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## THE EFFECT OF MAITAKE MUSHROOMS THICK EXTRACT ON THE SIGNS OF INFLAMMATORY PROCESS UNDER THE CONDITIONS OF TESTOSTERONE-INDUCED BENIGN PROSTATIC HYPERPLASIA IN RATS

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### ІНФОРМАЦІЯ

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maitake extract;  
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### АНОТАЦІЯ

**The aim of the work.** To study the effect of maitake mushrooms dense extract on the development of inflammatory processes in white rats with testosterone-induced benign prostatic hyperplasia.

**Materials and Methods.** The investigation was carried out on male white rats, randomized into 7 groups of 8 animals each. Benign prostatic hyperplasia was modeled by subcutaneous injection of testosterone propionate at a dose of 3 mg/kg body weight of the animal for 21 days. A thick extract of maitake mushrooms was used to correct the damage caused. The extract was given orally each day for a period of three weeks simultaneously with testosterone, with a dosage of 150 mg/kg based on the animal's body weight. "Prostatofit" was chosen as a reference drug, which was administered intragastrically according to the same scheme as the studied extract in a dilution of 1:10 at a dose of 1 ml/100 g of rat body weight. Rats were euthanized using sodium thiopental on the 15th and 22nd days of experiment. The anti-inflammatory effect of dense extract from maitake mushrooms was evaluated by the following biochemical indicators: the number of leukocytes, the erythrocyte sedimentation rate value, the content of C-reactive protein, interleukin-6, tumour necrosis factor- $\alpha$ , testosterone and dihydrotestosterone in the blood serum of animals.

**Results and Discussion.** The effect of maitake mushrooms dense extract on the development of prostate adenoma in white rats induced by subcutaneous injection of testosterone propionate was studied. It was determined through experimentation that the subcutaneous administration of testosterone propionate to rats for 3 weeks in order to simulate benign prostatic hyperplasia results in the initiation of an inflammatory process, which is confirmed by a significant increase in the number of leukocytes, erythrocyte sedimentation rate, the content of C-reactive protein, interleukin-6, tumour necrosis factor- $\alpha$ , testosterone and dihydrotestosterone in blood serum of experimental animals. Administration of 150 mg/kg dosage of maitake mushroom thick extract in parallel with testosterone showed a reliable positive effect on the investigated biochemical indicators in all terms of the experiment.

**Conclusions.** The results acquired affirm the anti-inflammatory properties of the concentrated extract obtained from maitake mushrooms. This supports the idea of exploring its potential as a protector for the prostate and considering its integration into a comprehensive treatment plan for benign prostatic hyperplasia.

**Introduction.** Benign prostatic hyperplasia is a urological disease caused by the benign enlargement of the prostate with age in men. Inflammation, oxidative stress, proliferative and apoptotic changes play an important role in the development of this pathology. Timely diagnosis of prostate adenoma (PA) gives the patient a chance to do without surgical intervention. Removal of prostate gland (PG) is recommended only in case of severe symptoms. In other cases, urologists recommend complex therapy, which includes medications, special biologically active supplements, traditional medicine and mandatory preventive measures [1, 2].

For the treatment of prostate adenoma, drugs from the group of  $\alpha$ 1-adrenoblockers and  $5\alpha$ -reductase inhibitors are currently most often prescribed. They alleviate the symptoms of the ailment and enhances patients' conditions by decreasing the production of dihydrotestosterone (DHT). However, the use of these drugs is limited due to their side effects, including decreased libido, erectile dysfunction, tachycardia, edema of the lower limbs, etc. Considering this, the search for drugs that effectively suppress the development of benign prostatic hyperplasia (BPH) and do not cause negative effects characteristic of synthetic agents has a high priority in biomedical research [3, 4].

Phytotherapy for the treatment of BPH is becoming increasingly popular worldwide. In the treatment of prostate adenoma, herbal preparations obtained from various plants are used, such as American dwarf palm, *Sophora japonica*, African plum, plant pollen, prickly pear, nettle root, Chromolena, pumpkin seed oil and green tea. Although herbal preparations are very popular in the world due to the minimal number of adverse reactions, their role in the medical therapy of prostate hyperplasia has not yet been fully determined. According to the recommendations of the World Health Organization regarding the therapy of prostate hyperplasia, further studies of herbal preparations are necessary to study their pathogenetic mechanism of action, to evaluate their effectiveness and to determine their place among many medicinal products [5, 6, 7].

That is why we chose maitake mushrooms for our research. They are natural raw materials, practically non-toxic and could potentially be used as prostate protectors in the complex treatment of prostate adenoma, as well as for the prevention of this disease [8, 9].

Scientific works of previous years have proven that maitake mushrooms exhibit various pharmacological activities, such as antitumor, hypoglycemic, antioxidant, prostate protective and immunoregulatory. Most scientific studies indicate that the key ingredient in mushrooms that has proven to be effective is a protein-related polysaccharide or proteoglycan. Especially, its D-fraction shows a significant antitumor effect [10, 11].

**The aim** – to determine the effect of maitake mushrooms dense extract on the development of inflammatory processes in rats with testosterone-induced prostate hyperplasia.

**Materials and Methods.** The experimental work was carried out using 56 white male rats with weights ranging from 200 to 250 grams. The animals were kept on a regular diet at the vivarium of I. Horbachevsky Ternopil National Medical University. All procedures adhered to the standards of good laboratory practice (GLP) and followed the principles of bioethics outlined in the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes." [12], the principles of the Directive of the European Parliament and the Council of the European Union dated September 22, 2010 "On the protection of animals used for scientific purposes" [13]. The conducted studies were approved by the Ethics Commission of I. Horbachevsky Ternopil National Medical University.

The object of the research was a maitake mushrooms thick extract (MMTE), which was produced for scientific research by the Department of Chemistry of Natural Compounds of the National University of Pharmacy and standardized by steroid compounds in accordance with the requirements of the of the State Pharmacopoeia of Ukraine.

Simulated BPH was reproduced by subcutaneous injection of testosterone propionate solution at a dose of 3 mg/kg for 21 days in male rats. The administration of MMTE was done through intragastric means to animals on a daily basis at a dosage of 150 mg per kilogram of rat body weight simultaneously with subcutaneous administration of testosterone propionate for 3 weeks. A dose of 150 mg/kg of animal body weight for MMTE was established by previous studies as conditionally therapeutic [14, 15]. "Prostatofit" was selected as the reference medication, and it was administered intragastrically in a dilution of 1:10 at a dose of 1 ml/100 g of the animal's body weight for 21 days. The comparison drug was selected according to the patented method [16]. According to the instruction 1 ml of the drug "Prostatofit" contains a tincture made from a mixture of medicinal plant raw materials (nettle roots (*Urticae radix*) 40 mg, yarrow roots (*Calami radix*) 20 mg, birch buds (*Betulae gemmae*) 20 mg, burdock grass (*Meliloti herba*) 20 mg, dog's nettle herbs (*Leonuri cardiaca herba*) 20 mg, chamomile flowers (*Matricariae flos*) 20 mg, Japanese sophora (*Sophorae japonicae fructus*) 20 mg, celandine herb (*Chelidonii herba*) 20 mg, sage medicinal leaves (*Salviae officinalis folium*) 20 mg)) (1:5) (extractant – ethanol 70 %).

White rats were randomly divided into seven groups, 8 animals in each: 1 – rats that were given the appropriate amount of purified water daily (for 3 weeks), control (C); 2 and 3 – animals injected subcutaneously with testosterone propionate solution, control pathology (CP), 15 and 22 day of the study; 4 and 5 – rats that were given intragastrically with a thick extract of maitake mushrooms simultaneously with subcutaneous injection of testosterone propionate, on days 15 and 22 day of the experiment; 6 and 7 - animals that were given intragas-

trically with "Prostatofit" simultaneously with subcutaneous injection of testosterone propionate, 15 and 22 day of the study.

Rats were euthanized using sodium thiopental on the 15th and 22nd day from the beginning of the experiment. Animals' blood serum was subjected to research.

The prostate protective effect of MMTE was evaluated dynamically according to the following indicators: the number of leukocytes, the erythrocyte sedimentation rate (ESR), the content of C-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), testosterone and of dihydrotestosterone in blood serum of white rats [17].

The concentration of interleukin 6 in the blood serum of rats was determined by the immunoenzymatic method using a commercial kit (GE Health care: Amersham, Great Britain) according to the manufacturer's method. The quantitative level of tumor necrosis factor (TNF) in blood serum was determined by competitive ELISA in vitro using the Rat Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) ELISA Kit MBS (USA) according to the method described in the technical documentation. The level of hormones in blood serum was determined by the enzyme-linked immunosorbent assay method using standard commercial enzyme-linked immunosorbent assay kits for the determination of testosterone (Testosterone-IFA test system manufactured by NVL "Granum") and dihydrotestosterone (Dihydrotestosterone IFA test kit, DRG ELISA, Finland). The content of C-reactive protein (CRP) was determined by the immunoturbidimetric method [14].

Data analysis was performed using TIBCO Statistica® 13.6.0 (2020) software. Both parametric and non-parametric methods were used for statistical processing of the obtained results. For each indicator, the arithmetic mean of the sample (M) and the error of the arithmetic mean (m) were calculated. The significance of the difference between independent quantitative values was determined using the Mann-Whitney test. The difference between values was considered statistically significant at  $p < 0.05$  [18].

**Results and Discussion.** BPH is a condition caused by prostatic epithelial and stromal cell overgrowth resulting from an imbalance between prostate cell proliferation and apoptosis [19, 20]. In the research, we studied the anti-inflammatory and prostate-protective effect of MMTE under conditions of simulated BPH, which was induced by subcutaneous administration of testosterone propionate for 21 days. The initiation of the inflammatory process in the bodies of rats under the influence of testosterone propionate is indicated through a substantial elevation in leukocyte count and ESR, which is consistent with the results of the prostate-protective effect study of other authors [2, 3, 20].

Conducted studies confirm development of testosterone-induced hyperplasia of the PG characterized by general inflammatory reactions, which were accompanied by leukocytosis and an increase in ESR in both terms of the study (Table 1). Thus, by the end of the experiment, a significant increase in the number of leukocytes and ESR was observed in the blood serum of the control pathology group of animals by 1.7 and 3.9 times compared to the control.

A significant decrease in the number of leukocytes and the ESR indicator was observed by 1.2 and 1.7 times, respectively, in the group of animals that on the background of pathology received MMTE at a dose of 150 mg/kg based on the animal's body weight on the 15th day of the experiment, relative to CP. It confirms the inhibition of the systemic inflammatory process. A significant decrease in the level of ESR and leukocytosis was also noted on the 22nd day of MMTE use, these indicators were close to those of the control group (Table 1). Similar dynamics were noted in the group of rats receiving the reference drug.

The main risk factor for the development of BPH is an imbalance of sex hormones. Testosterone and dihydrotestosterone (DHT) are related steroid hormones. DTS is formed from testosterone under the action of the enzyme 5 $\alpha$ -reductase and controls the process of cell division in the PG tissue. In this regard, an increase in the

**Table 1**

The effect of maitake mushroom extract on the content of leukocytes and ESR in the blood serum of rats with simulated BPH (M $\pm$ m; n=56)

Group of animals	Index			
	Leukocytes, 10 <sup>9/l</sup>		ESR, mm/hour	
	15 <sup>th</sup> day	22 <sup>th</sup> day	15 <sup>th</sup> day	22 <sup>th</sup> day
C	9,65 $\pm$ 0,43	9,65 $\pm$ 0,43	2,09 $\pm$ 0,07	2,09 $\pm$ 0,07
CP	13,58 $\pm$ 0,55*	16,02 $\pm$ 0,42*	5,11 $\pm$ 0,12*	8,09 $\pm$ 0,26*
CP+MMTE	11,14 $\pm$ 0,39**	11,24 $\pm$ 0,28**	2,93 $\pm$ 0,10**	3,28 $\pm$ 0,23**
CP+"Prostatofit"	10,35 $\pm$ 0,27**	10,97 $\pm$ 0,22**	2,66 $\pm$ 0,11**	2,95 $\pm$ 0,15**

Notes: \* – probable changes between the indicator of control animals and animals under the influence of testosterone; \*\* – probable changes between the indicator of testosterone-affected and treated animals;  $p < 0,05$

concentration of DHT leads to the growth of PG [2, 19]. An increase in the DHT content in the blood serum of animals throughout the experiment in the group of animals with simulated BPH indicates an increase in the functional activity of PG cells and, as a result, the development of PG hyperplasia.

The level of testosterone increased by 2.1 and 2.7 times in the blood of experimental animals with simulated BPH on the 15th and 22nd days of the study compared to the control. Accordingly, the level of DHT increased by 1.5 and 1.9 times compared to animals of the control group (Table 2).

Intragastric administration of maitake mushroom extract in parallel with testosterone propionate caused a significant decrease in the level of the studied hormones in the blood serum of rats. Thus, the testosterone content decreased by 2.0, and DHT by 1.6 times relative to CP on the 22nd day of the experiment. The comparison drug also showed a positive effect on testosterone and dihydrotestosterone levels in animals with induced BPH.

C-reactive protein is a protein associated with the acute phase of the inflammatory response, one of the important markers for assessing the complexity of in-

flammation [21]. The level of CRP in the blood increases in response to an inflammatory reaction in the body. A long-term elevation in the blood concentration of CRP indicates inflammation in the walls of blood vessels, which can lead to atherosclerosis and diseases of the cardiovascular system.

The subcutaneous injection of testosterone propionate over 21 days resulted in a notable elevation of CRP levels in the blood serum of white rats. An increase in the level of C-reactive protein (CRP) with high sensitivity indicates formation of the acute stage of inflammatory process occurring in the body. As can be seen from Table 3, the level of CRP in animals with simulated BPH significantly increases in both terms of the study by 58% and 126%, respectively, compared to the control (Table 3).

Introduction of MMTE under the conditions of testosterone-induced hyperplasia of the PG induced a notable reduction in the CRP level by 1.3 and 1.7 times on the 15th and 22nd day of the experiment, respectively, in relation to CP. The CRP level decreased by 1.4 and 2.0 times on the 15th and 22nd day of the study, respectively, in the affected animals under the influence of the comparison drug.

**Table 2**

The effect of maitake mushroom extract on the content of testosterone and dihydrotestosterone in the blood serum of rats with simulated BPH ( $M \pm m$ ;  $n=56$ )

Group of animals	Index			
	Testosterone, nmol/l		Dihydrotestosterone, nmol/l	
	15 <sup>th</sup> day	22 <sup>th</sup> day	15 <sup>th</sup> day	22 <sup>th</sup> day
C	8,84±0,25	8,84±0,25	147,92±1,84	147,92±1,84
CP	18,79±0,44*	23,80±0,88*	216,32±4,61*	284,96±4,78*
CP+MMTE	10,35±0,60**	12,18±0,28**	159,45±3,85**	176,06±4,12**
CP+"Prostatofit"	9,34±0,32**	11,65±0,55**	154,38±2,58**	169,57±2,50**

Notes: \* – probable changes between the indicator of control animals and animals under the influence of testosterone; \*\* – probable changes between the indicator of testosterone-affected and treated animals;  $p < 0,05$ .

**Table 3**

The effect of maitake mushroom extract on the content of CRP, IL-6 та TNF- in the blood serum of rats with simulated BPH ( $M \pm m$ ;  $n=56$ )

Group of animals	Index					
	CRP, mg/l		IL-6, pg/ml		TNF- $\alpha$ , ng/ml	
	15 <sup>th</sup> day	22 <sup>th</sup> day	15 <sup>th</sup> day	22 <sup>th</sup> day	15 <sup>th</sup> day	22 <sup>th</sup> day
C	3,30±0,13	3,30±0,13	3,06±0,17	3,06±0,17	1,21±0,05	1,21±0,05
CP	5,23±0,18*	7,46±0,51*	5,10±0,43*	7,45±0,40*	3,07±0,17*	5,81±0,40*
CP+MMTE	3,92±0,17**	4,39±0,18**	3,85±0,36**	4,70±0,37**	1,98±0,22**	3,28±0,40**
CP+"Prostatofit"	3,65±0,14**	3,73±0,26**	3,23±0,22**	4,16±0,23**	1,75±0,13**	2,52±0,33**

Notes: \* – probable changes between the indicator of control animals and animals under the influence of testosterone; \*\* – probable changes between the indicator of testosterone-affected and treated animals;  $p < 0,05$ .

A significant increase in serum levels of other markers of the inflammatory process – IL-6 and TNF- $\alpha$  – was also noted. The synthesis and release of cytokines in the body is always short-term and strictly controlled, because the consistency of the work of the immune, nervous and endocrine systems depends on them [20]. Interleukin-6 helps the body cope with the consequences of severe inflammatory processes, injuries and infectious diseases. Once the cause is removed, IL-6 production stops. If this does not happen, then the constant release of IL-6 can lead to damage to body tissues due to the development of autoimmune processes [21 22]. IL-6 is a representative of the cytokines class that regulate intercellular and intersystem interaction in the body. Cytokines need to reach minimum concentrations in the blood to manifest biological activity [21]. The content of IL-6 increased significantly in the blood serum of animals with simulated hyperplasia of the PG in both terms of the study. By the end of the experiment, it exceeded that of the control group by 2.4 times (Table 3). The obtained findings from the research confirm a significant reduction in the pro-inflammatory cytokine content under the influence of MMTE and the comparison drug by 1.3 and 1.6 times on the 15th day of the experiment relative to the affected rats. By the end of the study, IL-6 content decreased by 1.6 and 1.8 times under the corrective influence of maitake mushrooms and comparison drug, respectively, compared to the CP group.

The content of TNF- $\alpha$  correlates with the activity of inflammatory processes. It was observed a significant increase in the content of the studied indicator in the blood serum of animals with simulated PG pathology, which confirms the important role of TNF- $\alpha$  in the pathogenesis of BPH [22]. A significant increase in the serum level of TNF- $\alpha$  was observed by 2.5 and 4.8 times on the 15th and 22nd days of the study in animals with testosterone-induced hyperplasia of the PG, compared to the control group (Table 3). This indicates the development of inflammatory processes in animals with simulated BPH.

It has been experimentally proven that the intragastric administration of MMTE effectively prevents the progression of BPH caused by the administration of testosterone propionate. The content of TNF- $\alpha$  decreased in dynamics with the use of MMTE and the reference drug for 3 weeks. On the 22nd day of the experiment, the content of TNF- $\alpha$  decreased by 44 % and 57 % in the blood serum of animals with hyperplasia of the PG under the influence of maitake mushrooms dense extract and Prostatophyte, respectively, compared to the affected animals.

**Conclusions.** 1. The experimental findings validate that in animals with simulated hyperplasia of the prostate gland, induced through subcutaneous injection of a testosterone propionate solution, there is an advancement of inflammatory processes. This is evidenced by an increase in the number of leukocytes, erythrocyte sedimentation rate, and the levels of C-reactive protein, interleukin-6, tumor necrosis factor- $\alpha$ , testosterone, and dihydrotestosterone in the blood serum of rats with the induced pathology.

2. Following the administration of a thick maitake mushroom extract as a protective agent for the prostate, a notable reduction in the activity of inflammatory processes was observed in the bodies of animals undergoing experimental prostate gland hyperplasia. This is substantiated by a decline in the levels of leukocytes, erythrocyte sedimentation rate, C-reactive protein, pro-inflammatory interleukin-6, tumor necrosis factor- $\alpha$ , testosterone, and dihydrotestosterone in the blood serum of rats with testosterone-induced prostate hyperplasia.

3. The obtained results confirm the anti-inflammatory effect of the thick extract from maitake mushrooms and make it possible to propose its further study as a prostate protector and its inclusion in the complex therapy of benign prostatic hyperplasia with the aim of suppressing inflammatory processes and easing the course of the disease.

**Conflicts of interest:** authors have no conflict of interest to declare.

**Конфлікт інтересів:** відсутній.

## **ВПЛИВ ГУСТОГО ЕКСТРАКТУ З ГРИБІВ МАЙТАКЕ НА ОЗНАКИ ЗАПАЛЬНОГО ПРОЦЕСУ ЗА УМОВ ТЕСТОСТЕРОН-ІНДУКОВАНОЇ ДОБРОЯКІСНОЇ ГІПЕРПЛАЗІЇ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ У ЩУРІВ**

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**Мета роботи.** Дослідження впливу густого екстракту з грибів майтаке на розвиток запальних процесів у білих щурів із доброякісною гіперплазією передміхурової залози, індукованою тестостероном.

**Матеріали і методи.** Дослідження проведено на білих щурах-самцях, Доброякісну гіперплазію передміхурової залози моделювали шляхом підшкірного введення тестостерону пропіонату в дозі 3 мг/кг маси тіла тварини протягом 21 дня. Густий екстракт грибів майтаке використовувався для усунення викликаних порушень. Екстракт

застосовували перорально щодня протягом трьох тижнів одночасно з тестостероном в дозі 150 мг/кг маси тіла тварини. Як референс-препарат було обрано «Простатофіт», який вводили інтрагастрально за тією ж схемою, що і досліджуваний екстракт, в розведенні 1:10 у дозі 1 мл/100 г маси тіла щура. На 15 та 22 доби експерименту здійснювали евтаназію щурів із використанням тіопенталу натрію. Протизапальну дію густого екстракту з грибів майтаке оцінювали за такими біохімічними показниками: кількістю лейкоцитів, величиною швидкості осідання еритроцитів, вмістом С-реактивного протеїну, інтерлейкіну-6, фактора некрозу пухлин- $\alpha$ , тестостерону та дигідротестостерону в сироватці крові тварин.

**Результати й обговорення.** Встановлено експериментально, що підшкірне введення щурам тестостерону пропіонату протягом 3 тижнів з метою моделювання доброякісної гіперплазії передміхурової залози призводить до розвитку запального процесу, що підтверджується достовірним збільшенням кількості лейкоцитів, швидкості осідання еритроцитів, вмісту С-реактивного протеїну, інтерлейкіну-6, фактора некрозу пухлин- $\alpha$ , тестостерону та дигідротестостерону в сироватці крові піддослідних тварин. Застосування густого екстракту майтаке в дозі 150 мг/кг тіла тварини паралельно з тестостероном мало достовірний позитивний вплив на досліджувані біохімічні показники в усі терміни експерименту.

**Висновки.** Отримані результати підтверджують протизапальні властивості густого екстракту, отриманого з грибів майтаке. Це підтверджує ідею вивчення його потенціалу як простатопротектора та розгляду його інтеграції в комплексний план лікування доброякісної гіперплазії передміхурової залози.

**Ключові слова:** гриби майтаке; гіперплазія простати; простатопротекторна дія; протизапальна дія.

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