

Study of co-administration of Siberian fir polyphenols and Panax ginseng in a model of copulatory dysfunction in rats caused by androgen deficiency

Tatiana G. Borovskaya¹, Nikolai I. Suslov¹, Yulia A. Shchemerova¹, Maxim L. Korobov²

*1 Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center; 3 Lenina St., Tomsk 634028 Russia;
2 Prenols LLC; 13 Sovpartshkolny Lane, Office 213, Tomsk 634009 Russia.*

Corresponding author: Yulia A. Shchemerova (repropharm@yandex.ru)

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Abstract

Introduction: Impairment of the erectile component of the copulatory cycle represents a significant clinical and social problem, substantially reducing the quality of life in men. The highest incidence of this pathology is observed in male patients over 50 years of age, which is associated with an age-related decrease in gonadal hormonal function. In the present paper, the results of experimental studies evaluating the efficacy of **co-administration of Siberian fir polyphenols and Panax ginseng** in a model of copulatory function impairment caused by androgen deficiency are demonstrated.

Materials and Methods: The focus of the study was a herbal preparation being a pharmaceutical composition of Siberian fir polyphenols and Panax ginseng. The experiment was conducted in 26 sexually mature category-I male SD rats (Sprague Dawley with body weight of 250-300 g and aged 12 weeks). Siberian fir polyphenols were administered at a dose of 23 mg/kg combined with Panax ginseng at a dose of 1.5 ml/kg. The treatment course duration was 7 days. Tribestan (Sofarma, Bulgaria) at a dose of 70 mg/kg was used as a reference drug. Reduction in copulatory activity caused by androgen deficiency was modeled by administering synestrol to male rats. The level of copulatory activity was assessed by the paired sexual behavior test.

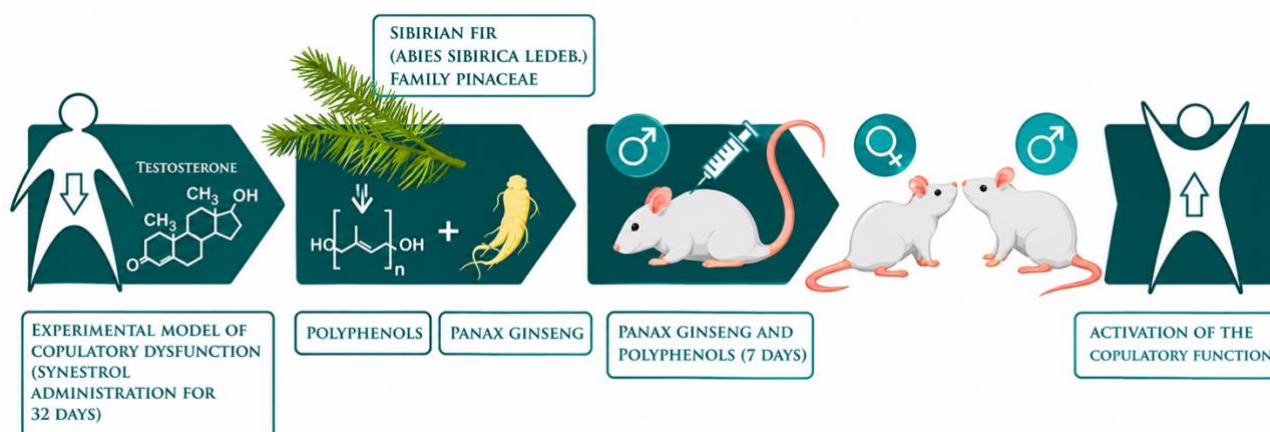
Results and Discussion: The results of experimental studies showed that the administration of synestrol to male rats led to the suppression of their copulatory activity. The groups of animals receiving Siberian fir polyphenols and Panax ginseng against the background of synestrol administration exhibited a statistically significant increase in the number of animals with rising copulatory activity (the number of mating attempts increased, and cases of ejaculation were reported). The pharmacological activity of the reference drug Tribestan was manifested at the level of tendencies.

Conclusion: The present paper demonstrates that Siberian fir polyphenols (dosed at 23 mg/kg) in combination with Panax ginseng tincture (dosed at 1.5 ml/kg) prove effective in stimulating the copulatory activity of male rats under conditions of androgen deficiency.



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Graphical Abstract



Keywords

hypogonadism, polyphenols, *Panax ginseng*, rats, Siberian fir, erectile dysfunction

Introduction

Copulatory dysfunction is a symptom complex encompassing a number of copulatory behavior disorders related to male sexual dysfunction (Sharypova and Sveshnikov 2013). It most commonly manifests itself as an impairment in the ability to achieve and maintain an erection. The latter represents a neurovascular tissue-related process under hormonal control involving dilation of cavernous arteries, relaxation of trabecular smooth muscle, and activation of the vein occlusion mechanism in the corpora cavernosa (Chaly et al. 2017). Impairment of the erectile component of the copulatory cycle is a serious clinical and social problem significantly reducing the quality of life in men. According to the World Health Organization (WHO), one in ten men over 21 years of age has erectile dysfunction (ED). The prevalence of ED has increased by 10% over the decades (Leslie and Sooriyamoorthy 2024). A high incidence (up to 60%) of this pathology is noted in men over 50 years of age, which is associated with an age-related decrease in gonadal hormonal function, namely, androgen deficiency (Wang and Jiang 2024).

Testosterone regulates almost all components of erectile function (Kataoka and Kimura 2017). It performs its central regulation by modulating the dopaminergic system, and peripheral regulation by increasing nitric oxide (NO) synthesis in the corpora cavernosa inhibiting the RhoA/Rho-kinase pathway and increasing the expression of PDE5 (Tikhonov et al. 2024). The role of NO in the physiology of erection is well researched (Traish and Kim 2005; Kataoka and Kimura 2017). It has been shown that NO activates the relaxation of cavernous body smooth muscle leading to increased blood supply and erection. Nowadays, a rather large number of ways and methods for treating erectile dysfunction are available (Argiolas et al. 2023). However, testosterone therapy remains the only pathogenetically justified ED treatment among other options in context of hypogonadism (Schardein and Hotaling 2022). Phosphodiesterase type 5 (PDE5) inhibitors can only enhance the effectiveness of testosterone. At the same time, the use of androgens is accompanied by low compliance. Furthermore, testosterone has contraindications and side effects (Grech et al. 2014). Thus, to date, the risk of blood clot formation, as well as the long-term risks of cardiovascular disease and prostate cancer remain controversial issues that still need to be clarified using evidence-based medicine methods (Schardein and Hotaling 2022).

Currently, an active search for new ED therapies in hypogonadism is underway (Kataoka and Kimura 2017). These may include the agents correcting testosterone deficiency or reproducing its effects necessary for achieving erection. In this context, a considerable effect is demonstrated

by preparations of natural origin (Lin et al. 2021; Xu et al. 2023). Their pharmacological activity can be sufficiently high, and unwanted effects – minimal (Pushkar et al. 2021).

Among herbal remedies capable of reproducing a number of testosterone effects or enhancing its production are polyprenolic compounds isolated from Siberian fir (C30-C110 (n=6-22), *Abies sibirica*, Pine family, fam. Pinaceae), as can be assumed based on the analysis of data available in the literature. Thus, it has been established that Siberian fir polyprenols have the ability to slow down the breakdown of acetylcholine, thereby activating cholinergic signaling pathway. They act as direct donors of acetylcholine neurotransmitter in presynaptic membranes of cholinergic neurons (Suslov et al. 2024). The latter is known to actively participate in achieving erection (Andersson 2011). It has also been shown that an increase in acetylcholine levels leads to increased production of luteinizing hormone (Vastagh et al. 2024), which in turn is known to activate testosterone synthesis by Leydig cells.

On the other hand, *Panax ginseng* is among herbal remedies capable of fulfilling most testosterone effects under conditions of hypogonadism (Lin et al. 2021). A study of its influence on nuclear androgen receptors established that ginsenoside, one of its main components, can increase their expression (Park et al. 2017), thereby enhancing its production.

It should be noted that both *Panax ginseng* and cholinesterase inhibitors can enhance nitric oxide production (Bykov et al. 2022; Xu et al. 2023).

The goal of the paper is to carry out the preclinical efficacy evaluation of co-administration of Siberian fir polyprenols and *Panax ginseng* in an experimental model of copulatory dysfunction in rats caused by androgen deficiency.

Materials and Methods

Research object

Panax ginseng tincture (Ivanovo Pharmaceutical Factory, Russia); Oil solution of Siberian fir (*Abies sibirica*) polyprenols with active substance content of 74% (polyprenols C30-C110 (n=6-22)) (Prenoly LLC, Russia).

Experimental animals

Experiments were conducted in laboratory animals – category-I male SD rats (Sprague Dawley, n=26, age 5 months, body weight – 250-300 g). To study the sexual activity of male rats in the paired sexual behavior test, intact female rats (SD Sprague Dawley, n=78) were used. The animals were obtained from the breeding facility of the Department of Experimental Biomedical Modeling at the Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center (Russia) (Ethical Committee Minutes no. 230052024 dated May 20, 2024).

Animal housing conditions

Animal housing conditions were approved by the Ethical Committee of the Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center (Russia) (Minutes no. 213092023 dated September 08, 2023).

Test substances and doses

Polyprenols dosed at 23 mg/kg; *Panax ginseng* tincture dosed at 1.5 ml/kg; Reference drug Tribestan (Sofarma Bulgaria) dosed at 70 mg/kg; Polyprenols (0.07 ml) were diluted with Polysorbate (TWEEN)-80 solvent to 1 mL. Tribestan was ground, 2% starch paste adhesive was added and the resulting suspension was administered to animals. Test substances were administered once daily for 7 days as agents capable of normalizing reduced copulatory activity in male rats caused by androgen deficiency.

Experimental model and study design

Reduction in copulatory activity caused by androgen deficiency was modeled by administering synestrol to male rats. Synestrol is equivalent to folliculin in its estrogenic activity (action similar to that of female sex hormones, i.e. estrogens): 1 mg of synestrol corresponds to 10,000 IU of folliculin.

The studied male rats were divided into 4 groups, with intact animals in the first one (baseline, n=8), rats receiving synestrol in the second one (control, n=6), animals receiving synestrol, as well as Siberian fir polyprenols and *Panax ginseng*, in the third one (n=6), and animals receiving synestrol and the reference drug Tribestan (n=6) in the fourth one. The level of copulatory activity was determined in the paired sexual behavior test (Agmo and Chu 2008), where each tested male was placed with a female rat in a separate cage.

Male rats were paired with female rats 3 times. The first pairing was done 2 weeks before the start of the experiment to allow the animals to acquire sexual behavior skills. For this, all studied males were paired with intact females for the duration of 2 estrous cycles (10 days). The second pairing for all animals involved in the experiment was carried out before the start of administration of the test substances to determine the initial (individual) copulatory activity of each animal. Then the first testing was conducted. Next, taking into account the data obtained during the first testing, rats receiving synestrol were divided into groups, so that the compared groups of male rats did not differ significantly from each other in sexual activity level. The third pairing of animals was carried out after the administration of the studied herbal preparations, with the second testing of sexual activity level in animals being conducted. For the purpose of the study, each animal was assigned an individual number.

Synestrol (Dalkhimpharm JSC, Russia) was administered to male rats from the control and experimental groups for 25 days, once daily, intramuscularly, in a single dose of 40 mg/kg/day. On the 25th day of the experiment, before the administration of herbal preparations, the paired sexual behavior test was performed (Agmo and Chu 2008). Then, from the 26th to the 32nd day of the experiment (seven days), the animals from the experimental groups, except the control, were intragastrically administered *Panax ginseng* tincture at a dose of 1.5 mL/kg, Siberian fir polyphenols at a dose of 23 mg/kg, (dose in mice 50 mg/kg) and the reference drug Tribestan (Sofarma Bulgaria) at a dose of 70 mg/kg (in group 4, Tribestan was ground, 2% starch paste adhesive was added and the resulting suspension was administered to animals). After the herbal preparation was administered, the second testing was conducted.

Experimental methodology

The copulatory activity in animals was studied in a 15-minute paired sexual behavior test (Agmo and Chu 2008). To study paired sexual behavior (before and after administration of herbal preparations), males were paired with sexually receptive females, the ones in the induced estrus phase. To initiate the estrus phase of the cycle, females received synestrol (0.05 mL/animal) for 4 days before testing. Then, the animals were placed in pairs, individually (each pair in a separate cage). After that, the parameters recorded within the 15 minute interval were as follows: the latency of the first mating attempt (LFMA), representing the period of time from the moment the female is introduced to the male until the first mating attempt. In addition, the number of mating attempts (MA) and the number of ejaculations (NE) were determined. Furthermore, the number (percentage) of male rats exhibiting normalized activity was calculated (within the respective group). Here, the MA value was taken as the main reference and was considered either “significantly” or “insignificantly” affected. A significant increase in copulatory activity was defined as an increase in the MA value by a factor of two or more and the appearance of ejaculation. Testing was performed in the evening in a darkened room, starting at 8:00 pm. The study was conducted in the autumn period (October 1 to November 2, 2024).

Statistical Analysis

Statistical analysis was performed using the Mann-Whitney U test and Fisher’s angular transformation. Differences from baseline (*) and control (#) values were considered significant at $P < 0.05$. Statistical data were processed using the licensed Statistica 13 software. To assess the sexual activity of animals, the results obtained from the same animal during the first and second testing were compared. In addition, comparisons between groups of animals were performed.

Results

The results of assessing the effect of polyphenols co-administered with *Panax ginseng* tincture on the number of mating attempts and ejaculations are presented in Table 1.

Table 1. Number of mating attempts and ejaculations in male rats receiving a combination of polyphenols and *Panax ginseng* tincture ($X \pm m$)

Group	Mating attempts total, (abs.)		Ejaculations total, (abs.)	
	Test 1	Test 2	Test 1	Test 2
Baseline	2.50±0.87	4.00±0.71	0.00±0.00	0.00±0.00
Synestrol (control)	1.67±0.67	1.50±0.50#	0.00±0.00	0.00±0.00
Polyphenols+panax ginseng	2.67±0.88	12.25±4.17*#	0.00±0.00	0.75±0.75
Tribestan	1.67±0.67	7.33±6.33	0.00±0.00	0.00±0.00

Note: * – shows the value comparison in the same animals in tests 1 and 2; # shows the comparison between groups. Differences are significant at $P \leq 0.05$, Mann-Whitney U test.

It was established that the average number of mating attempts based on the results of the 2nd testing in animals from the intact group (baseline) was 4.0 ± 0.71 . In rats receiving synestrol, this indicator was statistically significantly reduced compared to that in intact animals and amounted to 1.50 ± 0.50 ($P \leq 0.05$).

The number of mating attempts in animals receiving polyphenols and *Panax ginseng* under conditions of androgen deficiency statistically significantly increased and amounted to 12.25 ± 4.17 (control – 1.50 ± 0.50 ; $P \leq 0.05$). The respective value in rats receiving synestrol and tribestan also increased (to 7.33 ± 6.33), but the differences compared to the control turned out to be statistically insignificant (control – 1.50 ± 0.50 ; $P \geq 0.05$).

No instances of ejaculation were detected during the first testing in any studied animals. During repeated testing, ejaculations were only observed in rats receiving polyphenols and *Panax ginseng*, while none were reported in the groups of intact, control animals and rats receiving Tribestan.

A comparison of the number of mating attempts in the same animals, obtained based on the results of the first and second testings (Table 1) showed no statistically significant differences in male rats from the intact group. Similar data were obtained in the synestrol only group. Statistically significant differences in the number of mating attempts (within the group based on the results of the first and second testings) were identified in male rats receiving polyphenols and *Panax ginseng*. The MA value increased from 2.67 ± 0.88 to 12.25 ± 4.17 ($P \leq 0.05$). The number of ejaculations was 0.75 ± 0.75 , while not reported during the first testing. When the reference drug Tribestan was administered, an increase in the number of mating attempts was recorded, but the differences were statistically insignificant; ejaculations were reported in neither the first nor the second testing.

The results of assessing the number (percentage) of male rats exhibiting normalized copulatory activity in each of the studied groups are presented in Table 2.

Table 2. Integral assessment of the dynamics of sexual activity indicators in animals of the intact and experimental groups ($\bar{X} \pm m$)

Group	Number of animals confirming the initial activity level, %	Number of animals exhibiting increased activity, %		
		Significant increase	Insignificant increase	Increased activity total
Baseline (intact)	50	25	25	50.0
Control (synestrol)	83.3	0	16.6	16.7*
Synestrol+polyphenols+ <i>Panax ginseng</i>	33.3	50	16.7	66.7#
Synestrol+Tribestan	83.31	16.7	0	16.7

Note: * – at $P \leq 0.05$ compared to intact rats (baseline), Fisher's angular transformation test; # – at $P \leq 0.05$ compared to animals from the control group (synestrol), Fisher's angular transformation test.

Judging by the results of the 1st and 2nd testings of animals in the intact group, 50.0% of them confirmed their initial activity level during repeated testing. The remaining rats (25%) improved the studied indicators to an insignificant degree, and 25% rats significantly increased their activity. In other words, 50% male rats in this group exhibited increased activity (overall). The increase in activity in part of the intact rats during the second testing is obviously associated with the animals acquiring additional sexual behavior experience.

The number of animals in the control group (synestrol, Table 2) that retained the initial level of copulatory activity during repeated testing was 83.3%; 16.7% exhibited an insignificant increase. During repeated testing, none of the animals in this group showed significant increase in their activity. Thus, the total number of rats demonstrating increased activity (overall) was 16.7%. The value was compared with that in the group of intact animals (baseline), and the differences turned out to be statistically significant compared to the control (Table 2). Thus, rats receiving synestrol were characterized by reduced sexual activity.

The number of male rats retaining initial activity in the group of rats receiving polyphenols and *Panax ginseng* against the background of synestrol administration was 33.3%, while 16.0% of animals in this group showed an insignificant increase, and in 50% of male rats a significant increase in activity was observed (Table 2). The number of rats showing increased activity (overall) was 66.7%. Compared to the control (synestrol, 16.6%), the differences were statistically significant (Table 2). In the group of rats receiving the reference drug Tribestan, the majority of animals (83.4%) showed a similar level of sexual activity during the initial and the repeated testing.

The results of assessing the effect of polyphenols and *Panax ginseng* on LFMA are presented in Table 3.

Table 3. Effect of polyphenols and *panax ginseng* on LFMA

Group	LFMA	
	Test 1	Test 2
Baseline	706.40 ± 56.04	535.00 ± 83.80
Synestrol (control)	672.00 ± 139.08	570.75 ± 123.45
Polyphenols+ <i>panax ginseng</i>	650.00 ± 190.73	363.25 ± 124.97
Tribestan	456.00 ± 214.44	575.33 ± 125.35

Note: Statistical processing of the results was done using the Wilcoxon-Mann-Whitney test at $p \leq 0.05$. The indicators compared were as follows: baseline and control; control and experiment 1; control and experiment 2. No statistically significant differences have been observed.

Judging by LFMA, statistically significant differences were neither observed between the animals from different groups nor within groups (tests 1 and 2). However, the average values were reduced in the group of males receiving polyphenols with *Panax ginseng* during repeated testing.

Discussion

The results of the study indicate that rats receiving synestrol were characterized by reduced sexual activity. Literature data indicate that an increase in estrogen concentration in the male body is accompanied by an increase in concentration of sex hormone-binding globulins, which leads to a decrease in concentration of free testosterone, the presence of which determines erection, sexual motivation, and other manifestations of sexual activity (Gladkov 1998). Reduced copulatory activity against the background of synestrol administration is an evidence of androgen deficiency status of animals.

Analysis of the obtained data in terms of the number of mating attempts and the percentage of animals that improved copulatory activity, makes it possible to conclude that the use of polyphenols in combination with *panax ginseng* in male rats with androgen deficiency activates their copulatory activity. The effectiveness of the reference drug was not statistically significantly confirmed in the experiment discussed.

As noted above, the mechanism of the stimulating effect of Siberian fir polyphenols co-administered with *panax ginseng* on the copulatory activity in rats with androgen deficiency may be due to their ability to stimulate LH production (polyphenols) and increase the expression of androgen receptors (*panax ginseng*). It should be noted that the main cause of erectile dysfunction in patients with testosterone deficiency is a decrease in the bioavailability of NO (Maiorino et al. 2015; Kataoka and Kimura 2017), and the combined use of polyphenols and *panax ginseng* may influence this process. The latter assumption may be reinforced by the facts indicating the ability of cholinesterase inhibitors, which include fir polyphenols, and the main active compounds of *panax ginseng*, to enhance nitric oxide synthesis in copulatory disorders (Bykov et al. 2022; Xu et al. 2023). Polyphenols can drive an increase in NO levels by increasing the amount of acetylcholine, which exerts its effect indirectly through increased release of nitric oxide in the penile cavernous bodies via M2-cholinergic receptors on smooth muscle fibers and M3-cholinergic receptors on endothelial cells, as well as nicotinic receptors located on NO-ergic nerve fibers. Furthermore, acetylcholine prevents the vasoconstrictive action of norepinephrine, which contributes to the weakening of erection via muscarinic receptors on adrenergic nerve endings (Bykov et al. 2022). It is known that *panax ginseng* does not show inhibitory activity against PDE5, but it can act directly on the mechanism of erection, i.e. promote relaxation of cavernous bodies by increasing nitric oxide level through the L-arginine/NO pathway. The latter is the known capability of saponins constituting the main component of *panax ginseng* (Xu et al. 2023).

The latency of the first mating attempt is the motivational component of copulatory behavior (Agmo and Chu 2008; Sharypova and Sveshnikov 2013). In rats receiving polyphenols and *Panax ginseng*, the average LFMA values were 36% lower than those in the control (synestrol) and 44% lower than those in the same males during the first testing. However, the differences turned out to be statistically insignificant. It cannot be ruled out that a longer regimen of the studied agent is required to stimulate the motivational component of copulatory behavior.

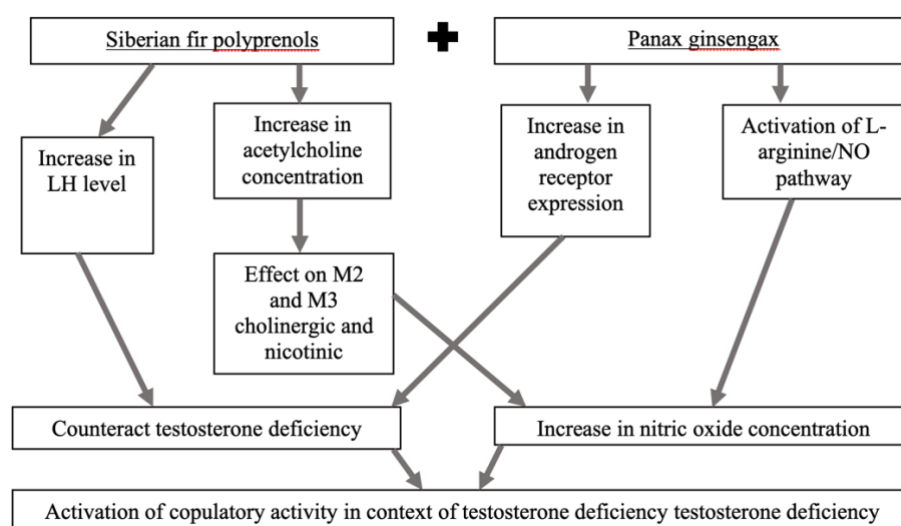


Figure 1. Mechanism of the stimulating effect of Siberian fir polyphenols and panax ginseng on the copulatory activity in rats with androgen deficiency.

Conclusion

The increase in the number of mating attempts, as well as the percentage of animals that improved copulatory activity, indicates that the use of Siberian fir polyphenols (dosed at 23 mg/kg) in combination with Panax ginseng (dosed at 1.5 ml/kg) in male rats with androgen deficiency activates their copulatory activity.

The presented paper demonstrates that Siberian fir polyphenols in combination with Panax ginseng can be used in the therapy of erectile dysfunction associated with hypogonadism.

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Author Contributions

- **Tatyana G. Borovskaya**, Doctor of Biological Sciences, Professor, Head of the Laboratory of Reproductive System Pharmacology, E.D. Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Tomsk, Russia; e-mail: repropharm@yandex.ru; **ORCID ID:** <https://orcid.org/0000-0002-0651-4841>. The author was the principal investigator and played a key role in the design of the study, analysis, and interpretation of the results.
- **Nikolay I. Suslov**, Doctor Habil. of Medical Sciences, Professor, Head of the Laboratory of Phytopharmacology and Special Nutrition, E.D. Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Tomsk, Russia; e-mail: nis-51@mail.ru; **ORCID ID:** <https://orcid.org/0000-0001-9300-5334>. The author contributed to the development of the research concept.
- **Yulia A. Shemerova**, Candidate of Biological Sciences, Researcher at the Laboratory of Reproductive System Pharmacology, E.D. Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Tomsk, Russia; e-mail: julifarm@mail.ru; **ORCID ID:** <https://orcid.org/0000-0002-0895-9000>. The author participated in data collection and statistical processing.
- **Maxim L. Korobov**, Advisor, Prenoly LLC, Tomsk, Russia; **ORCID ID:** <https://orcid.org/0009-0008-6927-7506>. The author contributed to the development of the research concept.