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Effect of *Foeniculum vulgare* and Metoclopramide on the Mammary Glands of Lactating *Mus musculus*

Israa Hashim Ali, Reem Saleh Awad

Department of Biology, College of Sciences, University of Tikrit, Tikrit, Iraq

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ABSTRACT

Medications affect lactation by affecting all stages of mammary gland development and function. In particular, medications may interfere with normal mammary gland development, the hormonal environment of the lactating mammary gland, milk secretion, and nutrient delivery to lactating mammary cells. This study aimed to determine the effect of Foeniculum vulgare and metoclopramide on mammary gland development in lactating female *Mus musculus* mice. The present study was conducted in the animal house of the College of Veterinary Medicine and the laboratories of the College of Science at Tikrit University during the period from 10/27/2024 to 1/27/2025, where 80 female mice were used in the experiment for 20 days and divided into four of groups as follows: The first group (control): included 20 lactating females (T1) given normal food and water. The second group (T2): included 20 lactating females given *Foeniculum vulgare*. The third group (T3) included 20 lactating females given 2 mg metoclopramide. The fourth group (T4) included 20 lactating females given 10% Foeniculum vulgare and 2 mg metoclopramide. Histological examination of the lactating groups showed increased lobule and alveoli size, with larger cavities than in the control group. The results showed increased mothers' weights during the dosing period, suggesting the materials used in the study were more effective than in the control group. Among all groups, the highest increase in mothers' weight was found in the group given fennel and metoclopramide. The current study concluded that the *Foeniculum vulgar* extract and metoclopramide had positive effects on the mammary glands by increasing their secretion. The drug had a greater effect than the extract, and the best results were observed in the group treated with the extract and the drug together.

Keywords: Female *Mus musculus*, *Foeniculum vulgare* and metoclopramide, Mammary glands.

Name: Israa Hashim Ali **E-mail:** iAli@tu.edu.iq

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تأثير الشمر *Foeniculum vulgare* وعقار ميتاكلوبرامايد على الغدد الثديية للفئران البيض المرضعة

اسراء هاشم علي، ريم صالح جواد

قسم علوم الحياة، كلية العلوم، جامعة تكريت، تكريت، العراق

الملخص

تؤثر الأدوية على الرضاعة من خلال تأثيرها في جميع مراحل نمو الغدة الثديية ووظائفها. وعلى وجه الخصوص، قد تتداخل الأدوية مع نمو الغدة الثديية الطبيعي، والوسط الهرموني للغدة الثديية المرضعة، وإفراز الحليب، وتوصيل المواد الغذائية إلى الخلايا الثديية المرضعة. هدفت هذه الدراسة إلى تحديد تأثير كل من الشمر والميتوكلوبراميد على تطور الغدد الثديية لدى إناث الفئران البيضاء المرضعة. أجريت هذه الدراسة في بيت الحيوانات بكلية الطب البيطري ومختبرات كلية العلوم بجامعة تكريت خلال الفترة من 2024/10/27 إلى 2025/1/27، حيث استخدم 80 فأرًا أنثى في التجربة لمدة 20 يومًا وقسمت إلى عدد من المجموعات على النحو التالي: المجموعة الأولى (الضابطة): تضمنت 20 أنثى مرضعة (T1) أعطيت طعامًا وماءً عاديين. المجموعة الثانية (T2): تضمنت 20 أنثى مرضعة أعطيت الشمر. المجموعة الثالثة (T3): تضمنت 20 أنثى مرضعة أعطيت 2 ملغ من ميتوكلوبراميد. المجموعة الرابعة (T4): تضمنت 20 أنثى مرضعة أعطيت 10٪ من حبة الحلوة و 2 ملغ من ميتوكلوبراميد. أظهرت الفحص النسيجي للمجموعات المرضعة زيادة في حجم الفصيصات والحويصلات، حيث كانت تجاويفها أكبر من تلك الموجودة في المجموعة الضابطة. كما وأظهرت النتائج الحالية زيادة في أوزان الأمهات خلال فترة التجريع بسبب فعالية المواد المستخدمة في الدراسة مقارنةً بالمجموعة الضابطة. عند مقارنة جميع المجموعات، وُجدت أعلى زيادة في أوزان الأمهات في المجموعة التي أعطيت الشمر والميتوكلوبراميد. خلصت الدراسة الحالية إلى أن مستخلص الشمر والميتوكلوبراميد كانت له نتائج إيجابية على الغدد الثديية بزيادة افرازها وكان تأثير العقار أكثر من المستخلص ولوحظت النتائج الأفضل في المجموعة المعاملة بالمستخلص والعقار معا. كما ان المواد المستخدمة في الدراسة لها تأثيرات على تركيب الغدد الثديية اذ لوحظ زيادة في حجم الحويصلات الافرازية للغدة وزيادة سمك جدرانها مع زيادة واضحة في تفرعات جدران هذه الحويصلات كما بينت المقاطع النسيجية للدراسة.

INTRODUCTION

The mammary gland is a complex, branching tubuloalveolar structure and a defining feature of animals. It is originated from the epidermal apocrine gland, functioning as a bilateral supplementary reproductive organ situated on the ventral aspect of the animal [1]. Mammary cells, create and secrete prolactin, which is necessary for the mammary glands' final preparation for milk production and secretion [2, 3]. Pregnancy and lactation are physiological conditions that alter the animal metabolism. All metabolic pathways is necessary to support the growth of the fetus are active throughout pregnancy[4]. The physiological and nutritional conditions of the animal have an impact on the physicochemical characteristics of the milk chemical composition [5]. Human milk production is increased by the use of both herbal and pharmacological galactagogues [6]. Medicinal plants are recognized as a rich source of secondary metabolites that play significant roles both *in vivo* and *in vitro* during ovarian folliculogenesis and steroidogenesis across various animal species. With technological advancements, there is an increased application of these drugs in assisted reproductive technologies [7, 8]. Additionally, certain secondary metabolites can function as

antioxidants primarily by scavenging reactive oxygen species (ROS) or by regulating ovarian hormone production. Certain plants include bioactive compounds that have been utilized to address reproductive problems[9]. *Foeniculum vulgare* is a biennial herbaceous plant of the Apiaceae family, known for its medicinal and fragrant properties. It is utilized in traditional medicine to address several disorders associated with the digestive, endocrine, reproductive, and respiratory systems. Moreover, it serves as a galactagogue for lactating moms, attributed to the presence of various beneficial chemical constituents, including volatile chemicals, flavonoids, phenolic compounds, fatty acids, and amino acids [10].

Metoclopramide is a powerful antagonist of dopamine receptors utilized for its antiemetic effects. It is utilized in conditions of diminished intestinal motility, gastroesophageal reflux, dyspepsia, nausea and vomiting linked to numerous gastrointestinal illnesses, migraines, postoperative states, and cancer therapies. It is utilized as a hydrochloride salt in medicinal formulations, owing to its superior bioavailability[11]. Because *Foeniculum vulgare* contains phytoestrogen that may stimulates mammary glands development, while metoclopramide increases prolactin secretion by blocking dopamine. Therefore, this study aimed to determine the effect of both *Foeniculum vulgare* and metoclopramide on the development of mammary glands of lactating female mus musculus mice.

MATERIALS AND METHODS

The study was performed in the animal facility of the College of Veterinary Medicine and the laboratories of the College of Science at Tikrit University from October 27, 2024, to January 27, 2025. A total of 80 female mice, their ages (15-20) weeks, were utilized in the investigation over a duration of 20 days, categorized into several groups as follows: The initial group (control) (T1) comprised 20 lactating females provided with standard food and drink. The second group (T2) comprised 20 lactating females administered *Foeniculum vulgare*. The third group (T3) comprised 20 nursing females administered 2 mg of metoclopramide. The fourth group (T4) comprised 20 lactating females administered *Foeniculum vulgare* and 2 mg metoclopramide.

Plant Collection

The plants used in the experiment were obtained from local sources in their raw form. Fennel was used as food for rats. It was ground up and mixed with brown flour. The rats were given 10% of this mix as part of their normal food. This was then dried and fed to the animals as a plant paste

Dosage determination

funnel was used as fodder by grinding it and mixing it with brown flour at a rate of 10% of the rats' daily diet, creating a plant paste that was dried and fed to the animals [12]. Metoclopramide was used as an oral dose of 2 mg/day [13].

Preparation of Microscopic Slides

Females were anesthetized with chloroform and dissected 21 days. Chloroform is more effective and induce anesthesia more quickly. The abdomen was incised, and the mammary glands were removed. Microscopic preparation were carried out according to methods described in references [14, 15], as follows: The samples were preserved in formalin for 18-24 hours, depending on the sample size, and then transferred to 70% alcohol. Formalin-fixed tissues were dehydrated by substituting an ascending alcohol gradient (35%, 50%, 70%, 95%, 100%). Clearing in xylene and Embedding in paraffin wax and then sectioning in microtome. The staining process was then carried out with Harris Hematoxline and eosin.

Statistical analysis

The results of current study were analyzed statistically using the statistical program (SPSS) version (23) by testing the mean and standard deviation and using the Duncan test to determine

the differences between the groups at the level of probability (0.05).

RESULTS AND DISCUSSION

Histopathological appearance of the normal mammary gland (T1) consists of several lobes surrounded by adipose tissue. These lobes were composed of lobules separated by dense connective tissue. Each lobule was composed of several alveoli, whose walls are composed of a single row of cuboidal epithelial cells using hematoxylin and eosin staining as shown in Figure (1). In the group given the *Foeniculum vulgare***.** In T2, the cavity and branching were greater than in the control group, resulting in larger lobes, lobules, and alveoli. Internal folds indicated alveolar wall branching and secretory material growth. They also contained fat droplets in secretory materials. The group administered metoclopramide (T3) exhibited an enlargement of the lobules and alveoli, along with alterations in the morphology and size of the epithelial cells lining the alveoli. The quantity of released chemicals in the alveolar lumen also rose, accompanied by an increase in lipid droplets within the secretions relative to the control group. The same results were observed in the group receiving *Foeniculum vulgare* and metoclopramide(T4). The lobules and lobes were larger, with a reduced amount of adipose tissue, and the alveolar volume, secretion, and alveolar branching were significantly increased. Histologically, the decline in adipose tissue was seen as a definite drop in the quantity and size of adipocytes—which show up as distinct vacuolated gaps in tissue sections. Expanded lobular and alveolar structures took place in treated groups to indicate a change from fat storage to active glandular growth. The amount of secretion within the alveoli and the presence of lipid droplets were also increased, with the secretions being more fatty than in the other groups. The increase in lobular and alveolar size is due to the estrogenic activity of *Foeniculum vulgare*, which stimulates ductal and lobular growth. Metoclopramide increases prolactin levels, enhancing alveolar differentiation and milk secretion. The combination promotes glandular tissue proliferation, reduces adipose content, and increases lipid-rich secretions.

The results showed in Table (1) that the weights of the mothers during the dosing period increased during the breastfeeding period. The highest increase was in the group given a *Foeniculum vulgare* and metoclopramide, as the average weight of the mothers reached 28.01±0.9 grams in the first week, 29.33±0.86 grams in the second week, and 30.05±1.09 grams in the third week compared to the control group, which was 24.02 ±1.01grams in the first week, 24.54 ±0.93grams in the second week, and 25.87±0.88 grams in the third week.. All groups recorded a weight gain in the first week after dosing, along with the control group.

Table 1: Effect of treatments on the weight of mice according to weeks.

Weight / Groups	At birth	First week	Second week	Third week
Control groups	22.11 ±1.03 c	24.02 ±1.01c	25.54 ±0.93 c	25.87±0.88 c
***Foeniculum vulgare* Group**	23.06±1. 12 c	24.96±0.75 b	26.30±0.72 b	27.01±1.31b
Metoclopramide group	24.74 ±0.9 b	25.18 ±0.95 b	27.08 ±0.98 b	28.017 ±1.16 a
***Foeniculum vulgare* and metoclopramide group**	25.41 ±1.11 a	28.01±0.9a	29.33 ±0.86a	30.05 ±1.09 a

*Different letters vertically means there is a significant difference at p-value<0.05

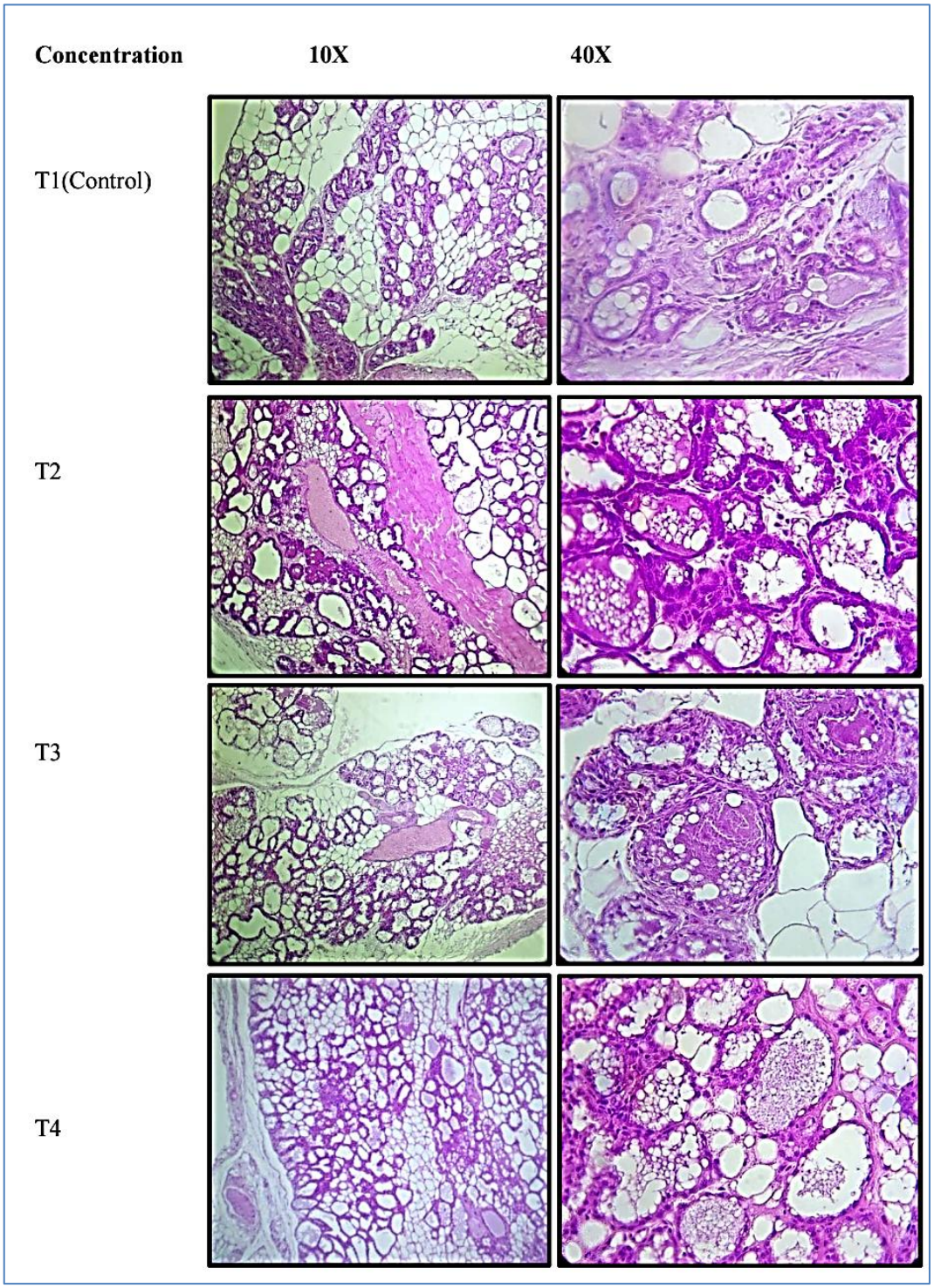

Fig. 1: Histological sections of the mammary gland of a lactating female mouse (control). Lobules and alveoli contain secretory materials A and fatty tissue B, (H&E). T2, Histological section of the mammary gland of a lactating female mouse given *Foeniculum vulgare*. Lobules and alveoli containing secretory material A, adipose tissue B, and branches of alveoli C, (H&E). T3, Histological section of the mammary gland of a lactating female mouse given metoclopramide only. Lobules and alveoli containing secretory material A, adipose tissue B, and alveolar branches C, X10 (H&E)., (H&E). T4, Histological section of the mammary gland of a lactating female mouse given *Foeniculum vulgare* and metoclopramide. Lobules and alveoli containing secretory substances A, adipose tissue B, and alveolar branches C, (H&E).

The prior histological findings in the group administered *Foeniculum vulgare* indicated enhanced growth and development of the mammary glands, alongside an elevation in the quantity of secreted material, potentially attributable to the presence of numerous volatile oils in *Foeniculum vulgare*. The findings of the current study align with [12], which showed the influence of fennel on mammary gland development, observing an enhancement in growth within the lacting group, comparable to the effects of estrogen and progesterone. A study done by [16], which demonstrated the impact of fennel on milk and prolactin levels, indicating that fennel, whether consumed alone or in herbal tea, can enhance breast milk production and promote weight gain in neonates.

herefore, one of the expected mechanisms through which anethole, the major active compound in Foeniculum vulgare, enhances milk secretion is by competing with dopamine for its receptor sites. This action inhibits dopamine's suppressive effect on prolactin secretion, thereby increasing prolactin levels and promoting milk production. The study by[17] indicated that administration of milk stimulants leads to an increase in prolactin levels and a decrease in dopamine levels. therefore, milk stimulants work by inhibiting dopamine receptors, increasing prolactin secretion and, consequently, mammary gland development and increased milk production. Previous studies have demonstrated that metoclopramide administration enhances milk production by increasing the number of secretory granules in mammary epithelial cells. This effect is primarily attributed to its antagonistic action on dopamine D2 receptors, which stimulates prolactin release from the anterior pituitary gland, ultimately promoting lactogenesis [18]. Its effect on the structural composition of the secretory vesicles was also observed, as their walls were thicker with a significant increase in their branches. This leads to an increase in the surface area of the secretion, which in turn plays a role in increasing the amount of secreted material per vesicle, thus enhancing breast activity in general. The results of our current study are consistent with [19], which results proved that metoclopramide drug led to an increase in prolactin levels in the serum of mothers compared to the control group. After three weeks of taking the drug, as indicated by [20] in this study, the group that received metoclopramide at a rate of 10 mg three times a day for two weeks, led to an increase in the percentage of milk, thus leading to an increase in daily breastfeeding. The drug's effect on increasing milk secretion is expected to be through stimulating increased secretion of prolactin (PRL). Many studies, such as [21], indicate that metoclopramide leads to an increase in prolactin by inhibiting dopamine activity [22, 23]Dopamine is the primary agent that suppresses the pituitary gland's release of prolactin, either via a direct inhibitory effect on the gland or by enhancing the production of prolactin inhibitory factor from the brain [21, 24]. Another study [21] indicated that metoclopramide stimulates the pituitary gland's release of PRL, An activity ascribed to an antidopaminergic mechanism, achieved by obstructing dopamine receptors in the hypothalamus, hence diminishing PRL levels. The results of the current study showed that the highest maternal weight was in the group receiving the *Foeniculum vulgare* and metoclopramide. This may indicate a synergistic effect of *Foeniculum vulgare* and metoclopramide, which is reflected in increased prolactin secretion, which in turn increases milk production and thus increases its nutritional value. These results are consistent with those of [22, 23], who conducted a study on 46 breastfeeding mothers to evaluate the effect of fennel on serum prolactin levels. The mothers took 3 grams of fennel powder in six 500 mg capsules daily. Serum prolactin was measured before and 15 days after the intervention. An increase in prolactin levels was observed, indicating that fennel increased serum prolactin levels, confirming the current study's role in prolactin's key role in milk production.

CONCLUSION

Foeniculum vulgare and metoclopramide had positive effects on the mammary glands, increasing their secretion. The drug's effect was greater than that of the extract, with the best results observed in the group treated with both the extract and the drug. The substances used in the study affected the structure of the mammary glands, as an increase in the size of the gland's secretory vesicles and an increase in the thickness of their walls was observed, along with a clear increase in the branching of these vesicle walls, as shown in the histological sections of the study.

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