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Effects of a New Herbal Formula and Low-Intensity Electromagnetic Radiation of Ultrahigh Frequencies in Obesity and Metabolic Syndrome: an Experimental Study

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ABSTRACT

INTRODUCTION. The high prevalence of metabolic syndrome (MS) is becoming a serious problem for the entire world.
AIM. Experimental evaluation of metabolic syndrome-induced changes in the microcirculation, kidney structure, serum biochemistry, the stress resistance of rats and the possibility of their correction with complex phytoadaptogens (CPhA) and low-intensity extremely-high-frequency electromagnetic radiation (EHF EMR) and their combination.
MATERIAL AND METHODS. The experiment was performed on 40 male Wistar rats (body mass 330±20 g), divided into 4 groups: Group 1 – control, Group 2 – metabolic syndrome (MS), Group 3 – treatment of metabolic syndrome with complex phytoadaptogens (CPhA), Group 4 – treatment with CPhA and EHF EMR. In Groups 2, 3, 4, the animals received a high-carbohydrate, high-fat diet for 16 weeks. The CPhA of official 70% tincture of *Glycyrrhiza glabra* and 40% tincture of *Rhodiola rosea, Acantopanax senticosus* in a ratio of 1:2:1. Group 3 animals were administered CPhA for 14 days with drinking water after 16 weeks on the diet.
RESULTS AND DISCUSSION. The study in question showed that a combined application of CPhA and EHF EMR has systemic effects on the nervous, endocrine, immune systems with changes in the content or synthesis of biologically active substances (hormones, cytokines, neurotransmitters) playing an essential role in the regulatory mechanisms of blood microcirculation. It is a very important aspect for the treatment of metabolic syndrome (MS), with endothelial dysfunction being the key pathophysiological element.
CONCLUSION. Phytoadaptogens are promising drugs for the treatment of MS, especially in combination with EHF EMR, since their effects potentiate each other. CPhA affect the etiology and pathogenesis of metabolic syndrome through several mechanisms; therefore, they are promising medicines in the complex fight against excess weight.
KEYWORDS: Acanthopanax senticosus, dyslipidemia, Glycyrrhiza glabra, hypertension, insulin resistance, metabolic syndrome, obesity, Rhodiola rosea

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Эффекты новой растительной формулы и низкоинтенсивного электромагнитного излучения крайневысокой частоты при ожирении и метаболическом синдроме: экспериментальное исследование

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РЕЗЮМЕ

ВВЕДЕНИЕ. Высокая распространенность метаболического синдрома (МС) становится серьезной проблемой для всего мира.
ЦЕЛЬ. Провести экспериментальную оценку вызванных метаболическим синдромом изменений микроциркуляции, структуры почек, биохимии сыворотки крови, стрессоустойчивости крыс и возможности их коррекции комплексными фитоадаптогенами (CPhA) и низкоинтенсивным электромагнитным излучением крайневысокой высокой частоты (КВЧ ЭМИ) и их комбинацией.
МАТЕРИАЛ И МЕТОДЫ. Эксперимент проводили на 40 крысах–самцах породы Вистар (масса тела 330±20 г), разделенных на 4 группы: 1–я группа – контрольная, 2–я группа – с метаболическим синдромом (МС), 3-я группа – проходившая лечение метаболического синдрома комплексными фитоадаптогенами (CPhA), 4-я группа – проходившая лечение CPhA и КВЧ-ЭМИ. В группах 2, 3, 4 животные получали диету с высоким содержанием углеводов и жиров в течение 16 недель. CPhA состоит из официальных 70% настойки *Glycyrrhiza glabra* и 40% настоек *Rhodiola rosea*, *Acantopanax senticosus* в соотношении 1:2:1. Животным 3-й группы вводили CPhA в течение 14 дней с питьевой водой после 16 недель диеты.
РЕЗУЛЬТАТЫ И ОБСУЖДЕНИЕ. Представленное исследование продемонстрировало, что комбинированное применение CPhA и ЭМИ КВЧ оказывают системное воздействие на нервную, эндокринную, иммунную системы с изменением содержания или синтеза биологически активных веществ (гормонов, цитокинов, нейромедиаторов), что играет существенную роль в механизмах регуляции микроциркуляции крови. Это очень важный аспект для лечения метаболического синдрома, при котором эндотелиальная дисфункция является ключевым патофизиологическим элементом.
ЗАКЛЮЧЕНИЕ. Фитоадаптогены являются перспективными препаратами для лечения метаболического синдрома, особенно в сочетании с КВЧ-ЭМИ, поскольку их эффекты усиливают друг друга. CPhA влияют на этиологию и патогенез метаболического синдрома несколькими механизмами, поэтому они являются перспективными препаратами в комплексной борьбе с лишним весом.

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INTRODUCTION

The increasing prevalence of metabolic syndrome (MS) is becoming the most serious health problem worldwide. According to WHO reports, more than 1.9 billion people are overweight [1, 2].

The pathophysiology of metabolic syndrome is very complicated and necessitates the development of drugs with a wide range of pharmacological activity that would affect several pathogenic elements and etiological factors of this condition. Low-intensity extremely-high-frequency electromagnetic radiation (EHF EMR) is a promising tool for correcting the physiological functions affected by adverse factors and pathological processes, as it exerts pronounced physiological effects with minimal energy consumption and does not cause tissue heating or structural changes in the body. EHF-therapy has no side effects or long-term adverse consequences. It is non-invasive and can be easily combined with other methods (medicinal, surgical, physiotherapeutic, etc.), augmenting their efficacy, eliminating side effects, reducing treatment duration and exhibiting multiple therapeutic effects. On the other hand, there has been little fundamental research into the mechanisms of action of this physical factor on the human body in health and various disorders [3-5].

AIM

We evaluated a new herbal formula that can potentially be used in MS and obesity; it consists of the well-known and widely used phytoadaptogenes – *Glycyrrhiza glabra, Rhodiola rosea, Acanthopanax senticosus*. *Rhodiola rosea* and *Glycyrrhiza glabra,* which have anti-inflammatory and antioxidant effects [6, 7]. *Acanthopanax senticosus* regulates homeostatic responses via the neuroendocrine immune system (NEIM). They control stress-activated molecular chaperons (Hsp70), cortisol and nitric oxide (NO) [8]. Under stress conditions, adaptogens increase the function of the pineal gland [8, 9]. Therefore, the aim of this study was to define the structural changes in the kidneys and functional changes in microcirculation, anxiety, motor behavior in the presence of metabolic syndrome and during its treatment with complex phytoadaptogens alone or in combination with low-intensity extremely-high-frequency electromagnetic radiation.

MATERIAL AND METHODS

Diet-induced metabolic syndrome in rats

The experiment was performed on Wistar male rats (9-10 weeks old, weighing 330±20 g, n=30) obtained from the North Caucasus Environmental Management Nursery. The animals were housed in a 12-h light/dark controlled room with regulated temperature (21±1°C) and humidity (50-55%). The rats were kept in cages (5 animals in each); food and water were given *ad libitum*.

The study was approved by the Ethics Committee of the Institute of Biomedical Investigations – a branch of Vladikavkaz Scientific Centre of the Russian Academy of Sciences (Protocol No. 7, February 20, 2019). The study was conducted in accordance with the ethical standards established by the Declaration of Helsinki (2013).

After the first adaptation period (2 weeks), the animals were randomly divided into 3 experimental groups: Group 1 – control, Group 2 – metabolic syndrome, Group 3 – treatment of metabolic syndrome with complex phytoadaptogens (CPhA), Group 4 – treatment of metabolic syndrome with complex phytoadaptogens (CPhA) and low-intensity extremely-high-frequency electromagnetic radiation (EHF EMR) (Fig. 1). Animals of Groups 2, 3, 4 were fed the high-carbohydrate, high-fat diet (HCHF).

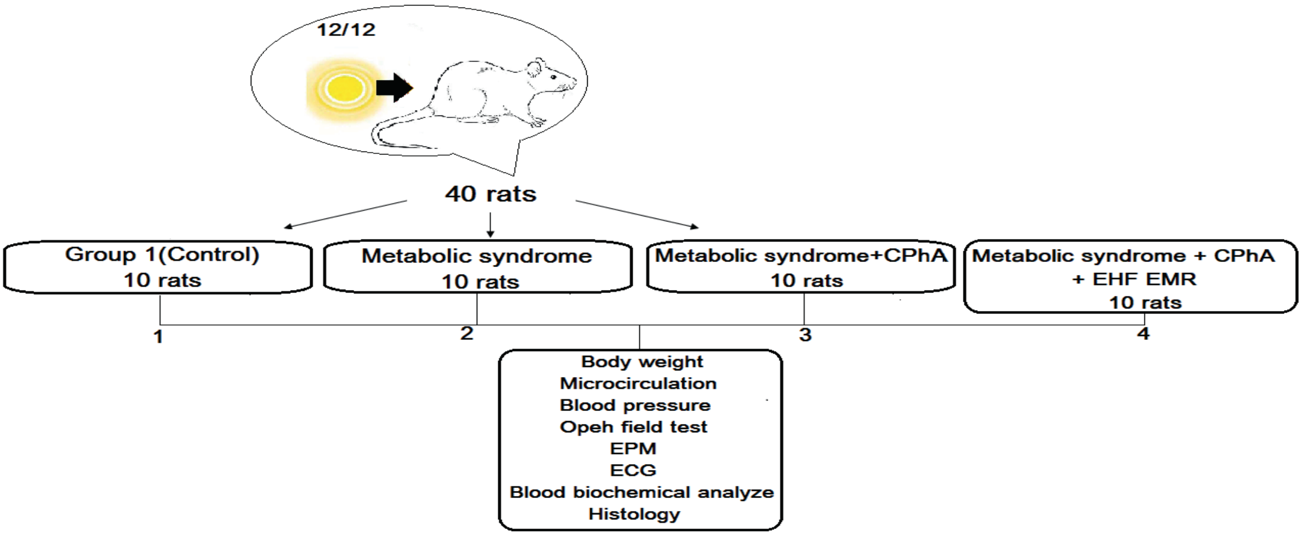

Fig. 1. *Study design*

Note: *EPM – elevated plus-maze test; ECG – electrocardiography; EHF EMR – low-intensity extremely-high-frequency electromagnetic radiation; 1 (Week 1), 2 (Week 16), 3 (Week 18), 4 (Week 18) – evaluation points of the experiment*

The HCHF diet consisted of 175 g of fructose, 395 g of sweetened condensed milk, 200 g of beef tallow, 155 g of powdered rat food, 25 g of Hubble, Mendel and Wakeman salt mixture and 50 g of water per kilogram of diet. In addition, the drinking water for the HCHF group was supplemented with 25% fructose. Total feeding time was 16 weeks [10]. The rats from Group 2 were euthanized after 16 weeks of feeding to assess the progression of the pathophysiological changes of metabolic syndrome. After the 16 weeks of the HCHF diet, the rats from Group 3 received complex phytoadaptogens (CPhA) for 14 days and the animals in Group 4 received complex phytoadaptogens (CPhA) and were treated with 30-min EHF EMR sessions daily for 7 days.

Microcirculation (MC), anxiety and motor behavior assessments, histological examination, blood chemistry tests were performed in Group 1 once at the first time point, in Group 2 after 16 weeks of the HCHF diet, in Group 3 after 16 weeks of the HCHF diet and 1-week CPhA treatment, in Group 4 after 16 weeks of the HCHF diet and 2-week use of CPhA and EHF EMR.

Physiological and metabolic tests

Blood chemistry samples were collected through cardiac puncture and left to stand for 2 hours in a vacutainer (VISIO PLUS Needle, Austria). Serum triglyceride, glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CRE) and blood urea nitrogen (BUN) levels were analyzed with a blood analyzer.

Doppler ultrasound (MM-D-K Minimax-Doppler-K, 25 MHz probe, Saint-Petersburg, Russia) was used to study microcirculation (MC) disorders. Each rat was fixed on a wooden board in the supine position. MC was measured 3 times in each area of each rat at each (Fig. 1) evaluation time point and the average value was calculated. The evaluations included: Vas – maximum systolic blood flow velocity; Vam – average blood flow velocity; Vakd – final diastolic blood flow velocity; Qas – maximum systolic volumetric blood flow velocity; Qam – average volumetric blood flow velocity; PI – pulsation index (index Gosling) and RI – peripheral resistance index (Purcell index) indicative of the elasticity of vessels.

Preparation of a complex phytoadaptogens (CPhA) extract

CPhA extract is composed of official 70% tincture of *Glycyrrhiza glabra, Rhodiola rosea, Acantopanax senticosus* in a ratio of 1:2:1 [11]. The dose was calculated based on the average daily volume of liquid consumed and the coefficient (x10) for small laboratory animals (0.1 ml/100g) per day. CPhA were administered in Group 3 for 14 days after the metabolic syndrome simulation.

Low-intensity extremely-high-frequency electromagnetic radiation (EHF EMR)

An EHF-ND high-frequency generator (NKF RESLA, Russia) was the source of EHF EMR. Technical characteristics of the generator: operating wavelength 7.1 mm; the frequency of the output signal was set at 42.3 GHz; the incident power density in the plane of the exposed object was 0.1 mW/cm^2. For exposure to EMR EHF, experimental animals were immobilized in special transparent chambers for the duration of the procedure (228x89x84mm) (Neurobotics, Russia). The length and width of the chamber were adjusted depending on the size of the rat. The emitter was brought to the irradiated occipital-collar area of the animal through a hole in the pencil case corresponding to the size of the emitter. Irradiation was carried out for 30 minutes, daily for 7 days, after 16 weeks of HCHF.

Stress-dependent changes in anxiety-like behaviour of rats

Anxiety and motor behavior were recorded and calculated with computerized activity monitoring software (RealTimer, OpenScience, Russia) in open field (OFT) and elevated plus maze (EPM) tests.

The OFT arena is a square platform with sides equal to 100 cm and a height of 40 cm, divided into identical 25 squares (40×40×30 cm^3). It has been shown that the open field test with a gray arena cannot reveal intergroup differences (stress-resistant, intermediate and stress-resistant) in behavioral indicators in animals. In the gray open field arena, due to the transitional state between the habitats, a special type of stress behavior occurs, manifested in a mixed anxiety-phobic state in animals, regardless of their predicted resistance to stress. Based on this, animals in this experiment were not divided into groups according to their resistance to stress [12]. The OF test parameters included horizontal activity (distance, expressed in squares), vertical activity (number of vertical counts), number of groomings and defecations episodes.

The elevated plus maze is a plus-shaped apparatus with four arms at right angles to each other as described by Handley and Mithani. The EPM apparatus consists of two closed (30×5×30 cm^3) and two open arms (30×5×1 cm^3) perpendicular to each other and connected by a central arena (5×5 cm^2). The closed arms have a high wall (16 cm) to enclose the arms, whereas the open arms have no side wall. The rats were placed in the central platform facing the closed arm and their behavior was recorded for 5 min. The parameters recorded in EPM: the number of entries and the total time spent exploring open and closed arms, the number of racks; hanging from the sleeve; acts of defecation. An arm entry was recorded when a rat entered into the arm with all four limbs [12, 13].

On the test day, the rats were transported to the testing room for 2 h. Each rat was then placed in the same corner of the open field arena and elevated plus-maze, its behavior was recorded for 5 minutes. To avoid the presence of olfactory signals, all the testing apparatuses (open field test, elevated plus-maze) were thoroughly cleaned with 20% ethanol and then wiped with dry paper after each trial.

Histology

Kidney tissue samples were fixed in ice-cold 10% paraformaldehyde for 72 h, before dehydration and fixation in paraffin blocks for histology. The fixed tissue was then sectioned into 5 lm sections using a microtome. Sections were then stained with hematoxylin and eosin (H&E). The frames were observed at 100× under a microscope.

Statistical analysis

Data analysis was performed using Statistica 10.0 software (StatSoft Inc., Russia). The distribution of continuous variables was tested for normality with the Shapiro-Wilk test. The Kruskal-Wallis test was used to compare independent data sets. The Wilcoxon test was used to compare dependent data sets. Median (25–75 ‰) values were given as descriptive statistics due to the small number of variants in the sample. A *P* value of < 0.05 was accepted as statistically significant.

RESULTS AND DISCUSSION

Body weight

Body weight (BW) was significantly higher in metabolic syndrome (Group 2) compared to control (P=0.008) (Group 1). No differences were found between CPhA (Group 3) and MS. Complex phytoadaptogens combined with EHF EMR for metabolic syndrome (Group 4) was the only group with a significant body weight reduction vs. MS (Group 2) (P=0.035) and no significant differences were observed with the control group (Group 1). Moreover, Group 4 showed a significant difference with Group 3 (P=0.023) (Fig. 1).

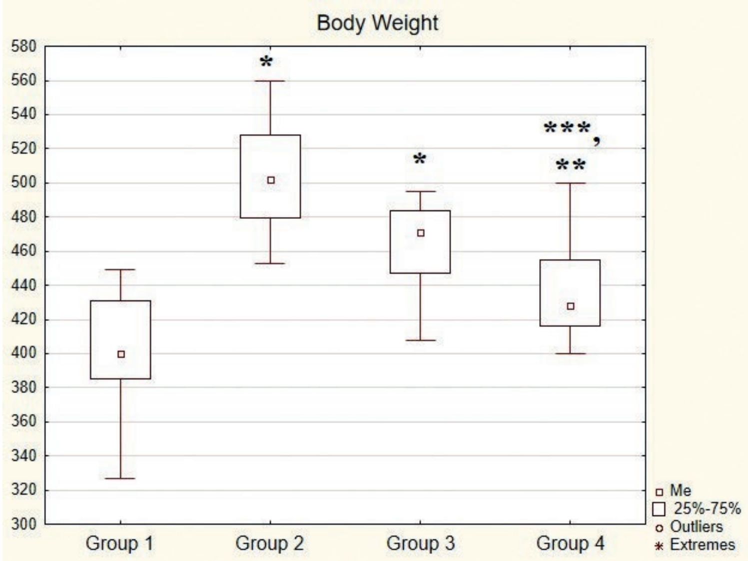

Fig. 2. *Changes over time in body weight in all experimental groups*

Note: *Group 1 – control, Group 2 – metabolic syndrome, Group 3 – treatment of metabolic syndrome (MS) by complex phytoadaptogens (CPhA), Group 4 – treatment of metabolic syndrome by complex phytoadaptogens (CPhA) and low-intensity extremely-high-frequency electromagnetic radiation (EHF EMR), *– vs. control, ** – vs. MS, *** – vs. Group 3.*

Microcirculation

The changes over time in microcirculation in all experimental groups are presented in Table 1. In metabolic syndrome, there was a significant decrease in systolic (Vas) (P=0.002), diastolic (Vas) (P=0.003) and mean blood flow velocities (Vam) (P=0.002) relative to the control. In the group of metabolic syndrome treated with complex phytoadaptogens, there was a significant increase in Vas (P=0.047) and Vakd (P=0.046). However, there were significant differences in Vas (P=0.046), Vam (P=0.046) and Vakd (P=0.027) with the control group. The combination of complex phytoadaptogens and EHF EMR for metabolic syndrome affected microcirculation was as follows: an increase in Vas (P=0.017) was noted, significant differences in Vakd (P=0.017) with the control group remained. Unlike the group of MS, treated with complex phytoadaptogens, the combination with EHF EMR had a more pronounced effect on Vas; there were no significant differences with the control group.

In metabolic syndrome, along with a reduction of the linear blood flow velocities (Vas, Vam, Vakd), volumetric blood flow velocity was naturally decreased: Qas (P=0,018) and Qam (P=0.002).

The analysis of volumetric blood flow rates in the treatment groups revealed the following: after MS was exposed to complex phytoadaptogens, there was a tendency to increase in Qas and Qam, but significant differences with the control group remained. After MS was exposed to the combination of EHF therapy and complex phytoadaptogens, the Qas and Qam were within the confidence interval of the control group.

Metabolic syndrome has an adverse effect on the structure of low-resistance arteries due to an increase in the thickness of the arterial wall. This leads to hypertrophic remodeling of the vascular wall. Therefore, metabolic syndrome is associated with a natural increase in vascular resistance manifested by a significant increase in PI (P=0.007) and RI (P=0.017). The combination of EHF therapy and complex phytoadaptogens was most effective in improving vascular tone: there were significant differences in PI (P=0.017) with respect to MS (Table 1). There were significant differences between Groups 3 and 4 in these parameters: Vas (p=0.03), Qas (p=0.000), PI (p=0.02) (Table 1).

Table 1. *Microcirculation parameters in all experimental groups*

	Control (Group 1)	MS (Group 2)	MS+CPhA (Group 3)	MS+CPhA+ EHF EMR (Group 4)
Vas	0.65(0.56;0.68)	0.5(0.47;0.54)*	0.53(0.51;0.56)*.**	0.61(0.53;0.64)**.***
Vam	0.24(0.19;0.27)	0.17(0.15;0.18)*	0.2(0.18;0.22)*	0.19(0.14;0.21)**
Vakd	0.25(0.21;0.3)	0.19(0.18;0.2)*	0.2(0.19;0.21)*.**	0.24(0.2;0.27)**
Qas	0.52(0.47;0.62)	0.4(0.38;0.46)*	0.46(0.44;0.48)*	0.52(0.43;0.54)**.***
Qam	0.24(0.19;0.25)	0.15(0.14;0.16)*	0.19(0.17;0.19)*	0.21(0.19;0.23)**
PI	4(3.3;4.2)	4.92(4.71;5.15)*	4.78(4.33;5.48)*	3.87(3.7;4.4)**.***
RI	0.98(0.97;1)	1(0.99;1)*	1(1;1)*	1(0.98;1)*

Note: *MS – metabolic syndrome; CPhA – complex phytoadaptogens; EHF EMR – low-intensity extremely-high-frequency electromagnetic radiation; significant differences: * – vs. control;*
*** – vs. MS, *** – vs. Group 3*

Stress-dependent changes in anxiety-like behavior in rats

Open field test

Rats with metabolic syndrome (MS) (Group 2) showed a trend towards a decrease in horizontal locomotor activity (HLA) compared to control (Group 1) within 5 min. The number of rearings with a support (vertical locomotor activity (VLA)) on the arena wall in Group 2 showed significant differences with the control (p=0.017) (Table 1). This means that metabolic syndrome is associated with a decrease in orientation-exploratory activity (↓HLA and VLA). In the complex phytoadaptogens group, no significant differences with the control were observed in HLA or VLA, with a recovery of test results within the confidence interval of the control, that is, there was a tendency to normalized orientation-exploratory activity (Table 2).

The main significant manifestation of strong fear in animals with metabolic syndrome in the OFT was the duration of the immobility period, which was significantly different from control values (p=0.011). This fact confirms the significant differences in this parameter with the control animals in Group 3 (p=0.025). But the use of CPhA resulted in a significant difference with the MS group in terms of periods of immobility (p=0.014) (Table 2).

There was a significant difference in the grooming number between the CPhA and MS groups (P=0.017) and a significant difference with control (P=0.017). The difference in the grooming number between the EHF therapy plus CPhA and the MS groups (P=0.017) was significant, and the difference with the control group was insignificant, which indicates that the combination was the most effective option. There were no significant differences in the parameters between Groups 3 and 4.

Table 2. *Changes over time in the open field test parameters in all experimental groups*

Parameters	Control (Group 1)	MS (Group 2)	MS+CPhA (Group 3)	MS+CPhA+ EHF EMR (Group 4)
Open field test				
Horizontal activity (distance, expressed in squares)	58.5(36;65.5)	29.5(25;45) p*=0.017	45(33.5;53)	45(37.5;49)
Vertical activity (number of rearings with support on the wall)	9(5.5;13)	2.5(2;6) p*=0.017	7(3.5;8.5)	7(6;9.5) P**=0.046
Vertical activity (number of rearings without support on the wall)	7(3;8.5)	6.5(4;9)	5(3;7)	5.5(5;6.5)
Period of immobility (sec)	20(15;32.5)	60(45;75) p*=0.011	39(32.5;45) P*=0.025 P**=0.014	42.5(27.5;50) P*=0.035 P**=0.027
Number of grooming episodes	7(3.5;13.5)	27.5(20;40) p*=0.011	15.5(14.5;16) P**=0.017	18.5(14;21) P**=0.017

Note: *Control (healthy animals), MS (metabolic syndrome), MS + CPhA (treatment of metabolic syndrome with complex phytoadaptogens), MS + EHF EMR + CPhA (treatment of metabolic syndrome with low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens), the results are presented as Me (25‰;75‰); significant differences: *- vs. control 1, ** – vs. MS; p<0.05*

Elevated-plus maze test

MS causes changes in the behavioral reactions of rats, which is also demonstrated by the degree of anxiety of the animals in the elevated plus maze. Significant (p<0.05) decreases in the number of intersections of the central platform, exits to the open arms of the maze, an increase in the period of stay in the dark sleeves compared to the control group indicate a reduction in the motor and exploratory activity of animals (Table 3).

Table 3. *Changes over time in elevated plus maze test parameters in all experimental groups*

Parameters	Control (Group 1)	MS (Group 2)	MS+CPhA (Group 3)	MS+CPhA+ EHF EMR (Group 4)
Elevated plus maze				
Number of entries	3(0;5)	0(0;2) p*=0.027	0(0;0,5)	1.5(1;2)
Number of defecation events	3(2;3)	4.5(2;6) p*=0.017	0(0;2)	0(0;1)
Number of grooming events	2(2;3)	2(1;3)	2(1;3)	4(2.5;5)
Time spent in the light sleeve	70.6 (13.45;81.61)	59.73 (52.19;109.16)	27.28 (25.8;49.35)	80.24 (42.93;136.66) p***=0.021
Time spent in the dark sleeve	236.4 (191.29;274.56)	208.76 (174.02;221.07) p*=0.043	228.8 (214.78;244.99) p*=0.017	181.74 (110.1;208.1) p***=0.015

Note: *Control (healthy animals), MS (metabolic syndrome), MS + CPhA (treatment of metabolic syndrome with complex phytoadaptogens), MS+ EHF EMR + CPhA (treatment of metabolic syndrome with low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens), the results are presented as Me (25‰;75‰); significant differences: *- vs. control 1, ** – vs. MS; *** – Group 3 vs. Group 4, p<0.05*

Analysis of the parameters of the elevated plus maze test revealed increased anxiety and symptoms of fear in animals. In Group 2 rats (MS), the following differences with the control were observed: decreased time spent in the open arm (p=0.012), increased time spent in the dark arm (p=0.043), increased number of entries (p=0.043), which indicated increased anxiety. In the complex phytoadaptogens group, the time spent in the open and closed arms of the maze did not significantly differ from the respective values in the control (Table 3).

The number of defecation events was increased in the metabolic syndrome group compared with the control (p=0.017), reflecting the emotional responses of the animals. In the treatment group, the obtained result did not significantly differ from the control (Table 3).

The most pronounced difference between the metabolic syndrome (MS) and the control groups was in dark sleeve time. The combination of EHF therapy and CPhA was the most effective treatment of metabolic syndrome in this regard, since there were no significant differences with the control. There were significant differences between Groups 3 and 4 in time spent in the light sleeve (p=0.021), time spent in the dark sleeve (p=0.015) (Table 3).

Blood chemistry test results

The analysis of serum chemistry parameters revealed that animals fed a diet high in carbohydrates and fats had significant increases in total cholesterol (p=0.049), triacylglycerides (p=0.011), LDL (p=0.038), C-reactive protein (p=0.016), as well as a decrease in creatinine (p=0.011) compared with the control (Table 4).

When metabolic syndrome was treated with complex phytoadaptogens and their combination with EHF therapy, the results of these tests did not differ from the respective values of the control group. There were no significant differences between Groups 3 and 4 in these parameters.

Table 4. *Changes over time in the blood chemistry parameters in all experimental groups*

	Control (Group 1)	MS (Group 2)	MS+CPhA (Group 3)	MS+CPhA+ EHF EMR (Group 4)
Total cholesterol (mmol/l)	1.5(1.1;1.6)	1.66(1.42;1.81)* p=0.049	1.25(1.23;3.48)** p=0.017	1.29(1.13;1.49)
Creatinine (µmol/L)	53(47;54)	44(39.5;48)* p=0.011	43(39;55)	45.5(42;50.5)
Triglyceride (mmol/l)	1.7(1.31;3.05)	5.02(2.66;9.87)* p=0.011	3.19(2.29;3.48)** p=0.017	2.34(1.75;2.75)** p=0.011
High-density lipoprotein (HDL) (mmol/l)	0.58(0.48;0.8)	0.72(0.52;0.84)	0.45(0.3;0.51)** p=0.042	0.47(0.42;0.59)
Low-density lipoprotein (LDL) (mmol/l)	0.14(0.12;0.27)	0.23(0.12;0.38)* p=0.038	0.09(0.07;0.25)**p=0.017	0.11(0.06;0.24)
C-reactive protein (mg/l)	357.4(346.5;402.5)	658,1(586,4;764,3) p*=0,0002	364,6(349,7;379,2)	357,2(334,9;389,4)

Note: *Control (healthy animals), MS (metabolic syndrome), MS + CPhA (treatment of metabolic syndrome with complex phytoadaptogens), MS + EHF EMR + CPhA (treatment of metabolic syndrome with low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens), the results are presented as Me (25‰;75‰); significant differences: *- to control 1, ** – to MS; p<0.05*

Impact of CPhA and CPhA+ EHF EMR on kidney histopathology in MS rats

Examination of H&E-stained sections from rats with metabolic syndrome showed pronounced histopathological changes, especially in the renal cortex: abnormalities were observed mainly in the glomeruli (G) and proximal convoluted tubules and renal stroma, as compared with the control (Fig. 3 C, D).

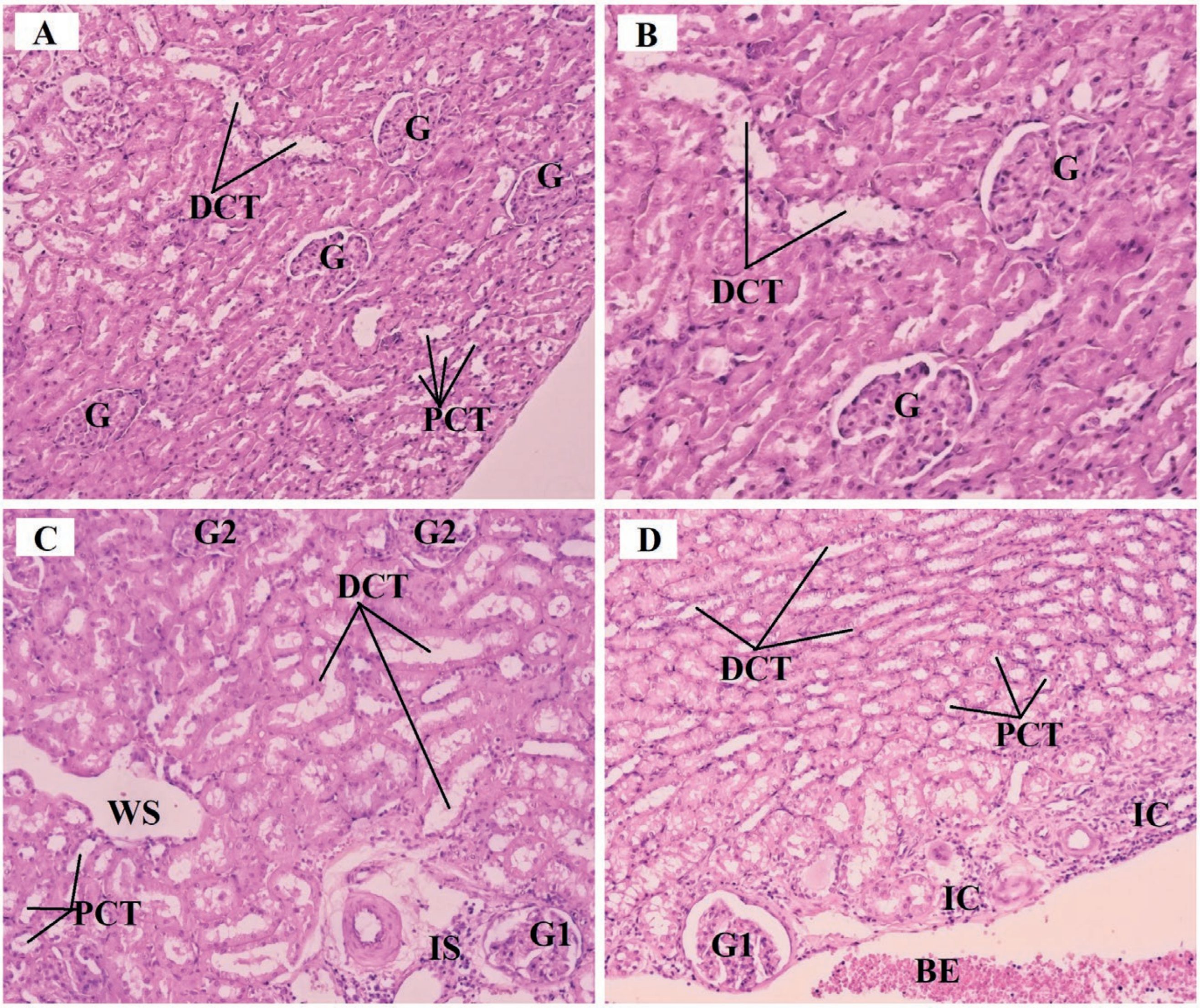

Fig. 3. *Histological structure of the renal cortex in control and metabolic syndrome rats*

Note: *Control group (A, B) shows normal renal glomeruli (G) and tubules (PCT, DCT), while in the metabolic syndrome group (C, D) some glomeruli appeared atrophic (G1) while others appeared hypertrophic (G2). Most of the PCTs appeared degenerated, with widened lumen, loss of brush border and pyknotic nuclei. Note the presence of interstitial wide spaces (WS), blood extravasation (BE) and infiltration with inflammatory cells (IC); (H&E– A – C × 200)*

The kidneys of the control rats had a normal structure of the renal cortex (Fig. 3 A, B), which contained mainly renal corpuscles consisting of glomerular capillaries enclosed by a Bowman's capsule. In addition, there was a capsular space between the proximal (PCTs) and distal convoluted tubules (DCTs). In the rats with MS, the glomeruli were hypertrophic (G2) with expanded glomerular capillaries, while other glomeruli seemed atrophic (G1). In addition, most PCTs were expanded and lost the brush border; their cells had vacuolated cytoplasm and dark pyknotic nuclei. In addition, interstitial wide spaces (WS), blood extravasation (BE) and infiltration with mononuclear inflammatory cells (ICs) were observed in various areas of the renal cortex.

Comparing rats with metabolic syndrome treated with CPhA (Fig. 4 A, B) and CPhA with EHF EMR (Fig. 4 C, D), CPhA and EHF EMR showed a marked improvement in the histological profile of the kidneys manifested by almost normal glomeruli and PCTs without signs of degeneration (decrease in interstitial wide spaces) and infiltration by inflammatory cells.

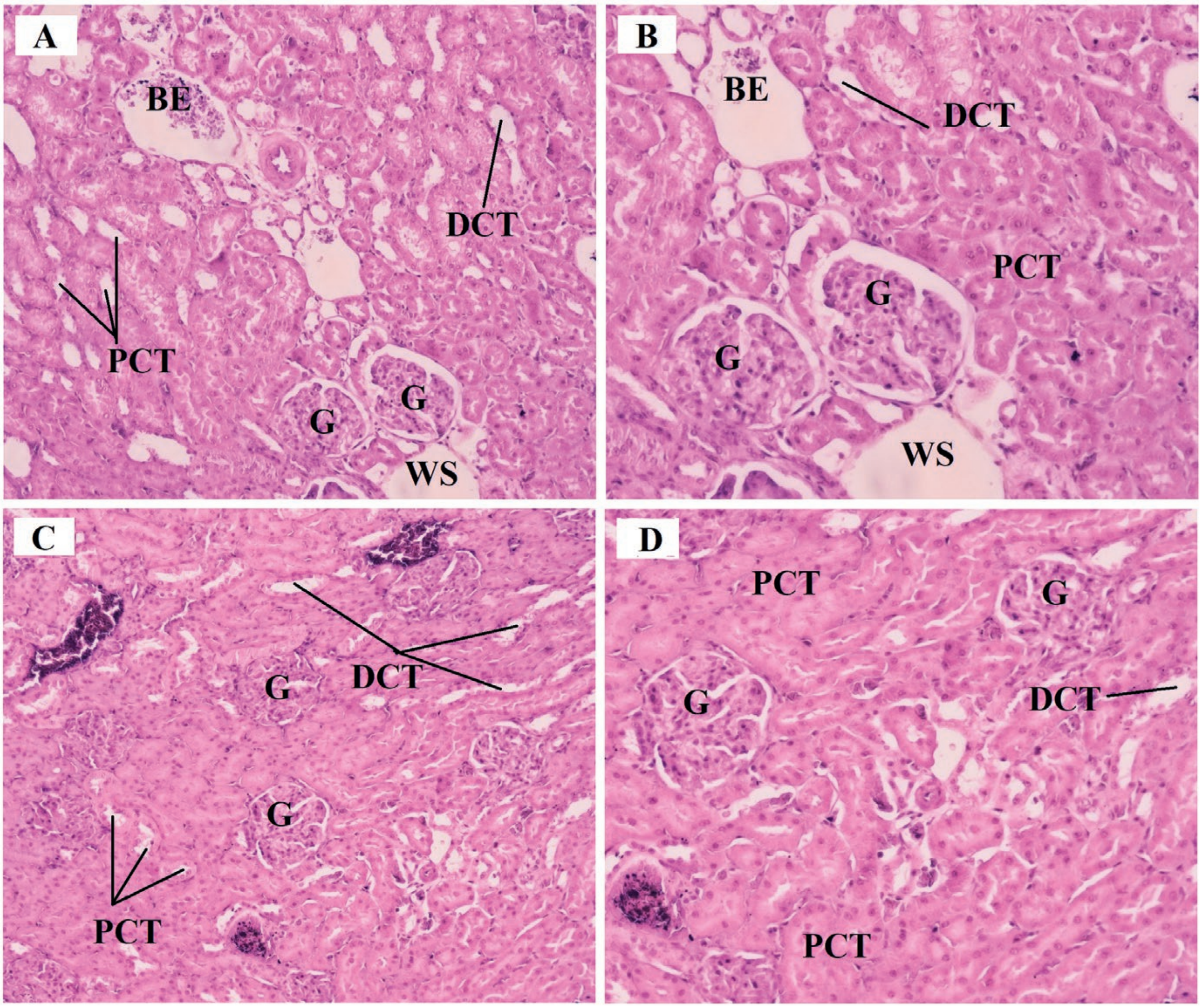

Fig. 4. *Histological structure of the renal cortex in the groups of rats with metabolic syndrome treated with complex phytoadaptogens (A, B) or low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens (C, D)*

Note: *Appearance is nearly back to normal as compared to the control group in terms of the glomeruli (G) and tubules (PCT, DCT), interstitial wide spaces (WS), blood extravasation (BE) and infiltration with inflammatory cells (ICs); (H&E–A – D × 200)*

Evaluating the microcirculation, serum chemistry parameters, anxiety-like behavior and kidney histology, we demonstrated significant differences in metabolic syndrome treatment outcomes in favor of the combined use of complex phytoadaptogens and low-intensity extremely-high-frequency electromagnetic radiation.

Effects of low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens on microcirculation parameters in metabolic syndrome

The decreased availability of endogenous vasodilators necessary to maintain optimal vascular tone and tissue blood flow explains the changes at the microcirculation level in metabolic syndrome, as compared with the control group: significant decreases in systolic (Vas) (P=0.002), diastolic (Vas) (P=0.003) and mean (Vam) (P=0.002) blood flow velocities were obtained during our study. In metabolic syndrome, along with a decrease in linear blood flow (Vas, Vam, Vakd), there were decreases in the volumetric flow rates: Qas (P=0.018) and Qam (P=0.002). Metabolic syndrome has an adverse effect on the structure of low-resistance arteries due to an increase in the thickness of the arterial wall. This leads to hypertrophic vascular wall remodeling. Therefore, metabolic syndrome is typically associated with increased vascular resistance, which was evidenced by significant increases in PI (P = 0.007) and RI (P= 0.017).

Complex phytoadaptogens produced significant increases in Vas (P=0.047) and Vakd (P=0.046) in metabolic syndrome; however, there were significant differences in Vas (P=0.046), Vam (P=0.046) and Vakd (P=0.027) with the control group. The effect on MC of the combination of CPhA and EHF EMR led to an increased Vas (P=0.017), while significant differences in Vakd (P=0.017) with the control group remained. When combined with EHF therapy, complex phytoadaptogens had a more pronounced effect on Vas in metabolic syndrome than alone; there were no significant differences with the control group. Analysis of volumetric blood flow rates in the treatment groups demonstrated a tendency to increased Qas and Qam, when MS was treated with complex phytoadaptogens, but significant differences with the control group remained. When MS was treated with the combination of EHF therapy and complex phytoadaptogens, the Qas and Qam were within the confidence interval of the control group. The combination of EHF therapy and complex phytoadaptogens was most effective in improving a vascular tone: there were significant differences in PI (P=0.017) with MS.

The results obtained can be explained as follows: homeostasis of the vascular network is ensured by the integrity of endothelial tissue, which is a central link in the regulation of a complex balance between substances with vasodilating activity and vasoconstrictive properties [14, 15]. Endothelial dysfunction is one of the earliest vascular changes observed in obesity. This is characterized by a decrease in the availability of NO both due to its accelerated degradation as a result of the excessive dominance of vascular generation of reactive oxygen species (ROS) and due to altered endothelial enzyme NO synthase production (eNOS). Nitric oxide (NO) is the main compound involved in the regulation of vascular homeostasis; it is produced by endothelial cells as a result of the conversion of L-arginine into citrulline under the action of the constitutive eNOS [15]. An increased concentration or activity of arginase can reduce the amount of L-arginine available for eNOS, which reduces the production of NO and induces endothelial dysfunction [16].

Obesity is associated with inflammation and specific chemokines produced by visceral fat (adipokines) play an important role in controlling inflammation [17, 18]. The production of adipokines by fat cells can be considered an endocrine function and makes adipose tissue the largest endocrine organ of the body. The main adipokines produced by fat cells – leptin, resistin and adiponectin – can affect vascular homeostasis in different ways. Leptin, the main protein produced by adipocytes, can stimulate the secretion of TNF-α and interleukin-6 (IL-6), which, in turn, contribute to endothelial dysfunction directly or by inducing an increase in ROS production in endothelial cells [19]. TNF-α can stimulate ROS production by activating NADPH oxidase or by activating nuclear transcription factor-kappa B (NF-kB), which leads to activation of macrophages, migration and proliferation of smooth muscle cells and induction of expression of adhesion molecules by endothelial cells [20]. IL-6 increases the production of ROS by activating xanthine oxidase and the reduced form of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) [20,21].

The effects in Group 4 (treatment of metabolic syndrome with low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens) can be explained as follows: complex phytoadaptogens affect the hemostasis system, improving the rheological properties of blood, modulating coagulation and fibrinolysis by increasing the production of anti-thrombotic substances such as NO, PG EI, EETs, prostacyclin, thereby normalizing vascular tone and blood flow due to vasodilation (↑NO) [6-8, 22]. In its turn, EHF EMR increases the release of secretions from mast cells (histamine, proteases, serotonin, heparin) with their degranulation; it seems to be one of the mechanisms in the cascade of events leading to a systemic response of the body to the effects of low-intensity EMR. The main humoral agent of the anticoagulation system, heparin, released into the bloodstream after degranulation of mast cells, forms complex compounds with blood proteins and amines in response to the thrombin appearing in the bloodstream. The resulting complexes have non-enzymatic fibrinolytic activity, anticoagulant, anti-polymerization and anti-aggregation properties [24, 25].

Effects of low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens on anxiety and behavioural reactions in metabolic syndrome

Stress is an important etiological factor in the development of metabolic syndrome. Understanding the connections and interactions between stress, neurobiological adaptations and obesity is important for developing effective strategies for the prevention and treatment of obesity and related metabolic diseases. Therefore, we also studied the behavioral parameters of animals in health and MS and during the treatment of the latter. The combination of complex phytoadaptogens and EHF EMR was shown to be most effective. When metabolic syndrome was treated with complex phytoadaptogens or their combination with EHF EMR, the horizontal and vertical motor activity increased statistically significantly ($p<0.05$) compared with the animals with metabolic syndrome (MS) in the "Open Field" test, specifically the number of crossed squares (locomotor activity) and the number of racks, suggesting a trend to recovery of the motor activity disturbed by stress. In its turn, the most pronounced changes in the "Elevated plus maze" test in animals with metabolic syndrome (MS) were in dark sleeve time, as compared with control 1. The combination of complex phytoadaptogens and EHF therapy was the most effective in the treatment of metabolic syndrome in this regard, since there were no significant differences with the control group, apparently due to the pronounced stress-limiting effect of both complex phytoadaptogens and EHF therapy [5, 13]. EHF EMR promotes the release of serotonin from mast cells, which stimulates endothelium-dependent vasodilation. Biologically active substances released from the mast cells also have an effect on numerous nerve endings, which may contribute to the overall response to EHF EMR [3, 26]. Stress-limiting systems, which include the serotonergic system, inhibit the release of KA from the nerve endings and adrenal glands and the action of these monoamines, thereby limiting the excessive stress response and its damaging effect on the body. It has also been shown that many mediators of stress-limiting systems play a key role in preventing platelet aggregation and adhesion, which can determine their protective effect during stress activation of thrombosis.

CPhA modulate the synthesis of cortisol and adrenocorticotropic hormone under stress, increase the level of neurohormones ("hormones of joy" – endorphins, dopamine), exhibit neuroprotective activity, prolong the stage of resistance of the Selye triad [47, 49]; secondary metabolites of CPhA promote the adaptation of cells to stress, which is called the phenomenon of hormesis or preconditioning [6,7]. Glycyrrhiza glabra significantly reduces the secretion of tumor necrosis factor-α, IL-1β and IL-6, decreases the formation of ROS, inducing phosphorylation of AMPK (AMP-activated protein kinase), which leads to increased activity of antioxidant enzymes [22].

EHF EMR activates mechano-, thermo- and pain receptors and other nerve endings and peripheral fibers located in the skin; the signal from the peripheral nerve endings and fibers enters the central nervous system, which may cause a reflex change in the tone of blood vessels [46]. Circulating catecholamines, norepinephrine and epinephrine, play an important role in the regulation of skin vessels [5, 3, 26]. Normally, when sympathetic innervation is preserved, the effect of blood catecholamines on vascular tone is insignificant, and the regulatory role of circulating catecholamines manifests itself under stress. EHF radiation reduces the stress-induced increase in the content of catecholamines in peripheral blood erythrocytes of animals, the thymus and spleen, structures of mesenteric lymph nodes, up to normalization under the influence of preliminary or subsequent EHF radiation [26, 27].

Effects of low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens on kidney histology

The relationship between MS and chronic kidney disease is controversial, but possible mechanisms of renal impairment may include the systemic release of pro-inflammatory cytokine mediators, free radicals and oxidative stress in MS [28, 29]. Our study also showed structural disturbances in the kidneys associated with metabolic syndrome: abnormalities, especially in the renal cortex, were observed in the glomeruli (G), proximal convoluted tubules (PCTs) and renal stroma, as compared with the control; some glomeruli appeared atrophic (G1), while others appeared hypertrophic (G2). Most of the PCTs appeared degenerated, with widened lumen, interstitial wide spaces (WS), blood extravasation (BE) and infiltration with inflammatory cells. The combination of low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens improved the histological profile of the kidneys. We think that the kidney structure was restored due to the antioxidant effect of the complex phytoadaptogens, as well as the direct effect of EHF EMR on microcirculation, which will be the subject of our further study.

Effects of low-intensity extremely-high-frequency electromagnetic radiation and complex phytoadaptogens on serum chemistry parameters in metabolic syndrome

It was found that the animals on a diet high in carbohydrates and fats had significant increases in total cholesterol (p=0.049), triacylglycerides (p=0.011), LDL (p=0.038), C-reactive protein (p=0.016), as well as a decrease in creatinine (p=0.011) compared with the control. These data are consistent with the pathogenesis of metabolic syndrome.

In our study, the biochemical markers of metabolic syndrome were affected by complex phytoadaptogens – *Glycyrrhiza glabra, Rhodiola rosea, Acanthopanax senticosus*, as well as their combination with EHF therapy. It has been shown that the consumption of *Acanthopanax senticosus* (AS) leaves regulates plasma levels of triglycerides and cholesterol due to the significant fiber content in the leaves, inhibiting the absorption of cholesterol or the reabsorption of bile acids [6, 7]. Dietary fibers increase the excretion of bile acids with feces by increasing the expression level of cholesterol 7a-hydroxylase mRNA (CYP7al), which limits the rate of conversion of cholesterol into bile acids [9].

The effects exerted by AS on lipid metabolism are due to the potential activity of anthocyanins included in the composition. Anthocyanins reduce the accumulation of lipids in the liver and improve insulin sensitivity through 5'AMP-activated protein kinase (AMPK) in peripheral tissues. In the liver, activation of AMPK inhibits the synthesis of fatty acids and cholesterol by phosphorylation and deactivation of acetyl-CoA carboxylase and 3-hydroxy-3-methylglutaryl-CoA responsible for enhancing fat oxidation [6, 7, 22].

Recent studies show that an increase in the production of reactive oxygen species from accumulated fat mass causes increased systemic oxidative stress, contributing to the development of chronic diseases associated with obesity [28, 29]. Obesity-induced oxidative stress in adipose tissue can lead to an increase in inflammatory signals, impaired regulation of adipokines and insulin resistance [29]. Therefore, the use of antioxidants is very important in the treatment of obesity. AS extract increases the activity of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, catalase in the liver of experimental mice with obesity/type 2 diabetes. It was found that AS extract reduces the accumulation of ROS (superoxide anion radical and H_2O_2). The best-known antioxidant of plant origin is *Rhodiola rosea*, which augments the endogenous antioxidant enzymatic response. The use of *Rhodiola rosea* extract inhibits the activity of proline dehydrogenase (PDH) and glucose-6-phosphate dehydrogenase (G6PDH). Inhibition of PDH and G6PDH activity by *Rhodiola rosea* prevents the oxidation of proline necessary for the formation of ATP, which is associated with an endogenous antioxidant enzymatic response via PPR, resulting in inhibition of adipogenesis. *Rhodiola* extract and its main biologically active substance, tyrosol, increase the activity of superoxide dismutase, promoting a decrease in the content of reactive oxygen species during adipogenesis [7, 9, 23].

Glycyrrhizin from *Glycyrrhiza glabra* reduces oxidative stress by decreasing the concentration of free fatty acids, possibly due to the inhibition of ROS formation in metabolic syndrome, which, in turn, reduces oxidative damage to cardiolipin and other enzymes, resulting in an improvement in mitochondrial function. All of the above effects of complex phytoadaptogens can explain the changes over time in blood chemistry parameters in the treatment groups obtained during the experiment [24, 25].

C-reactive protein levels decreased in all treatment groups; there were no significant differences with the control due to the anti-inflammatory effect of complex phytoadaptogens [6, 7].

CONCLUSION

The reported study demonstrated that skin microvessels, blood cells, as well as nerve endings and peripheral nerves of the skin, are directly affected by EMR EHF radiation, this effect is systemic and can trigger reactions from the nervous, endocrine, immune systems with changes in the content or synthesis of biologically active substances (hormones, cytokines, neurotransmitters), which plays an essential role in the mechanisms of regulation of blood microcirculation. This is a very important aspect for the treatment of metabolic syndrome, in which endothelial dysfunction is a key pathophysiological element. Based on the above, phytoadaptogens are promising addition for the treatment of metabolic syndrome, especially in combination with EHF EMR, since their effects potentiate each other. CPhA affect the etiology and pathogenesis of metabolic syndrome by several mechanisms; therefore, they are promising medicines in the complex fight against excess weight.

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