the concentration of the hormone when treating the (R2) group 33.90 ± 2.99 µIU/mL of blood compared with the (R) group (14.81 ± 2.95 µIU/mL of blood and compared with (C) group 30.85 ± 2.89 µIU/mL of blood.)

Table 2: Effect of aqueous extract of *O. majorana* L. leaves and Dostinex on uterus and ovary weight of experimental animals.

Treatments	*Uterine weight mg/100g*	*Right ovary weight 100 mg/g*	*Left ovary weight 100 mg/g*
C	175.01 ± 3.82	16.23 ± 1.36	15.38 ± 0.78
A1	160.76 ± 4.22	13.995 ± 1.787	13.21 ± 0.97
A2	161.62 ± 3.1	13.38 ± 2.03	12.91 ± 1.58
R	191.76 ± 2.76	20.39 ± 1.69	19.61 ± 0.66
R1	176.83 ± 2.85	16.41 ± 2.69	14.63 ± 1.86
R2	175.80 ± 2.10	15.15 ± 1.19	14.54 ± 1.28
LSD (0.05)	2.91	1.99	1.36

C: Control group

DISCUSSIONS

The results of Table 3 showed the effect of some variables on the hyperprolactinemia of some hormones in white female rats, where the results of the aqueous extract of *O. majorana* leaves gave a significant decrease in the level of prolactin, and the results of the study agreed with[10] that was in his study. The use of *O. majorana* extracted at a concentration of 0.27 g/kgm of body weight in 4.5 mL of boiled water and dosed orally, is traditionally used for its ability to restore hormonal balance and reduce hyperprolactinemia and compare it with the effect of bromocriptine on female albino rats in three groups where the *O. majorana* group showed a significant result In lowering the level of prolactin, *Origanum majorana* was effective in reducing the level of prolactin.

While the results of our study also gave a significant increase in the luteinizing hormone LH compared with the control group when treated with an aqueous extract of *O. majorana* leaves, and this was confirmed by the study[11] using an aqueous extract of *O. majorana* leaves in three concentrations, and a significant increase in hormone levels was recorded compared to The control group attributed the rise in the ovulation hormone to the fact that marjoram contains a biologically active substance that can manufacture and build hormones, which is Diosgenin.

The results of the study agreed with[12] a significant increase in the luteinizing hormone LH when treating women with PCOS with *O. majorana* leaf extract, which indicates the effect of reducing androgen, especially for adrenal androgens, as *O. majorana* has the ability to Activation of PPAR-A and PPAR-C, with stronger agonist activity and greater dose dependence of the gamma subtype. The ethanolic extract of marjoram has the role of PPAR-γ agonists in improving insulin sensitivity. Insulin sensitivity is known to improve in hyperprolactinemia women.

The study results indicated a significant increase in the follicle-stimulating hormone (FSH) when treated with an aqueous extract of *Origanum majorana* leaves compared to the control group. The gonads of mature rats, where the researcher explained that the methanolic extract of *Origanum majorana* leaves at the maximum dose gave a stimulating effect of sex hormones and could affect the activity of different levels of the pituitary-gonadal axis and increase the secretion of reproductive hormones.

The results of the study of *Origanum majorana* extract on the progesterone showed a significant increase for the group treated with the extract compared with the control group, and the results of our study agreed with[13] to the increase in progesterone and estradiol levels as a result of the increase in the activity of cytochrome p450, 17 α-hydroxylase and regulatory protein steroidogenic acute in females, enhances the synthesis of hormonal steroids when treated with alcoholic extract of marjoram.

The results of our study indicated a significant increase in estrogen hormone when treated with an aqueous extract of marjoram, and the results were in agreement with[14] who used marjoram extracts. To increase the conversion of progesterone due to the high availability of aromatase with an excess of adipose tissue and thus, recording a relationship between increased aromatase activity and increased estrogen with a decrease in both the percentage of testosterone, which is particularly responsible for the development of infertility in obese, and leads to increased estrogen production who Obese people have a negative feedback effect on LH secretion through the presence of E2 receptors.

We note the effect of Dostinex drug similar to the effect of the aqueous extract of marjoram with a significant decrease in prolactin levels, and the results of the study agreed with[15] who recorded the role of cabergoline treatment (the dopamine

Table 3: Effects of the aqueous extract of *O. majorana* L. leaves and Dostinex on serum levels of prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone and estrogen.

Parameters	*Prolactin (μIU/mL)*	*LH (μIU/mL)*	*FSH (μIU/mL)*	*Progesterone (μIU/mL)*	*Estrogen (μIU/mL)*
Treatments	*Mean ± S.E*				
C	0.051 ± 0.005	0.053 ± 0.003	0.04 ± 0.005	8.48 ± 1.86	30.85 ± 2.89
A1	0.022 ± 0.002	0.070 ± 0.003	0.07 ± 0.004	10.69 ± 1.80	34.60 ± 3.14
A2	0.024 ± 0.004	0.073 ± 0.005	0.06 ± 0.006	11.78 ± 1.82	35.51 ± 2.92
R	0.098 ± 0.006	0.048 ± 0.008	0.02 ± 0.003	8.56 ± 1.81	14.81 ± 2.95
R1	0.060 ± 0.004	0.051 ± 0.005	0.06 ± 0.003	15.20 ± 1.86	34.25 ± 2.87
R2	0.043 ± 0.005	0.066 ± 0.004	0.07 ± 0.004	16.99 ± 1.82	33.90 ± 2.99
$LSD_{(0.05)}$	0.012	0.058	0.010	4.358	7.064
p-value	0.0001**	0.667*	0.0001**	0.024**	0.0001**

A1: Group of female laboratory animals treated with aqueous extract of *Origanum majorana* L. leaves.
A2: Group of female laboratory animals treated with Dostinex.
R: Group of female laboratory animals induced to hyperprolactinemia for chlorpromazine.
R1: Group of female laboratory animals treated with chlorpromazine and aqueous extract of *origanum Majorana* L. leaves.
R2: Group of female laboratory animals treated with chlorpromazine and Dostinex.
All data are presented as Mean ± SEM, n = 10.
*Indicts that there are no significant differences (P < 0.05).
** Indicates a significant difference (P < 0.05).

agonist of Dostinex) in reducing plasma prolactin by 88%. It is effective in patients Suffering from androgen-independent advanced prostate cancer, and elevated prolactin levels have a role in the development of these malignancies. That was by targeting effective therapy to inhibit lactotropic pituitary production from suppressing the concentration of prolactin in the plasma.

While the results of the study showed a significant increase in the luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, and estrogen in comparison with the control group, the results of our study agreed with,[16] where it indicated an increase in the luteinizing hormone LH when using 3 concentrations of Dostinex, where the researcher indicated that cabergoline. It is used to prevent excessive prolactin with a duration of effect up to 21 days after taking the oral dose, and there is an inverse relationship between the luteinizing hormones LH and prolactin by affecting the pituitary-gonadal axis and GnRH hormone from the arcuate nucleus in the brain and reducing dopamine.

The results of our study indicated a significant increase in prolactin in white female rats when treated with chlorpromazine compared with the control group. The concentrations of prolactin and progesterone in the blood increased significantly, while the concentrations of estradiol, LH, and FSH were significantly decreased in the blood when 32 female rats were used, depending on the dose of CPZ. The different groups on the amount of chlorpromazine dosed; CPZ attributed the reason that dopamine plays an important role in activating the secretion of prolactin. Dopamine acts on the lactotroph cells in the anterior pituitary gland and increases the secretion of prolactin. As chlorpromazine works to inhibit the secretion of dopamine, the current study results showed a significant decrease in the value of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) compared with the control group in female laboratory rats treated with chlorpromazine. The concentrations of LH, FSH, and estradiol in the blood depended on the dose of chlorpromazine, attributing to the decrease in GnRH secretion in the hypothalamus, which reduced the stimulation of stimulation LH and FSH secretion in the pituitary gland. Blood prolactin relies on hypothalamic-pituitary axis suppression, which inhibits gonadotropin secretion. Additionally, the positive feedback of E2 estradiol was eliminated in the pituitary gland to secrete LH, so serum levels of LH and FSH were significantly decreased in animals that received LH. Chlorpromazine dose.[17]

CONCLUSIONS

- There is no negative effect of the aqueous extract of *O. majorana* on the general health of animals.
- *O. majorana* Causes the loss of excessive weight caused by hyperprolactinemia.
- The aqueous extract of *O. majorana* lowers the hormone prolactin, so it has a positive effect in the treatment of hyperprolactinemia disease.
- The results measurement of hormones in the blood serum showed the extract of *O. majorana* enhances female fertility through effect hormonal (Sex hormones and prolactin)

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