ISSN 2518-1432 (Online); ISSN 2227-4782 (Print) https://doi.org/10.21856/j-PEP.2024.3.05

ЕКСПЕРИМЕНТАЛЬНІ ДОСЛІДЖЕННЯ

THE IMPACT OF HOP EXTRACT ACTIVE COMPONENTS ON METABOLIC DISTURBANCES IN ESTROGEN DEFICIENT FEMALE RATS WITH PREDIABETES*

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In recent years, the global burden of metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) has led to a dramatic increase in disability and mortality of worldwide population due to cardiovascular diseases (CVD) [1, 2].

A number of studies have shown that negative differences in cardiovascular risk factors between individuals with T2DM and normal glucose metabolism are more pronounced in women than in men. Consequently, women with T2DM face up to 50 % higher risk of CVD than men [3]. In particular, diabetes confers a 44 % greater excess risk of coronary heart disease and a 27 % greater excess risk of stroke in women compared to men [4].

A significant increase in cardiometabolic risk may be due to more excessive manifestation in women of such MS components as impaired glucose tolerance, insulin resistance, obesity, hypertension, atherogenic dyslipidemia, endothelial dysfunction, proinflammatory and prothrombotic states during the prediabetes stage [5].

Estrogen deficiency, which occurs in women after menopause, is considered to be an additional independent risk factor for cardiovascular pathology. In this regard, the use of hormone replacement therapy (HRT) was pathogenetically rational. However, prospective studies carried out in postmenopausal women confirmed a reduction in insulin resistance and the risk of T2DM, but did not establish an inhibitory effect of exogenous estrogens on the progression of CVD. Instead, the side effects were revealed: increased incidence of stroke,

* The study was carried out within the framework of the state budget theme for SI «V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine»: «The determination of sex differences in cardiometabolic risk and rationale of the effectiveness of new agents for its pharmacological correction in prediabetes» (state registration No 0121U111554).

The institution that finances the study is the National Academy of Medical Sciences of Ukraine.

The authors assume responsibility for the published work.

The authors guarantee absence of competing interests and their own financial interest when carrying out the research and writing the article.

The manuscript was received by the editorial staff 07.06.2024.

venous thromboembolism, gallbladder disease, breast and ovarian cancer [6, 7].

An alternative method for prevention of CVD in women with prediabetes after menopause can be the use of compounds of plant origin capable to show estrogen-like effects (phytoestrogens) without risk of developing the negative side effects specific to HRT.

In recent years, much attention has been paid to the studying of pharmacological properties of prenyl flavonoids contained in hops (Humulus Lupulus), among which the greatest estrogenic potential is inherent to 8-prenylnaringenin (8-PN). The results of experimental and clinical studies confirmed the possibility of both hop extract and 8-PN to reduce the menopausal symptoms, in particular osteoporosis, vasomotor and sexual disorders [8].

In addition, it was shown that hop extract components xanthohumol and isoxanthohumol also have a wide range of biological activity, exhibiting antioxidant, antitumor and anti-inflammatory effects, and may regulate energy metabolism, reducing the risk of developing dyslipidemia and obesity [9, 10].

Considering all the above, the **aim** of our study was to evaluate the effect of hop extract on metabolic disturbances in female rats with prediabetes under estrogen deficiency.

MATERIALS AND METHODS

The study was approved by the bioethics committee of the SI «V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine» (Kharkiv, Ukraine) and performed in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

The experiment was carried out on 30 female Wistar rats (12-week-old, 150–200 g body weight, b.w.), which were housed in Plexiglas cages (three animals per cage) at a temperature of 22 ± 1°C in a constant 12-hour light/dark cycle.

The animal model of MS induced by a high calorie diet in hypoestrogenic rats was used [11].

Estrogen deficiency was performed in animals by a bilateral ovariectomy under brief ether anesthesia [12].

Control intact rats (n = 6) were fed a standard diet for eight weeks. Experimental ovariectomized rats (n = 24) were fed the high calorie diet containing 15% lard, 25% sucrose, 1% bile salts and 59% standard feed for eight weeks. The animals had free access to water.

Four weeks after the beginning of dietary feeding, experimental rats were divided into four groups: untreated insulin resistant rats (MS + solvent, n = 6), insulin resistant rats treated with hop extract in a dose of 20 μg/kg b.w. (MS + hop extract, 20 μg, n = 6) or 200 μg/kg b.w. (MS + hop extract, 200 μg, n = 6) in recalculation on 8-prenylnaringenin, and insulin resistant rats treated with drug «Progynova» (Delpharm Lille S.A.S., France) in a dose of 200 μg/kg b.w. (MS + estradiol, 200 μg, n = 6) in recalculation on estradiol. Animals received substances in the form of aqueous suspension once per day intragastrically by gavage beginning from the fifth week after MS induction. Untreated rats received solvent (distilled water) along the same scheme.

The animals were sacrificed according to the protocol of the ethics committee.

Glucose homeostasis was assessed by indexes of basal glucose, intraperitoneal glucose tolerance test (IPGTT, 3 g/kg b.w.) and intraperitoneal insulin tolerance test (IPITT, insulin 0.5 U/kg b.w., followed by i.p. glucose 2 g/kg b.w. 10 min after) [13]. Subsequently, tail blood glucose levels were measured using a glucose analyzer Eksan-G (Analita Firm Joint Stock Company Ltd., Vilnius, Republic of Lithuania).

The mass of heart, visceral fat and uterus as *integral indicators* was determined.

Lipid metabolism was characterized by concentrations of total lipids, triglycerides (TG) and total cholesterol (TC), determined by diagnostic kits Filicit (LLC NPP «Filicit-Diagnostics», Ukraine) and Cormay (PZ Cormay S.A., Poland), and by level of free fatty acids (FFA) [14] in serum.

Intensity of free radical oxidation was estimated spectrophotometrically by level of conjugated dienes [15], catalase activity [16] and total antioxidant activity [17] in blood serum.

Nitric oxide (NO)-dependent vasodilation system was assessed by serum concentration

of nitrites and nitrates (NOx) [19] and by the activity of NO-synthase (NOS) in heart homogenate [18] of experimental animals.

All *spectrophotometry* was performed using double-beam UV-VIS spectrophotometer Shimadzu UV-1800 (Shimadzu Corporation, Kyoto, Japan).

Statistical analysis. Data are presented as mean ($\bar{X}$) ± standard error of mean ($S_{\bar{X}}$). The Shapiro-Wilk test was used to test normality of data distribution. For multiple comparisons of data with a normal distribution, a parametric one-way analysis of variance (ANOVA) was performed and the Student–Newman–Keuls method was used to test difference in means [20]. Values were considered statistically significant at $p < 0.05$.

RESULTS AND THEIR DISCUSSION

As a result of our study, feeding of ovariectomized rats with HCD for eight weeks led to the development of glucose intolerance, as evidenced by increase in the area under glycemic curves obtained during IPGTT compared to intact animals (Table 1). The results of the IPITT also confirmed a decrease in the sensitivity of peripheral tissues to the hormone in rats with MS under estrogen deficiency (see Table 1).

Administration of hop extract in a dose of 200 μg/kg (in terms of 8-prenylnaringenin), similar to the reference substance estradiol led to improvement in glucose tolerance and a decrease in insulin resistance compared to the group receiving solvent. At the same time, the indexes in these groups did not reach the levels of intact rats (see Table 1).

In support of estrogen deficiency state in experimental animals an almost tenfold decrease in the relative mass of uterus after bilateral ovariectomy was determined (Table 2). Use of estradiol resulted in significant restoration of uterus, while hop extract in a dose of 20 and 200 μg/kg b.w. had no effect on the mass of this organ, indicating the absence of test substance stimulating effect on proliferative processes in endometrium.

One of the main components of MS is obesity, which is closely associated with insulin resistance and dyslipidemia. According to modern concepts, obesity induced by HCD is a result of hyperphagia in experimental animals. The latter is associated with the progression of central resistance to the anorexigenic action of insulin and a decrease in the expression of hypothalamus anorexigenic peptides [21]. In addition, estrogen receptors are found in various regions of hypothalamus, as estrogens are involved in the central regulation of metabolism, mainly through eating behavior (anorexigenic effect), and estrogen deficiency can also lead to hyperphagia [22].

We found that combination of hypoestrogenia with MS resulted in twofold increase in

Table 1

Indexes of glucose homeostasis in control and hypoestrogenic rats with metabolic syndrome, ($\bar{X} \pm S_{\bar{X}}$), n = 6

Group	Basal glucose, mmol/L	IPGTT, AUC, mmol/L*min	IPITT, AUC, mmol/L*min
Control	4.85 ± 0.11	646.90 ± 19.42	490.34 ± 28.06
MS + solvent	5.56 ± 0.11[1)]	981.56 ± 55.94[1)]	665.95 ± 42.87[1)]
MS + hop extract, 20 μg	5.39 ± 0.17[1)]	989.10 ± 86.81[1)]	707.68 ± 60.95[1)]
MS + hop extract, 200 μg	5.26 ± 0.15[1)]	815.23 ± 25.68[1)2)]	586.15 ± 16.47[1)2)]
MS + estradiol, 200 μg	5.48 ± 0.08[1)]	836.78 ± 21.85[1)2)]	572.89 ± 14.36[1)2)]

Notes:
AUC — area under curve;
IPGTT — intraperitoneal glucose tolerance test;
IPITT — intraperitoneal insulin tolerance test;
MS — metabolic syndrome;
[1)] $p < 0.05$ vs Control group;
[2)] $p < 0.05$ vs group «MS + solvent».

Table 2

Integral indexes in hypoestrogenic rats with metabolic syndrome, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Group	Body weight gain, %	Relative mass of visceral fat, mg/g b.w.	Relative mass of uterus, mg/g b.w.
Control	49.08 ± 5.84	31.52 ± 2.44	2.07 ± 0.27
MS + solvent	93.78 ± 9.83[1)]	78.22 ± 3.97[1)]	0.22 ± 0.02[1)]
MS + hop extract, 20 μg	91.87 ± 14.86[1)]	72.62 ± 2.83[1)]	0.20 ± 0.02[1)]
MS + hop extract, 200 μg	58.38 ± 8.37[1)2)]	49.87 ± 6.47[1)2)]	0.22 ± 0.03[1)]
MS + estradiol, 200 μg	63.72 ± 8.21[1)2)]	45.99 ± 4.48[1)2)]	0.70 ± 0.05[1)2)]

Notes:
MS — metabolic syndrome;
[1)] $p < 0.05$ vs Control group;
[2)] $p < 0.05$ vs group «MS + solvent».

body weight gain compared to intact animals (see Table 2). In the same group, there was also a significant increase in the relative mass of visceral fat (see Table 2), which allow us to consider the body weight growth as a consequence of the development of central obesity.

Administration of hop extract only in the dose of 200 μg/kg, similar to estradiol, was accompanied by a significant decrease in body weight gain and visceral fat. The latter is consistent with the results of other studies that have demonstrated the positive effect of hop extract as a drug preventing the development of obesity in various experimental models *in vivo* [23–25].

The above-described effect of hop extract may be based on a complex of molecular mechanisms, associated with the estrogen-like activity of its components. It is now known that estrogens play an important role in the regulating of amount, distribution and metabolic activity of adipose tissue [26].

It is also of interest to consider the possible mechanisms of the influence of hop components on adipose tissue, which are not directly related to their estrogen-like activity. A number of *in vitro* studies have shown that xanthohumol, a component of hop extract with very low affinity to estrogen receptors, inhibited differentiation, prevented lipid accumulation and increased apoptosis in adipocytes [27, 28].

In addition, the hop active components can affect adipose tissue indirectly, acting on other organs and tissues. For example, administration of dietary purified xanthohumol from hop pomace to obese, insulin-resistant KKAy mice was shown to reduce the activity of pancreatic lipase and, as a consequence, to decrease the absorption of fats in small intestine [24].

One of the possible mechanisms of the impact of hop components on the development of obesity was well described in the work of Kirkwood J. S. et al., who showed that xanthohumol causes a modest increase in ROS and uncouples the oxidative phosphorylation in muscle mitochondria. The latter leads to an increase in the oxidative capacity of mitochondria, in particular to fatty acids, and thereby prevents the accumulation of neutral lipids in adipose tissue [9].

Dyslipidemia is an important component of MS and an independent risk factor for cardiovascular pathology. It is known that hypertriglyceridemia is often observed in postmenopausal women probably due to estrogen deficiency, which promotes the activation of TG synthesis in liver and the development of obesity. In addition, hypoestrogenia is accompanied by increase in TC concentration and change in the lipoprotein profile towards an increase in pro-atherogenic low-density lipoproteins [29].

In our study we revealed that animals with MS under estrogen deficiency had an increase in the concentration of total lipids in serum mainly due to increase in the level of TG and TC (Table 3). The concentration of FFA did not differ in all experimental groups.

In animals receiving hop extract in the highest dose, as well as estradiol, normalization of the content of total lipids in serum was

observed. Noteworthy is the fact, that hop extract resulted in decrease of hypertriglyceridemia, but did not affect the level of TC, while estradiol, on the contrary, reduced the concentration of TC, and had no effect on the level of TG (see Table 3).

The obtained data allow to conclude that hop extract and estradiol act on different regulatory and metabolic pathways of lipid metabolism. It was previously shown that administration of hop extract to male rats kept on a high-fat diet leads to a decrease in the expression of the transcription factor SREBP-1c, which is one of the main regulators of acylglycerol synthesis in the liver [23]. These animals also showed a decrease in the activity of the key enzyme of fatty acid synthesis *de novo* — fatty acid synthase, and, as a result, a decrease in the concentration of TG in blood. In addition, it was found that xanthohumol directly inhibits the activity of diacylglycerol acyltransferase, an enzyme that catalyzes the final stage of TG synthesis in liver [9].

Despite the fact that the hypocholesterolemic effect of estrogens has been known for a long time, the molecular mechanisms of this effect are not fully understood. It was shown that estrogens reduce the synthesis and nuclear translocation of the transcription factor SREBP-2, which regulates the expression of a number of cholesterol synthesis enzymes, including gammamethylglutaryl-CoA-reductase [30]. However, a number of studies devoted to the estrogen role in cholesterol metabolism did not confirm this hypothesis and reported high variability in the effects depending on the form, dose and route of drug administration. Most authors agree that estrogens stimulate the expression of low-density lipoprotein receptor and scavenger receptor SR-BI (the HDL receptor) in liver, thus increasing elimination of cholesterol from the bloodstream. In addition, estrogens promote the cholesterol conversion to bile acids and subsequent secretion into bile [29, 31].

Today, there is convincing evidence that oxidative stress is a common pathogenetic mechanism that unites the main cardiovascular risk factors that constitute MS [32]. At the same time, it is known that estrogen regulation of the expression of various antioxidant enzymes may be one of the mechanisms of their cardioprotective effect [33]. It is also suggested that estrogens can reduce the production of ROS due to a positive effect on the biogenesis and functional state of mitochondria [34].

In our experiment hypoestrogenic animals with prediabetes had 50% higher level of serum conjugated dienes in comparison with intact rats (Table 4). In this group, an increase in the TAA of serum was also observed, which, apparently, is an adaptation reaction to increased free radical oxidation (see Table 4).

The use of hop extract only in a dose of 200 μg/kg, as well as estradiol, led to a signifi-

Table 3

Lipid levels in serum of hypoestrogenic rats with metabolic syndrome, ($\bar{X} \pm S_{\bar{X}}$), n = 6

Group	Total lipids, g/L	TG, mmol/L	TC, mmol/L	FFA, mmol/L
Control	1.66 ± 0.13	0.31 ± 0.04	1.85 ± 0.12	0.73 ± 0.02
MS + solvent	2.43 ± 0.11[1)]	0.66 ± 0.11[1)]	2.47 ± 0.14[1)]	0.73 ± 0.06
MS + hop extract, 20 μg	2.37 ± 0.10[1)]	0.54 ± 0.10[1)]	2.72 ± 0.07[1)]	0.74 ± 0.06
MS + hop extract, 200 μg	1.66 ± 0.04[2)]	0.33 ± 0.03[2)3)]	2.37 ± 0.10[1)]	0.67 ± 0.03
MS + estradiol, 200 μg	1.64 ± 0.15[2)]	0.63 ± 0.04[1)]	1.90 ± 0.17[2)]	0.72 ± 0.06

Notes:
FFA — free fatty acids;
MS — metabolic syndrome;
TC — total cholesterol;
TG — triglycerides;
[1)] $p < 0.05$ vs Control group;
[2)] $p < 0.05$ vs group «MS + solvent»;
[3)] $p < 0.05$ vs group «MS + estradiol, 200 μg».

cant decrease in the intensity of lipid peroxidation induced by MS under estrogen deficiency, as evidenced by a decrease in the concentration of conjugated dienes in the serum of animals. At the same time, the TAA of serum in these groups remained elevated compared to intact animals (see Table 4). Catalase activity did not change significantly regardless of diet and estrogen supply.

It is known that vasoprotective effects of estrogens are due to various factors, such as lipid profile, antioxidant defense system, and production of vasoactive molecules. Thus, estrogens prevent the development of endothelial dysfunction, which is the etiological basis of hypertension, atherosclerosis and cardiovascular events [35]. NO is a powerful vasodilator formed in the reaction of arginine oxidation catalyzed by NO synthase. Estrogens have been shown to regulate the activity of the endothelial isoform of NO synthase (eNOS), both by increasing its expression (genomic pathway) and stimulating its activity through posttranscriptional modifications (nongenomic pathway) [36].

To date, a form of eNOS has been described that is localized in the matrix or on the outer membrane of mitochondria of various cell types, the so-called mitochondrial NO synthase (mtNOS), which suggests the direct participation of NO in the regulation of mitochondrial function and biogenesis [37, 38].

Based on the above, it was of particular interest to study the content of stable metabolites of NO – nitrites and nitrates (NOx) in blood serum, that indirectly reflect the activity of NOS in the vascular endothelium, as well as the activity of NOS directly in the heart muscle, depending on the estrogen supply under the development of insulin resistance syndrome.

As a result of our study, rats with MS and hypoestrogenia had a decrease in the concentration of NO stable metabolites in serum and a decrease in the activity of NOS in heart homogenate (Table 5).

Table 4

Indexes of redox balance in serum of hypoestrogenic rats with metabolic syndrome, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Group	Conjugated dienes, μmol/L	Total antioxidant activity, a.u./mL	Catalase activity, mmol/min/L
Control	2.01 ± 0.18	93.26 ± 0.80	23.53 ± 2.01
MS + solvent	3.14 ± 0.19[1)]	120.79 ± 3.50[1)]	26.82 ± 4.32
MS + hop extract, 20 μg	3.20 ± 0.19[1)]	116.01 ± 5.55[1)]	23.75 ± 4.01
MS + hop extract, 200 μg	2.24 ± 0.22[2)]	116.18 ± 2.79[1)]	23.42 ± 2.73
MS + estradiol, 200 μg	2.26 ± 0.26[2)]	113.78 ± 2.88[1)]	22.88 ± 3.75

Notes:
MS – metabolic syndrome;
[1)] $p < 0.05$ vs Control group;
[2)] $p < 0.05$ vs group «MS + solvent».

Table 5

Indexes of redox balance in serum of hypoestrogenic rats with metabolic syndrome, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Group	NOS activity in heart, pmol/min/mg protein	NOx concentration in serum, μmol/L
Control	19.31 ± 1.45	22.15 ± 1.89
MS + solvent	11.26 ± 2.23[1)]	12.01 ± 1.78[1)]
MS + hop extract, 20 μg	11.03 ± 2.74[1)]	12.78 ± 2.06[1)]
MS + hop extract, 200 μg	19.84 ± 3.53[2)]	23.13 ± 3.55[2)]
MS + estradiol, 200 μg	18.55 ± 2.98[2)]	23.19 ± 4.03[2)]

Notes:
[1)] $p < 0.05$ vs Control group;
[2)] $p < 0.05$ vs group «MS + solvent».

In animals receiving hop extract in the highest dose or estradiol, complete normalization of the studied parameters was observed. The obtained results agree with data from literature on the relaxing effect of hop extract on the mesenteric arteries from C57BL/6 mice, an effect completely abolished in the absence of endothelium [39], and on acute beneficial hop's effects on the endothelial function in patients with high oxidative stress, suggesting hop extract capacity to restore bioavailability of NO [40].

CONCLUSIONS

Our study demonstrated that hop extract in a dose of 200 μg/kg b.w. (in terms of 8-prenylnaringenin) reduced insulin resistance, glucose intolerance, visceral obesity, hypertriglyceridemia, oxidative stress and improved endothelial function and myocardial NOS activity in female rats with metabolic syndrome under estrogen deficiency.

The revealed cardioprotective effect of hop extract indicates the prospects of its use for the prevention and treatment of cardiovascular complications in postmenopausal women with prediabetes.

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A number of studies have shown a greater cardiovascular risk in women with type 2 diabetes compared to men. The latter may be due to more excessive manifestations of metabolic disorders in women, in particular postmenopausal, that develop even at the stage of prediabetes. Since the use of hormone replacement therapy in women after menopause had adverse results on the progression of cardiovascular events, an alternative method of reducing cardiovascular risk in postmenopausal women with prediabetes may be the use of phytoestrogens, which possess estrogen-like activity without negative side effects specific to exogenous estrogens. The **aim** of our study was to evaluate the effect of hop extract on metabolic disturbances in female rats with prediabetes under estrogen deficiency.

Materials and methods. The study was conducted on three-month-old intact and ovariectomized Wistar rats with metabolic syndrome (MS) induced by high calorie diet (15% lard, 25% sucrose, 1% bile salts, 59% standard feed) for eight weeks. The test substances were administered intragastrically once per day in a dose of 20 μg/kg or 200 μg/kg b.w. in recalculation on 8-prenylnaringenin for hop extract and 200 μg/kg b.w. in recalculation on estradiol for the reference drug, from the fifth week after induction of metabolic syndrome.

Results. It was revealed that administration of hop extract in a dose of 200 μg/kg, similar to estradiol, led to improvement in glucose tolerance and decrease in insulin resistance ($p < 0.05$) in estrogen deficient rats with MS. In contrast to estradiol, hop extract had no effect on the mass of uterus in ovariectomized animals. The use of hop extract only in the dose of 200 μg/kg, similar to estradiol, was accompanied by a significant decrease in body weight gain and visceral fat, as well as normalization of the total lipids content in serum of experimental animals ($p < 0.05$). It is of note, that hop extract resulted in decrease of hypertriglyceridemia ($p < 0.05$), but did not affect the level of total cholesterol, while estradiol reduced the concentration of total cholesterol ($p < 0.05$), and had no effect on the level of triglycerides. Hop extract in a dose of 200 μg/kg, as well as estradiol, led to a decrease in the intensity of lipid peroxidation induced by MS under estrogen deficiency, as evidenced by reduced concentration of conjugated dienes in serum ($p < 0.05$). At the same time, the total antioxidant activity of serum in these animals remained elevated compared to intact group. In rats with MS and hypoestrogenia, hop extract in the highest dose and estradiol resulted in complete normalization ($p < 0.05$) of the decreased level of NO stable metabolites in serum and the reduced activity of NO-synthase in heart.

Conclusions. The revealed cardioprotective effect of hop extract that is realized due to the improved lipid profile and reduced insulin resistance, visceral obesity, oxidative stress and endothelial dysfunction in estrogen deficient female rats with MS indicates the prospects of its use for prevention and treatment of cardiovascular complications in postmenopausal women with prediabetes.

Keywords: metabolic syndrome, prediabetes, cardiovascular risk, estrogen deficiency, hop extract.

ВПЛИВ АКТИВНИХ КОМПОНЕНТІВ ЕКСТРАКТУ ХМЕЛЮ НА МЕТАБОЛІЧНІ ПОРУШЕННЯ У САМИЦЬ ЩУРІВ ІЗ ПРЕДІАБЕТОМ НА ТЛІ ДЕФІЦИТУ ЕСТРОГЕНІВ

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Відомо, що кардіоваскулярний ризик у жінок із цукровим діабетом 2 типу значно вищий, ніж у чоловіків. Останнє може бути обумовлене більш виразними проявами у жінок, зокрема після менопаузи, низки метаболічних порушень, які розвиваються ще на стадії прediабету. Оскільки застосування гормональної замісної терапії у постменопаузальних жінок з метою зниження ризику кардіоваскулярних подій мало несприятливі результати, альтернативним засобом попередження серцево-судинних ускладнень у жінок із прediабетом після менопаузи може бути використання фітоестрогенів, які виявляють естрогеноподібну дію без негативних побічних ефектів, притаманних екзогенним естрогенам. **Метою** дослідження було вивчення впливу активних компонентів екстракту хмелю на метаболічні порушення у самиць щурів із прediабетом на тлі дефіциту естрогенів.

Матеріали та методи. Дослідження проводили на тримісячних інтактних та оваріектомованих щурах Вістар із метаболічним синдромом (МС), який індукували за допомогою висококалорійної дієти (15% жиру, 25% цукрози, 1% жовчних кислот, 59% стандартного раціону) упродовж восьми тижнів. Досліджувані речовини вводили внутрішньошлунково один раз на добу в дозі 20 мкг/кг та 200 мкг/кг маси тіла в перерахунку на 8-пренілнарінгенін для екстракту хмелю та в дозі 200 мкг/кг в перерахунку на естрадіол для препарата порівняння, починаючи з п'ятого тижня індукції МС.

Результати. Встановлено, що введення екстракту хмелю в дозі 200 мкг/кг подібно до естрадіолу призводить до поліпшення толерантності до глюкози та зниження інсулінорезистентності ($p < 0,05$) у щурів із МС на тлі дефіциту естрогенів. На відміну від естрадіолу, екстракт хмелю не впливав на масу матки оваріектомованих тварин. Застосування екстракту хмелю лише в дозі 200 мкг/кг, як і естрадіолу, супроводжувалось достовірним зниженням приросту маси тіла та вісцерального ожиріння, а також нормалізацією вмісту загальних ліпідів в сироватці крові експериментальних щурів ($p < 0,05$). Разом із тим, введення екстракту хмелю зменшувало гіпертригліцеридемію ($p < 0,05$), але не впливало на рівень загального холестерину, в той час як естрадіол знижував концентрацію холестерину ($p < 0,05$), проте не змінював рівень тригліцеридів у сироватці крові тварин. Екстракт хмелю в дозі 200 мкг/кг подібно до естрадіолу призводив до зниження інтенсивності перекисного окислення ліпідів, індукованого МС на тлі дефіциту естрогенів, що підтверджувалось зниженням концентрації дієнових кон'югатів в сироватці крові щурів ($p < 0,05$). В той же час, загальна антиоксидантна активність сироватки даних тварин залишалась підвищеною порівняно з контрольною групою. У тварин із МС та гіпоестрогенією екстракт хмелю у найвищій дозі, як і естрадіол, повністю нормалізував ($p < 0,05$) знижений рівень стабільних метаболітів оксиду нітрогену в сироватці крові та знижену активність NO-синтази в серці.

Висновки. Виявлений кардіопротективний вплив екстракту хмелю, який реалізується за рахунок поліпшення ліпідного профілю та зниження інсулінорезистентності, вісцерального ожиріння, оксидативного стресу й ендотеліальної дисфункції у самиць щурів із метаболічним синдромом на тлі дефіциту естрогенів, свідчить про перспективність його використання з метою профілактики та лікування серцево-судинних ускладнень у постменопаузальних жінок із прediабетом.

Ключові слова: метаболічний синдром, прediабет, кардіоваскулярний ризик, дефіцит естрогенів, екстракт хмелю.