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Reproductive Health: Prospects of Using the *Euphorbia Fischeriana* Steud. Root Extract In Case Of Impaired Reproductive Function.

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ABSTRACT

This paper presents the results of long-term research of a unique endemic plant *Euphorbia Fischeriana Steud.* of the Trans-Baikal Territory. This plant has found its limited application in traditional medicine for the treatment of serious illnesses (such as adenoma, and prostate cancer), but there is no pharmaceutical milkweed-based drug, which is due to the raw material toxicity. The authors have proposed a method of treating raw materials for toxic agents (anthraglycosides) and proved its safety and biological effectiveness. The paper presents comparative data on the effect of the extract prepared in an original way, and the tincture prepared according to a recipe of traditional medicine on aphrodisiac activity of laboratory rats. It was revealed that the tincture has no aphrodisiac activity, and even oppresses it, especially a copulative component of sexual behavior of male rats. The authors have disclosed in this paper the mechanisms of influence of the *Euphorbia fischeriana Steud.* root extract on aphrodisiac function; the experiment on laboratory animals has shown by "pharmacological castration" that the main mechanism of aphrodisiac activity of *Euphorbia fischeriana Steud.* is a sensitization of tissue androgen receptors and increase in the production of testosterone.

Keywords: Adaptogenes, adaptation, hypogonadism, erectile dysfunction, nitric oxide, selenium deficiency, *Euphorbia fischeriana Steud.*, "pharmacological castration".

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INTRODUCTION

Currently, the reproductive health of Russian population stands in the spotlight of the government of the Russian Federation. According to various information, nearly 17% to 20% of couples in Russia are infertile. The reasons of childlessness in couples may equally be both female (40-45%) and male (45-50%) infertility. According to the experts' estimates, there is about 3 to 4 million abortions per year happening in Russia. 57% of all pregnancies ends with abortion. The teenagers under age 18 do every fifth abortion. Socially-related improper reproduction behavior of a multifactorial nature complicates the problems with reproduction. One of the reasons occupying a special place is the formation of improper reproductive attitude in youth. Dynamics of reproductive behavior depends on not only socio-economic factors, but also socio-psychological ones, which directly correlate with ethnic and cultural, and confessional conditions of socialization of the individual, and traditional/modernistic attitudes. The main components of reproductive behavior are sexual behavior, reproductive attitude and control (planning) of fertility. We used these parameters to study the ethnic and cultural differentiation of behavior in women of the Trans-Baikal Territory. The respondents included 30.9% of 15 to 21-year-old people, 33% - people aged 22 to 29 years, 23.2% - 30 to 37 years, and 11.9% - 38 to 45 years. In terms of ethnic composition, 70.6% of women constituted themselves Russian, 20.1% were of mixed ethnicity (the Gurans, the Karyms), and 9.3% represented the Buryats. The main indicators of reproductive attitudes are the mean ideal, desired, and expected (planned) number of children. The conducted survey has shown that the ideal number of children, namely a vision of an individual emerging without a specific real-life situation, depends on the ethnicity of the respondents. The Russian women consider 2.0 children to be an ideal number, while the Buryats – 2.20, and the women of mixed ethnicity – 1.93. The highest rate is observed in representatives of Buryat ethnic group that can be explained by quite compact living of this ethnic group within the Trans-Baikal Territory or in nearby border areas.

As opposed to the care taken by the government in terms of female reproductive health, the health state of the male population in Russia has just become a target of research; and no true picture has been set in the scientific literature yet. Sexual disorders in men are an urgent medical and psychological problem due to their high incidence. Thus, according to the Massachusetts Male Aging Study [1], the incidence of erectile dysfunction (ED) in men aged 40-70 years was 52%. ED can be a symptom of other serious diseases, such as diabetes, coronary heart disease, and depression [2]. For ED treatment, drugs of various pharmacological groups are used. Their efficiency does not exceed 30% and is slightly higher than that of placebo [3]. In addition, drugs have side effects; for example, yohimbine increases blood pressure, causes anxiety and frequent urination. The causes of sexual dysfunction may include a decreased production of androgens and a decrease in the sensitivity of receptors to sex hormones, metabolic diseases, long-term stresses, and inflammatory infections of the urogenital system.

Selenium deficiency also plays an important role in the development of endocrine system pathology in the ecopathogenic Trans-Baikal Territory. Selenium prevents the decomposition of testosterone, which, in turn, regulates the metabolism of nitric oxide being a key element in the erectile mechanism. Nitric oxide released by non-adrenergic, non-cholinergic nerve endings and the endothelium during the sexual stimulation leads to the activation of the enzyme guanylate cyclase, which catalyzes the formation of cGMP that activates the vasodilation in the cavernous bodies and the erection [4].

For the prevention of erectile dysfunction, the selenium-containing herbal adaptogenes can be used. One of such adaptogenes is *Euphorbia Fischeriana Steud.* (*Euphorbia Pallas*, Man-root, Trans-Baikal Ginseng) - a perennial herb, widespread in south-eastern Trans-Baikal Territory: Chita, Shilkinsky District, Olovyaninsky District, Nerchinsko-Zavodskoy District, Eastern Siberia, Northern Mongolia, and China [5,6,7]. Study of the chemical composition has found in roots such components as saponins, flavonoids, ascorbic acid, alkaloids, coumarins, glycosides, and high content of selenium and iodine [8,9]. Phytoandrogenes, and selenium preventing the decomposition of testosterone, increase sexual desire, erection, that contribute to the maintenance and prolongation of sexual activity in men [10].

There is a huge number of methods and means of treating the erectile dysfunction in traditional medicine, which are mostly phytogetic. However, the mechanisms of aphrodiatic activity of phyto-aphrodisiacs are understudied and their application is still an empirical question. For example, traditional medicine uses *Euphorbia Fischeriana Steud.* (EF) as a mean of treating impotence, adenoma, and prostate

cancer [11,12]. However, there is neither information on its mechanisms of influence on the sexual behavioral reactions nor evidence of clinical efficiency in reducing the libido or other components of the copulative cycle due to the use of drugs blocking more or less the effects of androgens. There is no pharmaceutical drug made of this unique plant due to its toxicity. Therefore, the investigation of the effect of the original, safe, and biologically active extract of the roots *Euphorbia Fischeriana Steud.* on the endocrine system is of scientific and practical interest.

Purpose of this study was to investigate the influence of *Euphorbia Fischeriana Steud.* root-based drugs on endocrine functions of reproductive glands in experimental hypogonadism caused by "pharmacological castration".

MATERIALS AND METHODS

The *Euphorbia Fischeriana Steud.* root extract was received in an original way, that allows removing the toxicity resulting from the content of tar and anthraglycosides in raw materials [13].

To elucidate the activation mechanism of aphrodisiac activity of the adaptogenes, an experiment was conducted to study the sexual behavior [14]. Experiments were performed on 90 white laboratory rats weighing 180-230 g. The experiments were carried out starting from November to February, when the rodent have seasonal decline in the physiological production of gonadotropins and androgens, and as a result, decreased sexual activity [15]. The animals were kept under stationary vivarium conditions, and grown with a standard diet and water in unlimited amount. The experiment involved the experimental and control groups, each of 10 animals [16].

The *Euphorbia Fischeriana Steud.* extract, the *Euphorbia Fischeriana Steud.* tincture and the ginseng tincture were administered intragastrically (i/g) at a dose of 1 ml/kg. Rats of control group received an equivolume amount of distilled water administered. Alcohol tinctures were de-alcoholized before use.

To determine the sexual activity of mature male rats, we evaluated the number of sniffing, licking, tank and ejaculations when mating males with females under artificially induced estrus [2]. Estrus state was induced by introducing s/c 0.05 ml of 2% synestrol oil solution for 5 days. Menstrual cycle phase was determined based on cytological examination of vaginal smears. Cytological pattern of the estrus state is characterized by sloughing of superficial nucleated cells. A keratinous layer becomes superficial, with 12 rows of nucleus-containing cells underneath. The number of mitosis has decreased, and white blood cells have disappeared.

During the first stage of the experiment we determined the effect of adaptogenes of the ginseng tincture (GT), the *Euphorbia Fischeriana Steud.* tincture (EFT) and the *Euphorbia Fischeriana Steud.* extract (EFE) on indicators of sexual behavior of adult males being kept in isolation from females for 30 days.

During the second stage of the experiment, we used the model of "pharmacological castration":

- Androcur - an androgen receptor blocking agent, administered enterally at a dose of 150 mg/kg for 30 days;
- Proscar - a specific inhibitor of 5-alpha reductase, that prevents transformation of testosterone into a more active 5-alpha-dihydrotestosterone at a dose of 1 mg/kg for 30 days;
- Synesterol - functional estrogen, androgen-antagonistic hormone, at a dose of 40 mg/kg for 30 days.

The third stage of the experiment involved the study of the extract effect shown against anti-androgen drugs: the extract was administered within 30 days simultaneously with Androcur, Proscar, and Synesterol at the same doses.

Along with indicators of sexual behavior, the content of testosterone in serum was determined by enzyme immunoassay using a standard set of "SterotidEIA-testosterone-01".

The obtained results were statistically processed. The significance of the differences between the compared parameters was evaluated by the Mann-Whitney test. Differences at 95% level at $P \leq 0.05$ were accepted as significant.

RESULTS OBTAINED

The assessment of the total index of sexual activity has revealed that the EFE prepared in traditional way suppresses twice sexual activity in the males as compared with the control animals. The *Euphorbia fischeriana Steud.* root extract significantly stimulates sexual activity in rats, increasing the overall rate of sexual activity 3 times. The sexual activity of the males treated with GT did not differ from the activity of the males in the control group.

The following results were obtained in the case of "pharmacological castration". Androcur reduces sexual activity by 47%, and the level of testosterone by 78%. EFE restores sexual activity, increasing its 6 times. The content of testosterone increases by 146% under the influence of EFE. Proscar reduces sexual activity by 75%, and the level of testosterone 3 times. Affected by Proscar, EFE has insufficient effect on sexual activity, and increases the content of testosterone by 8%. Synestrol reduces sexual activity by 65%, and the level of testosterone 3 times. EFE restores sexual activity to the control level, and increases the level of testosterone by 50%.

Thus, we can argue relying upon the conducted experiment that the EFE has a significant androgenic effect.

Upon determination of the content of testosterone in serum of experimental animals we found that the sexual activity of the male rodents treated with EFE is in positive correlation with the level of androgens (Table 1).

Table 1. Adaptogenes effect on testosterone content (nMol/L)

No.	Group	Testosterone content (M + m)
1	2	3
1	Control	11.05 ± 0.71
2	<i>Euphorbia fischeriana Steud.</i> root extract 1ml/kg	17.34 ± 0.58*
3	Ginseng tincture	11.36 ± 0.87
4	Androcur 150 mg/kg	2.38 ± 0.64**
5	Androcur 150 mg/kg + <i>Euphorbia fischeriana Steud.</i> root extract 1 ml/kg	5.85 ± 0.17**
6	Proscar 1 mg/kg	3.89 ± 0.18**
7	Proscar 1 mg/kg + <i>Euphorbia fischeriana Steud.</i> root extract 1 ml/kg	4.19 ± 0.78**
8	Synestrol 40 mg/kg	3.46 ± 0.13**
9	Synestrol 40 mg/kg + <i>Euphorbia fischeriana Steud.</i> root extract 1 ml/kg	5.18 ± 0.13**
Note: * significant differences ($P \leq 0.05$), ** significant differences ($P \leq 0.001$) in relation to control		

We have also investigated the effect of adaptogenes on aphrodiatic activity of old male Wistar rats weighing 250-380 g (n=40). It was found that the course administration of EFE has a strong stimulating effect on sexual behavior of old male rats. Sexual activity of old intact males is low; against a particular sexual interest in females under estrus, as indicated by such factors as sniffing and licking, the copulative component of sexual activity in older males is low: mounts have been observed only in half the animals in group, and no ejaculation registered.

The content of testosterone in old males is 10 times lower than that in mature rats. At course administration of EFE, the cumulative sexual activity of animals increases significantly 2.4 times, against the activation of copulative components dominating in the structure of sexual activity: increase in the number of mounts is 5.7 times, and in the number of ejaculations - 3.8 times.

SUMMARY

1. It was revealed that the *Euphorbia Fischeriana Steud.* root tincture prepared according to a recipe of traditional medicine has no aphrodiatic activity, and even oppresses it, especially a copulative component of sexual behavior of male rats.
2. Ginseng tincture has no aphrodiatic activity and does not affect the level of testosterone in experimental male rats.
3. The *Euphorbia fischeriana Steud.* root extract stimulates sexual activity in male rats, increases the sensitivity of tissue androgen receptor, increases the production of testosterone and has no effect on testosterone 5-alpha-reductase.
4. The *Euphorbia fischeriana Steud.* root extract stimulates sexual activity in old male rats, especially activating its copulative component.

CONCLUSION

As a result of our research we can argue that the *Euphorbia fischeriana Steud.* root extract stimulates aphrodiatic activity, increases the sensitivity of tissue androgen receptor, increases the production of testosterone and has no effect on testosterone 5-alpha-reductase.

Our preliminary studies had proven the stress protective (antihypoxic, antioxidant, anti-inflammatory, and endothelium protective) properties of *Euphorbia fischeriana Steud.*, [18,19,20,21], which certainly plays a complementary role in the implementation mechanisms of animal aphrodiatic activity.

The obtained results are due to a high content of selenium and phytoandrogenes in the *Euphorbia fischeriana Steud.* roots that prevent the decomposition of testosterone and take part in the implementation of the mechanism of tissue androgen receptors activation. Saponins, flavonoids, and ascorbic acid are involved in the implementation of the antioxidant effect of *Euphorbia fischeriana Steud.* *Euphorbia fischeriana Steud.* is undoubtedly a promising plant in terms of creating a drug on its basis for the prevention and treatment of different male genitalia diseases.

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