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Prevention of tumors in treating fibrocystic breast diseases using *Vitex agnus-castus*-based herbal remedy

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Background. Oncologists notice an increasing prevalence of female reproductive system pathological conditions that lead to benign and malignant diseases of mammary glands. Fibrocystic breast diseases (FBD) occur in approximately 80 % of women of reproductive age worldwide. Currently, there is no single widely accepted treatment for FBD. The therapy mainly includes surgery and hormonal treatment. A few herbal medicines effective against FBD include *Vitex agnus-castus* (VAC) medications. According to many studies, the absence of timely targeted preventive therapy puts patients with FBD at risk of developing malignant tumors. FBD is a risk factor for cancer development and turns into cancer in 3–6 % of patients.
Aim. To assess the effectiveness of VAC against FBD.
Materials and methods. In this study, 150 women aged 40+ with FBD were randomly assigned to the treatment group (n = 78) or the controls (n = 72). The groups were similar in demographic characteristics, including age, parity, menopause, history of abortions, family history of breast cancer, and alcohol and tobacco consumption. The treatment group received two tablets of VAC extract (each containing 162 mg) daily for six months. At baseline, weeks 12 and 24, all participants were evaluated using a visual analog scale and ultrasound examination.
Results. Breast pain decreased significantly in the treatment group, and the median visual analog scale scores at weeks 12 and 24 decreased significantly compared to baseline in the treatment group (89.7 % at baseline, 76.9 % at week 12, and 42.3 % at week 24) compared to the controls (66.3 % at baseline, 63.9 % at week 12 and 61.1 % at week 24). Furthermore, the breast ultrasound findings at weeks 12 and 24 revealed that regression rates in the treatment group were significantly higher than in the control arm (46.2 % *vs*. 6.9 % at week 12; 55.1 % *vs*. 8.3 % at week 24).
Conclusion. VAC is effective in managing patients with FBD. VAC treatment efficacy can be evaluated using a visual analog scale and ultrasound examination. The herbal remedy VAC extract used in this treatment for patients with FBD has proven effective in preventing breast cancer.

Keywords: fibrocystic breast disease, mastalgia, *Vitex agnus-castus*, herbal medicine

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Профилактика новообразований при лечении фиброзно-кистозных заболеваний молочной железы с использованием растительного лекарственного средства *Vitex agnus-castus*

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Введение. Увеличение распространенности патологических состояний женской репродуктивной системы, приводящих к доброкачественным и злокачественным заболеваниям молочных желез, является актуальной проблемой для онкологов. Фиброзно-кистозные заболевания молочной железы (fibrocystic breast diseases, FBD) встречаются примерно у 80 % женщин репродуктивного возраста во всем мире. В настоящее время не существует единого общепринятого метода лечения FBD. Терапия в основном включает хирургическое вмешательство и гормональное лечение. Некоторые растительные лекарственные средства, эффективные против FBD, включают препараты *Vitex agnus-castus* (VAC). Во многих научных работах показано, что пациентки с FBD при отсутствии своевременной целенаправленной профилактической терапии входят в группу риска развития злокачественной опухоли. FBD является фактором риска развития рака и переходит в рак у 3–6 % пациенток.
Цель исследования – оценить эффективность экстракта VAC против FBD.
Материалы и методы. В этом исследовании 150 женщин в возрасте 40+ лет с FBD были случайным образом распределены в 2 группы: группа терапии (n = 78) и контрольная группа (n = 72). Группы были схожи по демографическим характеристикам, включая возраст, число детей, менопаузу, аборты в анамнезе, семейный анамнез рака молочной железы, а также употребление алкоголя и табака. Участницы из группы терапии получали по 2 таблетки экстракта VAC (каждая по 162 мг) ежедневно в течение 6 мес (24 нед). Результаты лечения всех участниц оценивали с помощью визуально-аналоговой шкалы и ультразвукового исследования в начале эксперимента, через 12 и 24 нед.
Результаты. Боль в груди значительно уменьшилась в группе лечения, а средние баллы по визуально-аналоговой шкале на 12-й и 24-й неделях значительно снизились по сравнению с исходным уровнем в группе терапии (89,7 % – на исходном уровне, 76,9 % – на 12-й неделе и 42,3 % – на 24-й неделе) по сравнению с контрольной группой (66,3 % – на исходном уровне, 63,9 % – на 12-й неделе и 61,1 % – на 24-й неделе). Кроме того, по данным ультразвукового исследования молочных желез на 12-й и 24-й неделях показатели регресса в группе терапии были значительно выше, чем в контрольной группе (46,2 % против 6,9 % на 12-й неделе; 55,1 % против 8,3 % на 24-й неделе).
Выводы. VAC эффективен при лечении пациенток с FBD. Эффективность лечения VAC можно оценить с помощью визуально-аналоговой шкалы и ультразвукового исследования. Растительный экстракт VAC, использованный в данном исследовании при лечении пациенток с FBD, доказал свою эффективность в профилактике рака молочной железы.

Ключевые слова: фиброзно-кистозная болезнь молочной железы, масталгия, *Vitex agnus-castus*, фитотерапия

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Background

Fibrocystic breast disease (FBD) is a benign hormone-dependent change in breast tissue. It is a general term that includes different variants of nodular and cystic formations and areas of fibrosis, fibroadenomatosis, and other changes in the mammary glands [1]. The prevalence of FBD ranges from 30 % to 60 % and usually affects women aged 30 to 50 years [2]. In most cases, these changes do not require medical intervention, while some cases can turn into premalignant histological conditions, increasing the risk of developing breast cancer [3, 4]. Most cases of FBD are asymptomatic, and patients seek medical help only if they experience breast pain. Sixty percent of women with fibrocystic breast disease experience breast pain [5]. Pain may or may not be acute, varying from mild to severe intensity, and is generally described as a burning or nagging sensation. It can occur in one or both breasts; the upper outer quadrant is the most common localization. Breast pain can last from a few minutes to several days and severely affects quality of life. Evaluation of fibrocystic breast disease starts with a review of the patient's history. If a patient has breast pain, it is essential to assess its duration, location, severity, relationship to the menstrual cycle, and impact on daily life [6].

Lifestyle changes, proper nutrition, and certain non-pharmacological agents have a positive effect. Few herbal medicines are considered the most effective and safe in treating FBD, especially *Vitex agnus-castus* (VAC) medications [7]. VAC is a deciduous shrub native to the Mediterranean, Europe, and Central Asia. Its main pharmacodynamic effect is reducing the increased level of prolactin due to the dopaminergic effect, which contributes to the narrowing of the ducts, reducing the activity of proliferative processes and the formation of connective tissue, eliminating corpus luteum insufficiency, and normalizing estrogen-progesterone disorders through the hypothalamic-pituitary system. The drug significantly reduces swelling of the mammary glands, reduces pain, and promotes the reverse development of degenerative changes in breast tissue [8, 9]. VAC extracts are included in the drug Mastodynon, which has been used to treat many female pathologies, including menstrual disorders (amenorrhea, dysmenorrhea), premenstrual syndrome, corpus luteum insufficiency, hyperprolactinemia, infertility, acne, menopause, and lactation disorders [7, 10–13].

Few studies with limited cohorts have evaluated VAC effectiveness against FBD. Therefore, the pharmacodynamic abilities of drugs involving VAC cast doubt. Therefore, we evaluated the role of VAC in managing FBD using a pain measurement scale as a subjective evaluation and ultrasound as an objective evaluation.

Materials and methods

Participants. In this study, 150 patients with FBD were included in this prospective trial at the Kazakh Institute of Oncology and Radiology (Almaty, Kazakhstan). The diagnosis was made by considering the patient's complaints, performing a physical examination, and reviewing the ultrasound evaluation of the mammary glands. Patients over 40 years of age initially underwent mammography screening to exclude breast cancer. The patients were randomly assigned to the control group (n = 72) or the treatment group (n = 78) based on their hospital admission order.

The study included women aged 18 to 80 years diagnosed with FBD and able to meet with investigators as scheduled. However, women who were pregnant or breastfeeding at the time of enrollment had severe chronic comorbidities such as cancer, diabetes mellitus, systemic blood diseases, neuralgia, or suffered from mental illness or legal incompetence were excluded from the study. Furthermore, women who had previously participated in another clinical trial were not eligible to participate in this one.

Procedure. In the study, pain was considered persistent if it lasted more than 3 months, regardless of treatment. During the 6-month study period, the treatment group received two tablets daily containing 162 mg of VAC. The controls did not receive VAC pills but were still followed and monitored the same as the treatment group.

Objective and subjective methods were used to evaluate the effectiveness of treatment. Subjective methods included measuring the intensity of breast pain using a visual analog scale [14] ranging from "no pain" to "unbearable pain" and a set of pictures depicting various facial expressions ranging from a smile to a face with pain (Fig. 1).

To ensure an objective evaluation, the same investigator examined by touch and ultrasound at baseline and weeks 12 and 24 after treatment using the same tools. The state of the breast tissue was evaluated based on ultrasound findings. It was classified as progression (increase in size and/or number of cysts or fibrosis), stabilization (no clinically significant changes), or regression (partial or complete clinical response) [15].

The subgroups were compared using the Kolmogorov–Smirnov test for normality and the Levene test to assess whether the group variances were homogeneous. The Mann–Whitney U test was then used to determine whether the groups had significant differences in median (minimum-maximum) values due to their skewed distribution. Frequencies and percentages were presented to describe categorical variables.

Fig. 1. *Common pain measurement scale: the 11-point numeric scale from "no pain" to "unbearable pain" and the 5-point verbal rating scale (0 – no pain, 1–3 – mild pain, 4–6 – moderate pain, 7–9 – severe pain, 10 – unbearable pain)*

Рис. 1. *Обобщенная шкала измерения боли: 11-балльная числовая шкала от «отсутствия боли» до «невыносимой боли» и 5-балльная словесная шкала оценки (0 – боли нет, 1–3 – слабая боль, 4–6 – умеренная боль, 7–9 – сильная боль, 10 – невыносимая боль)*

When comparing subgroups, the Bonferroni method was used; if there was no difference between the groups, it was shown with the same letter; if there was a difference, it was shown with a different letter. The association between the groups and categorical variables was assessed with univariate analysis using Pearson's chi-square test or Fisher's exact test. A p-value less than 0.05 was considered significant for all statistical purposes. The IBM SPSS Statistics package v. 25.0 for Windows (USA) was used for calculations.

Results

The median age of the patients in the study cohort at baseline was 38.5 (18 to 77) years. There was no significant age difference between the treatment and control groups (p = 0.219). Most participants were Kazakh: 85.3 % of all study participants, 84.6 % of the treatment group, and 86.1 % of the controls. More than half of the patients had fibroadenosis. The groups were similar in terms of menopause, nulliparity, history of abortions, and family history of breast cancer. They were also similar in terms of alcohol consumption and smoking status. More detailed information is presented in Table 1.

Discussion

118/150 participants (78.7 %) had breast pain at baseline, including 70 (89.7 %) in the treatment group and 48 (66.3 %) among the controls. These numbers decreased significantly in the treatment group (76.9 % at week 12 and 42.3 % at week 24), with no significant decrease among the controls (63.9 % at week 12 and 61.1 % at week 24). Additionally, the median visual analog scale scores at weeks 12 and 24 decreased significantly in the treatment group compared to the controls (Fig. 2).

The breast ultrasound findings at weeks 12 and 24 revealed that the regression rates in the treatment group were significantly higher than among the controls (46.2 % *vs.* 6.9 % at week 12; 55.1 % *vs.* 8.3 % at week 24). Stable rates were significantly higher in the control group at both visits. However, the progression rates were similar for both groups at both visits (Table 2).

Table 1. *Main characteristics of the study cohort*
Таблица 1. *Основные характеристики исследуемой когорты*

Parameter Показатель	*n* (%) or median (minimum–maximum) *n* (%) или медиана (минимум–максимум)			*p*
	Total number of study participants, *n* = 150 Общее число участников исследования, *n* = 150	Treatment group, *n* = 78 (52 %) Группа терапии, *n* = 78 (52 %)	Control group, *n* = 72 (48 %) Контрольная группа, *n* = 72 (48 %)	
Age, years Возраст, лет	38.5 (18–77)	36.5 (18–73)	40 (21–77)	0.219*
Ethnicities, *n* (%): Этническая принадлежность, *n* (%): Kazakh казахи Russian русские Uighurs уйгуры	 128 (85.3) 18 (12.0) 4 (2.7)	 66 (84.6) 8 (10.3) 4 (5.1)	 62 (86.1) 10 (13.9) –	–
Diagnosis, *n* (%): Диагностика, *n* (%): cysts киста duct ectasia эктазия протоков fibroadenoma фиброаденома fibroadenosis фиброаденоз	 36 (24) 17 (11.3) 12 (8.0) 85 (56.7)	 21 (26.9) 10 (12.8) 6 (7.7) 41 (52.6)	 15 (20.8) 7 (9.7) 6 (8.3) 44 (61.1)	0.706**
Menopause, *n* (%) Менопауза, *n* (%)	35 (23.3)	18 (23.1)	17 (23.6)	0.938***
Pregnancy, *n* (%): Беременность, *n* (%): nulliparity нулипарность childbirth роды	 50 (33.3) 100 (66.7)	 27 (34.6) 51 (65.4)	 23 (31.9) 49 (68.1)	0.729***
History of abortions, *n* (%) История абортов, *n* (%)	40 (26.7)	20 (25.6)	20 (27.8)	0.767***
Alcohol consumption, *n* (%) Употребление алкоголя, *n* (%)	5 (3.3)	2 (2.6)	3 (4.2)	–
Smoking status, *n* (%) Статус курения, *n* (%)	5 (3.3)	1 (1.3)	4 (5.6)	–
Family history of breast cancer, *n* (%) Семейный анамнез рака молочной железы, *n* (%)	15 (10)	8 (10.3)	7 (9.7)	0.576***

**The Mann–Whitney U test was used.*
***The chi-square and Bonferroni methods were used to compare subgroups.*
****The chi-square was used to compare subgroups. n – number of patients.*
**Использовался U-критерий Манна–Уитни.*
***Для сравнения подгрупп использовались критерий χ^2 и метод Бонферрони.*
****Для сравнения подгрупп использовался критерий χ^2. n – число пациенток.*

Analysis of the relationship of these ultrasound findings with the underlying diagnoses showed that a significantly higher regression rate in the treatment group was primarily due to patients with fibroadenosis. Table 3 provides more details on the underlying pathological diagnosis and the response to treatment.

Fibrocystic breast disease occurs in at least 1 in 3 women of premenopausal age. More than half of them experience breast pain. It is interesting to note that some types of FBD respond well to pharmacotherapy while others do not. This randomized, placebo-controlled study evaluated the effectiveness of VAC in patients with persistent breast

Table 2. *Objective responses based on ultrasound results, n (%)*
Таблица 2. *Объективные ответы на основе результатов ультразвукового исследования, n (%)*

Parameter Показатель	Treatment group, *n* = 78 Группа терапии, *n* = 78	Control group, *n* = 72 Контрольная группа, *n* = 72	*p*
Baseline Исходный уровень Stable Стабилизация	78 (100)	72 (100)	–
Week 12: 12-я неделя: stable стабилизация progression прогрессирование regression регресс	 38 (48.7)[a] 4 (5.1)[a] 36 (46.2)[a]	 60 (83.3)[b] 7 (9.7)[a] 5 (6.9)[b]	<0.001*
Week 24: 24-я неделя: stable стабилизация progression прогрессирование regression регресс	 27 (34.6)[a] 8 (10.3)[a] 43 (55.1)[a]	 55 (76.4)[b] 11 (15.3)[a] 6 (8.3)[b]	<0.001*

**The chi-square test and Bonferroni method were used to compare subgroups.*
[a, b]Same letter indicates the lack of difference between the subgroups; different letters indicate a difference in the results. n – number of patients.
**Для сравнения подгрупп использовались критерий χ^2 и метод Бонферрони.*
[a, b]Одна и та же буква указывает на отсутствие различий между подгруппами; разные буквы указывают на разницу в результатах. n – число пациенток.

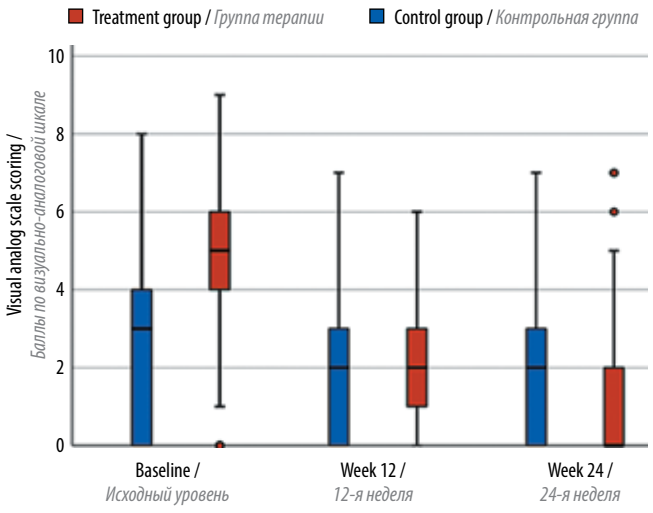

Fig. 2. *Box plot graph of treatment and control groups at baseline, weeks 12 and 24*
Рис. 2. *Гистограммы распределения по группам (контрольная группа, группа терапии) на исходном уровне, на 12-й и 24-й неделях*

pain due to FBD using subjective and objective responses to treatment.

Several randomized, placebo-controlled clinical trials have reported using VAC-containing drugs to treat mastalgia, fibrotic, and cystic changes in the mammary gland [10–13]. In a trial in Tabriz, Iran, M. Mirghafourvand et al. evaluated only daily breast pain using the Cardiff Pain Chart. In another study, VAC resulted in significantly higher regression rates in the treatment group than in the controls [12].

The study by M. Halaska et al., pioneers in the treatment of FBD, showed that breast pain in patients with FBD decreased significantly in the VAC treatment group. As in our study, VAC was effective in reducing the intensity of cyclical breast pain compared to placebo [10]. Another comparative study by A. Zeqiri et al. showed even better results, with a 50 % complete response after VAC treatment [13]. In our study, VAC reduced pain by 55.1 % in regression, especially in duct ectasia and fibroadenosis.

As is known, the main pharmacodynamic effect of VAC is reducing the increased level of prolactin due to the dopaminergic effect, which contributes to the narrowing of the ducts, reducing the activity of proliferative processes and the formation of connective tissue, eliminating corpus luteum insufficiency, and normalizing estrogen-progesterone disorders through the hypothalamic-pituitary system. That is, the drug significantly reduces swelling and pain in the mammary glands [8, 9]. V. Bernard et al. reported the benefit of antiprolactin drugs in cyclical and non-cyclical mastalgia [16].

Table 3. *Distribution of ultrasound findings at weeks 12 and 24 considering the underlying diagnosis, n*
Таблица 3. *Распределение результатов ультразвукового исследования на 12-й и 24-й неделях с учетом основного диагноза, n*

Diagnosis Диагноз	Week 12 12-я неделя			Week 24 24-я неделя		
	Control group, *n* = 72 Контрольная группа, *n* = 72	Treatment group, *n* = 78 Группа терапии, *n* = 78	Total Всего	Control group, *n* = 72 Контрольная группа, *n* = 72	Treatment group, *n* = 78 Группа терапии, *n* = 78	Total Всего
Cyst Киста						
Regression Регресс	2[a*]	9[a*]	11	3[a*]	10[a*]	13
Stable Стабилизация	12[a*]	10[b*]	22	9[a*]	7[a*]	16
Progression Прогрессирование	1[a*]	2[a]	3	3[a]	4[a]	7
Duct ectasia Эктазия протоков						
Regression Регресс	0[a*]	5[b*]	5	0[a*]	5[b*]	5
Stable Стабилизация	6[a*]	4[a*]	10	5[a*]	2[b*]	7
Progression Прогрессирование	1[a*]	1[a*]	2	2[a*]	3[a*]	5
Fibroadenoma Фиброаденома						
Regression Регресс	1[a*]	4[a*]	5	1[a*]	4[a*]	5
Stable Стабилизация	4[a*]	2[a*]	6	4[a*]	2[a*]	6
Progression Прогрессирование	1[a*]	0[a]	1	1[a*]	0[a*]	1
Fibroadenosis Фиброаденомотоз						
Regression Регресс	2[a*]	18[b*]	20	2[a*]	24[b*]	26
Stable Стабилизация	38[a*]	22[b*]	60	37[a*]	16[b*]	53
Progression Прогрессирование	4[a*]	1[a*]	5	5[a*]	1[a*]	6
All patients Все пациенты						
Regression Регресс	5[a*]	36[b*]	41	6[a*]	43[b*]	49
Stable Стабилизация	60[a]	38[b*]	98	55[a*]	27[b*]	82
Progression Прогрессирование	7[a*]	4[a*]	11	11[a*]	8[a*]	19
Total *Всего*	*72*	*78*	*150*	*72*	*78*	*50*

**The chi-square test and Bonferroni method were used to compare subgroups.*
[a, b] Same letter indicates the lack of difference between the subgroups; different letters indicate a difference in the results. n — number of patients.
**Для сравнения подгрупп использовались критерий χ^2 и метод Бонферрони.*
[a, b] Одна и та же буква указывает на отсутствие различий между подгруппами; разные буквы указывают на разницу в результатах. n — число пациенток.

M.A. Thorat et al. (2021) observed significant pain relief in 75 % of patients treated with tamoxifen 20 mg/day for 3 months, which outperforms the results of our study. However, antiestrogen therapy has a wide range of side effects, such as hot flushes (27 %) and vaginal discharge (17 %) [17].

Equally important is the unevidenced ability of VAC to prevent breast cancer. Therefore, we plan to use the cohort of this study for future research on breast cancer prevention in a high-risk group.

In our study, persistent pain decreased significantly from baseline to week 24 (89.7 % to 42.3 %) in the treatment group but remained in the placebo group (66.3 % to 61.1 %). We observed a significant decrease in the pain rate and intensity in the treatment group. We applied objective and subjective methods to evaluate treatment results, and our study provides new information on VAC prescribing in FBD. Ultrasound evaluation confirmed a statistically significant contribution of VAC in the regression of duct ectasia and fibroadenoma, as well as the stabilization of breast cystic disease. No recent comparative study has utilized objective methods to evaluate the effectiveness of VAC.

Conclusion

The study showed VAC's significant effectiveness in managing FBD. VAC could be included in the drug list of the national protocol for the treatment of benign breast diseases.

Limitations of the study. The limitations of our study were the disuse of placebo drugs, the absence of double-blindness, and the short duration of the study that did not allow the evaluation of long-term results. The differences in VAC effectiveness in various types of benign breast pathology that we found should be evaluated in future studies.

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