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Neurotropic and immunomodulatory properties of a novel bioflavonoid composition

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ABSTRACT

BACKGROUND: Flavonoids, a class of plant polyphenols, exhibit a wide range of biological (neuro- and immunotropic, antioxidant, anti-inflammatory, epigenome-modulating) properties involved in the mechanisms of management in various pathological processes, including nervous system diseases. Alcoholism is a pervasive social, medical, and economic issue of a modern society. Prolonged exposure to ethanol has a direct and mediated toxic effect on the human body through its metabolites negatively affecting nervous and immune systems that play a major role in adaptation. The ability of bioflavonoids to manage pathological disorders in a wide range of chronic diseases with neuroimmune pathogenesis mechanisms by interacting with specific cell surface receptors can provide therapeutic benefits in alcoholism.

AIM: To assess neurotropic and immunomodulatory properties of a novel curcumin-based bioflavonoid composition during prolonged ethanol consumption.

MATERIALS AND METHODS: The content of bioflavonoids in the composition was measured in aqueous-organic extracts using high-performance liquid chromatography (HPLC). Chronically alcoholized male (CBA × C57Bl/6)F1 mice who received a 10% ethanol solution as the sole source of fluid during six months were administered a bioflavonoid composition during 30 days. Subsequent studies assessed alcohol motivation by consumption of a 10% ethanol solution in free choice with water, as well as behavioral parameters in the open field test, cytokine content in the brain structures (prefrontal cortex, hypothalamus, hippocampus, striatum) using enzyme immunoassay. The intensity of the cellular and humoral immune response was determined by the severity of the delayed-type hypersensitivity response and relative number of splenic antibody-forming cells, respectively.

RESULTS: The quantitative content of bioflavonoids was determined in the composition consisting of curcumin, piperine, soybean isoflavonoids, epigallocatechin-3-gallate, triterpene saponins, and β-carotene. Taking this composition in the context of prolonged ethanol consumption was shown to have a positive effect expressed in correcting the alcoholism-related behavioral phenotype (reduced alcohol motivation, stimulation of locomotor and exploratory activity), accompanied by decreased levels of certain proinflammatory cytokines in the brain structures (most pronounced in the hippocampus). Stimulation of the humoral and cellular immune response was also demonstrated after a course of treatment with the described composition.

CONCLUSIONS: The data support the use of the novel bioflavonoid composition as an additional immunomodulatory and neurotropic agent in the treatment of chronic alcoholism.

Keywords: novel bioflavonoid composition; alcoholism; brain structures; cytokines; immune response.

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Нейротропные и иммуномодулирующие свойства инновационной композиции биофлавоноидов

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АННОТАЦИЯ

Актуальность. Флавоноиды, класс растительных полифенолов, обладают широким спектром биологических свойств — нейро- и иммунотропных, антиоксидантных, противовоспалительных, эпигеном-модулирующих, — вовлеченных в механизмы коррекции при различных патологических процессах, в том числе заболеваниях нервной системы. Алкоголизм — глобальная социальная, медицинская и экономическая проблема современного общества. Длительное воздействие этанола оказывает прямое и опосредованное продуктами его метаболизма токсическое воздействие на организм человека, негативно влияя на функции основных адаптационных систем — нервной и иммунной. Способность биофлавоноидов к коррекции патологических нарушений при широком спектре хронических заболеваний с нейроиммунными механизмами патогенеза путем взаимодействия со специфическими рецепторами на поверхности клеток может обеспечить позитивный терапевтический эффект при алкоголизме.

Цель — оценка нейротропных и иммуномодулирующих свойств инновационной композиции биофлавоноидов на основе куркумина при длительном употреблении этанола.

Материалы и методы. Содержание биофлавоноидов в композиции измеряли в водно-органических экстрактах методом высокоэффективной жидкостной хроматографии. Длительно алкоголизированным мышам-самцам (CBA×C57Bl/6)F1, которые получали 10 % раствор этанола в качестве единственного источника жидкости на протяжении 6 мес., вводили композицию биофлавоноидов в течение 30 дней. Затем оценивали алкогольную мотивацию по потреблению 10 % раствора этанола в условиях свободного выбора с водой, а также параметры поведения в тесте «открытое поле», содержание цитокинов в структурах мозга (префронтальной коре, гипоталамусе, гиппокампе, стриатуме) методом иммуноферментного анализа, интенсивность клеточного (по выраженности реакции гиперчувствительности замедленного типа) и гуморального иммунного ответа (по относительному числу антителообразующих клеток селезенки).

Результаты. Было определено количественное содержание биофлавоноидов в композиции — куркумина, пиперина, изофлавоноидов сои, эпигаллокатехин-3-галлата, тритерпеновых сапонинов и β-каротина. Показано, что прием данной композиции на фоне длительного употребления этанола оказывал позитивный эффект, выражающийся в редактировании характерного для алкоголизма поведенческого фенотипа (снижении алкогольной мотивации, стимуляции локомоторной и исследовательской активности) на фоне снижения уровней ряда провоспалительных цитокинов в структурах мозга, наиболее выраженного в гиппокампе. После курсового приема композиции показана также стимуляция гуморального и клеточного иммунного ответа.

Выводы. Полученные данные позволяют рассматривать возможность применения инновационной композиции биофлавоноидов в качестве дополнительного иммуномодулирующего и нейротропного средства в терапии хронического алкоголизма.

Ключевые слова: инновационная композиция биофлавоноидов; алкоголизм; структуры головного мозга; цитокины; иммунный ответ.

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BACKGROUND

Flavonoids are a class of plant polyphenols that enter the human diet with vegetables, fruits, and other plant foods. Although flavonoids are not essential nutrients, they exhibit a wide range of favorable biological (including neuro- and immunotropic, antioxidant, anti-inflammatory, and epigenome-modulating) effects, which are involved in the mechanisms of management in various pathological processes, such as neurodegeneration, neurotoxicity, and affective disorders.

Currently, alcoholism is a pervasive social, medical and economic issue of the modern society. It affects up to 4% of the adult population worldwide and is one of the leading risk factors for premature death and disability [1, 2]. Decades of research have shown that prolonged exposure to ethanol has a negative effects on functioning of the body's main adaptive systems. Thus, in the nervous system, alcohol affects functioning of almost all neurotransmitter systems (GABA-, dopamine-, serotonin-, acetylcholinergic, glutamate and endocannabinoid), altering the synthesis, release and metabolism of individual neurotransmitters and the process of receptor binding [3]. In addition, ethanol affects various hormones, neuropeptides, growth factors, enzymes, intracellular signaling molecules and transcription factors [4]. During long-term exposure, ethanol affects TLR7 signaling indirectly through Toll-like receptors (TLR), which contributes to neuroinflammation and neurodegeneration. Alcohol has also been shown to change the expression level of miR-let7b, miR-96, miR-182, and miR-155 micro-RNAs and the concentration of mRNA of amphoterin (HMGB1), TLR3, and TLR4 in the nucleus accumbens of the brain in rats after long-term alcohol exposure [5]. Ethanol intake increases lipid peroxidation and the levels of mitochondrial oxidized glutathione (GSSG), interleukin 1 β (IL1β), and tumor necrosis factor-α (TNF-α) in hippocampal tissues of experimental animals. Ethanol also causes a decrease in the activity of glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR), and decreases the levels of CREB transcription factor, brain neurotrophic factor BDNF and apoptosis regulator Bcl 2 [6]. Ethanol alters the activity of neurons, glial cells and their production of neuroimmune regulatory factors [7]. Currently, ethanol-induced behavioral changes, in particular, depressive-like behavior [8], memory impairment [9], neurodegenerative changes, including increased neuron death and decreased neuroplasticity (decreased neurogenesis and BDNF level), mainly in the hippocampus, as well as subclinical changes in other brain structures [10, 11], are associated with neuroinflammatory processes and oxidative stress [12].

Ethanol-induced changes in the immune system functions are another mechanism by which it alters physiological processes in the body [13]. In vivo and in vitro studies demonstrate that ethanol modulates the functional activity of the innate immunity cells. In particular, chronic alcohol abuse leads to suppression of phagocytosis, decreased production of several growth factors (hepatocyte growth factor (HGF), granulocyte colony-stimulating growth factor (G-CSF) and vascular endothelial growth factor (VEGF)), and increased secretion of pro-inflammatory cytokines by mononuclear cells in the blood through stimulation of TLR4, TLR7, and TLR8. Alcohol abuse also affects cell-mediated and humoral immunity by reducing the number of $CD4^+$ and $CD8^+$ lymphocyte subpopulations, altering naive T lymphocyte phenotype conversion and homeostatic proliferation, resulting in an increase in memory T cells [14]. Notably, the increase in the number of memory T cells is associated with the development of chronic inflammatory and age-associated diseases, such as osteoporosis, Alzheimer's disease, autoimmune, cardiovascular diseases, and cancer [13]. A decrease in the pool of naive T cells is associated with a decrease in the formation of an effective immune response to infection and vaccination [15], which is facilitated by functional, transcriptomic and epigenomic changes in monocytes and resident macrophages, increasing inflammation but weakening the antimicrobial response, as well as reducing the levels of circulating factors responsible for the recruitment of immune cells to the infection site (chemokines CCL3/4, metalloproteases MMP 9), but increasing the levels of cytokines IL-2, IL-7, IL-15, IL-12, TNF-α, regulated upon activation, normal T cell expressed and secreted chemokine (RANTES), and T-cell chemoattractant CXCL9 [14, 16].

The mechanisms of ethanol effect on the immune system can be realized both directly by receptor-mediated alteration of the functional phenotype of immunocompetent cells [17], and indirectly by modulating the activity of the hypothalamic-pituitary-adrenal system, thus providing glucocorticoid-mediated potentiation of the components of the innate immunity and suppression of the adaptive immunity through peripheral cytokine-induced activation of the vagus nerve [18]. Disruption of neuroimmune interaction in chronic ethanol intoxication also manifests as changes in the balance of central and peripheral cytokine production, and increased synthesis of autoantibodies to neurotransmitters [19–21]. The severity of clinical manifestations, uncertain prognosis, and insufficient effect of the existing treatment methods determine the need for development of new treatment strategies for alcohol abuse which will address the key mechanisms of pathogenesis of the disease.

Plant polyphenolic compounds can regulate various physiological processes, including protective reactions of the body, and correct pathological processes in a wide range of chronic diseases with neuroimmune pathogenesis mechanisms by interacting with specific receptors

on the surface of immune cells, as well as neurons and microglia, protecting cells from oxidative stress [22, 23]. Thus, bioflavonoids affect the receptor functions of various cytokines, G-protein-coupled receptors (GPCRs), and integrins (transmembrane protein signal transporters). Receptor-mediated signal transduction initiated by bioflavonoids can lead to changes in adhesive properties and cell motility, as well as modulation of gene expression, synthesis and production of biologically active substances, cell proliferation or apoptosis [24]. The primary mechanisms and pathways of bioflavonoid effects mediated by cellular receptor systems are schematically presented in Fig. 1.

Anti-inflammatory, antioxidant, neuroregenerative, and immunomodulatory properties of bioflavonoids, as well as their ability to influence epigenetic mechanisms of gene expression regulation and penetrate the blood-brain barrier, exerting a direct modulatory effect on brain cells, which were described in detail earlier [24], allow us to consider these substances as adjuvants in the therapy of alcohol abuse. We have also shown positive effects of curcumin in experimental alcohol abuse, which are

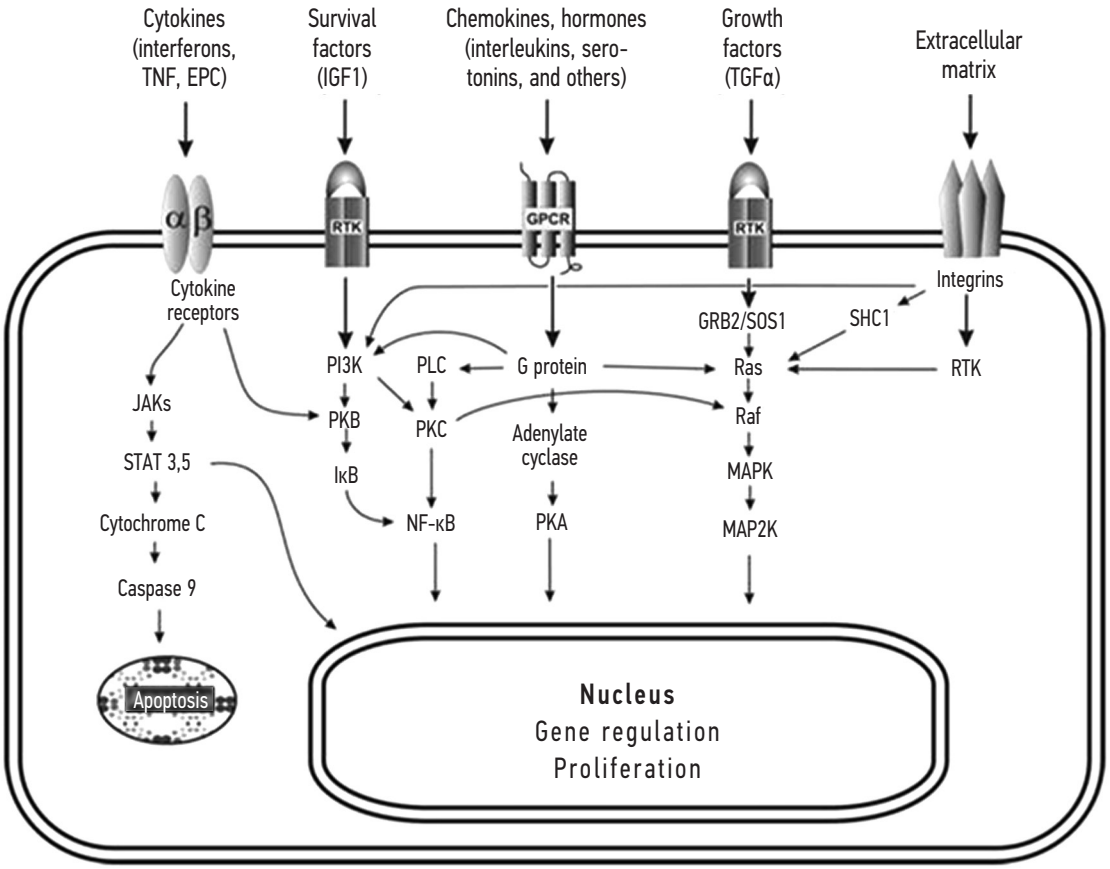

Fig. 1. Pathways of receptor-mediated effects of bioflavonoids on cell functions (according to Nelson J. Structure and function in cell signalling. John Wiley and Sons, Ltd., 2008). RTK, Receptor tyrosine kinase; GPCR, G-protein-coupled receptors; JAK, Janus kinase; STAT, is a member of the transcription factor/signal transducer and activator of transcription family; PKB, Protein kinase B; IκB, nuclear transcription NF-κB factor inhibitor; PLC, protein lipase C; PKC, protein kinase C; PKA, Protein kinase A; GRB2, Growth factor receptor-bound protein 2); SOS1, membrane protein involved in signaling cell growth and differentiation; Ras, a membrane-bound protein of the small GTPases family involved in signal transduction; Raf, proto-oncogene; MAPK и MAP2K, Mitogen-activated protein kinase; SHC1 — SHC-transforming protein 1

Рис. 1. Пути рецептор-опосредованного влияния биофлавоноидов на функции клеток (по: Nelson J. Structure and function in cell signalling. John Wiley and Sons, Ltd., 2008). RTK (Receptor tyrosine kinase) — рецептор тирозинкиназы; GPCR (G-protein-coupled receptors) — рецептор, связывающий G-белки, выполняет функцию активаторов внутриклеточных путей передачи сигнала; JAK (Janus kinase) — Janus-киназа; STAT — член семейства транскрипционных факторов / переносчик сигналов и активатор транскрипции; PKB (Protein kinase B) — протеинкиназа B; IκB — ингибитор ядерного фактора транскрипции NF-κB; PLC — протеинлипаза C (protein lipase C); PKC — протеинкиназа C (protein kinase C); PKA (Protein kinase A) — протеинкиназа A; GRB2 (Growth factor receptor-bound protein 2) — фактор роста; SOS1 — мембранный белок, участвующий в передаче сигналов клеточного роста и дифференцировки; Ras — мембраносвязанные белки семейства малых ГТФаз, участвующие в передаче сигнала; Raf — протоонкоген; MAPK и MAP2K (Mitogen-activated protein kinase) — митоген-активируемые протеинкиназы; SHC1 (SHC-transforming protein 1) — SHC-трансформирующий белок 1, играет важную роль в регуляции апоптоза и лекарственной устойчивости в клетках

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expressed in stimulation of orienting and exploratory behavior, proliferative activity of lymphocytes and cellular immune response [25–27].

A novel curcumin-based bioflavonoid composition (NBC) with therapeutic and preventive properties against age-associated diseases was developed as part of the agreement on scientific and technical cooperation between Research Institute of Fundamental and Clinical Immunology (Novosibirsk, Russia) and Doctor Kornilov LLC (Barnaul, Russia) novel (NBC) (Patent for Invention RU2654868C1) [28].

The study aimed to evaluate the neurotropic and immunomodulatory effects of curcumin-based NBC in long-term alcohol abuse, taking into account the multimodal effects of bioflavonoids.

MATERIALS AND METHODS

The studies were conducted on the NBC, containing turmeric root extract, 37.2% (curcumin content: not less than 95%), black pepper extract, 0.2% (piperine content: not less than 95%), soybean extract, 20% (isoflavones content: not less than 40%), green tea leaf extract, 20% (catechins content: not less than 40%), *Hedysarum* extract, 5% (content of catechins and saponins: not less than 25%), licorice root extract, 2% (content of glycyrrhizic acid: not less than 40%), sea buckthorn leaf extract, 15.6% [28].

Evaluation of bioflavonoids concentration in the composition

The concentration of bioactive substances in the NBC was measured in aqueous-organic extracts by high-performance liquid chromatography on Millichrome F 02 chromatograph with ProntoSil 120-5-C18 AQ column using appropriate eluents; solutions of the respective substances of analytical grade were used as standards.

Measurement of curcumin concentration: distilled water was acidified with phosphoric acid to pH 3.5; the dry substance and methanol were added to a concentration of 50% and extracted at 25 °C with stirring for 2 h. The samples were filtered through a glass filter and diluted with aqueous phosphoric acid at a ratio of 1:4, analyzed in an acetonitrile–aqueous phosphoric acid gradient. The samples were then filtered through a glass filter and diluted with aqueous phosphoric acid at a ratio of 1:4, analyzed in an acetonitrile–aqueous phosphoric acid gradient at pH 3.5 with a methanol gradient of 10 to 90%, flow rate of 100 μL/min, maximum pressure of 1.8 MPa, and column temperature of 30 °C. Detection was performed at a wavelength of 425 nm [29]. Piperine was extracted using methanol at 25 °C with stirring for 4 h; the samples were filtered through a glass filter, diluted with distilled water at a ratio of 1:9 and analyzed in a methanol–water gradient with a methanol gradient of 10 to 90%, flow rate of 100 μL/min, maximum pressure of 1.8 MPa, and column temperature of 25 °C; detection was performed at a wavelength of 343 nm [29]. Soybean isoflavonoids were extracted using a water–methanol mixture at 25 °C with stirring for 24 h; the samples were filtered through a glass filter and analyzed in a methanol–water gradient with a methanol gradient of 10 to 90%, flow rate of 100 μL/min, maximum pressure of 1.8 MPa, and column temperature of 25 °C; detection was performed at a wavelength of 256 nm [30]. Green tea epigallocatechin was extracted using distilled water at 80 °C under reflux and stirring for 2 h; the samples were filtered through a glass filter and analyzed in an acetonitrile–water gradient with an acetonitrile gradient from 10 to 90%, flow rate 100 μL/min, maximum pressure 1.8 MPa, and column temperature 40 °C; detection was performed at a wavelength of 235 nm [31]. Triterpene saponins were extracted from *Hedysarum* using distilled water acidified with phosphoric acid to pH 3.5; the dry substance and chloroform were added and ultrasonicated for 30 minutes; the resulting solution was cooled to 25 °C and filtered through a glass filter; the precipitate was transferred to a ground joint flask; the precipitate content was measured; methanol was added and extracted at 80 °C under reflux with stirring for 2 h; then the samples were filtered through a glass filter and diluted with distilled water in a ratio of 1:9, analyzed in a methanol–aqueous phosphoric acid gradient at pH 3.5 with a methanol gradient of 10% to 90%, flow rate of 100 μL/min, maximum pressure of 1.8 MPa, and column temperature of 30 °C; detection was performed at a wavelength of 210 nm [32]. The carotene content of sea buckthorn leaves was determined using the Murry method with acetone extraction followed by chromatography on an aluminum oxide column [31].

Experimental animals

The studies were performed on 10-month-old male mice (CBA × C57BL/6)F1, received at the age of 3 months from the nursery of the Research Laboratory of Experimental Medicine (Tomsk). The animals were kept in laboratory vivarium conditions, in cages of 10 individuals each, on a standard diet, under natural light regime. All manipulations were performed in the first half of the day.

Taking into account the presence in the population of (CBA × C57Bl/6)F1 mice of subjects with active and passive types of behavior that differ in the level of ethanol consumption [33, 34], the mice were pre-tested in the open field test to form homogeneous experimental groups of animals. Only subjects with an average level of orienting and exploratory behavior (OEB) were included in the study. The parameters of OEB were determined in the open-field test, as we have previously described [25, 33].

Modeling of chronic alcohol intoxication

To create a model of chronic alcohol intoxication, the method of forced intake was used: mice were forced to consume 10% ethanol solution (Kemerovo Pharmaceutical Factory, Russia) as the only source of liquid for 6 months. The formation of ethanol dependence was assessed by a single injection of naloxone (3 mg/kg, subcutaneously) followed by visual registration of withdrawal syndrome signs (convulsions, teeth grinding, wet dog shaking, ptosis, diarrhea). At the next stage, the chronically alcoholized mice were divided into 3 groups: control group 1 (n = 30), where the mice continued to take 10% ethanol solution for 30 days; control group 2 (n = 30), where the mice were administered curcumin (Sigma-Aldrich, USA) through a probe at a rate of 2 mg/mouse in 0.5 mL of 10% ethanol solution with continued free access to 10% ethanol solution as the only source of fluid for 30 days, and experimental group (n = 30), where the mice were administered the NBC through a probe at the rate of 2 mg/mouse in 0.5 mL of 10% ethanol solution with continued free access to 10% ethanol solution as the only source of fluid for 30 days. The fourth group (comparison group) included intact mice of the respective age, which were kept under similar conditions in the vivarium during the entire experimental period, including the formation of alcohol dependence and administration of the NBC. At the end of this period, the severity of alcoholic motivation, OEB parameters, concentration of cytokines in the brain structures, and intensity of humoral and cellular immune response were evaluated. At the end of experiments, the animals were decapitated under ether anesthesia.

Study of alcoholic motivation

Alcoholic motivation of animals in control and experimental groups was evaluated by consumption of 10% ethanol solution in free choice with water. For this purpose, two drinking bowls (with water and 10% ethanol solution) were located in each cage to allow the mice to consume fluids according to individual demand (two-bottle oral test). Quantitative consumption of 10% ethanol solution and water by mice in control and experimental groups (mL/day × mouse) was recorded daily at 10 A.M. for 10 days, starting from the first day after the end of the NBC administration.

Study of cytokine content

The quantitative concentration of cytokines in the brain structures was determined in the lysates of individual structure samples (hippocampus, hypothalamus, striatum, frontal cortex) by enzyme-linked immunosorbent assay (ELISA). The lysates of the brain structures were obtained by homogenization of tissues in RPMI 1640 medium with 0.1% Triton X 100 (GERBU Biotechnik GmbH, Germany), followed by centrifugation for 3 min at 10,000 rpm. The supernatant was used for the study. The concentration of cytokines in the samples was evaluated using eBioscience test systems (BenderMed Systems, Austria) for the measurement of IFN-γ, IL-6 and R&D Systems Inc. (USA) for the measurement of IL-1β, IL-10, TNF-α according to the manufacturers; instructions. The optical density of the samples was measured using an Anthos 2020 vertical light transmission spectrophotometer (Anthos Labtec Instruments GmbH, Austria) at a wavelength of 450 nm. The results were presented as mass concentration (pg) per mg of tissue.

Immune response study

The intensity of humoral immune response was determined based on the number of antibody-forming cells (AFC) of the spleen by the modified Cunningham method on Day 5 after intraperitoneal immunization with a T-dependent antigen (sheep red blood cells, SRBC) using the number of local hemolysis zones in semi-liquid medium. For this purpose, the spleen was minced; the cell suspension was filtered, and the final volume was diluted to 5 mL. Equal volumes of the cell suspension, 10% SRBC suspension and complement solution were mixed and poured into glass chambers, which were incubated for 45 min at 37 °C. Then the number of local hemolysis zones was counted under a binocular magnifying glass. The number of hemolysis zones per chamber, the number of nucleus-containing cells per 1 mL of cell suspension, the volume of the filled chamber, and the cellularity of the spleen were considered. The relative (per 106 nucleus-containing cells in the spleen) number of AFC was estimated. The intensity of cellular immune response was evaluated by the level of delayed hypersensitivity (DHS) reaction formed in response to the introduction of the T-dependent antigen, SRBC. For this purpose, mice were immunized by intraperitoneal injection of SRBC (0.5% SRBC, 0.5 mL). A challenging dose of antigen (50% SRBC, 0.05 mL) was injected under the aponeurosis of the foot of the hindlimb 96 h after immunization. The formation of the DHS response was assessed 24 h after the challenging injection of the antigen, by the degree of changes in the hindlimb thickness compared to the positive control hindlimb of the same animal in which RPMI 1640 medium was injected. The response index (RI) was determined for each mouse using the formula $RI = (R_e - Rc_к) / R_c$ and expressed as a percentage [35].

Statistica 10.0 commercial software package (StatSoft, USA) was used for statistical analysis of the results. The results were presented as a median and an interval between the 1st and 3rd quartile: Me [Q_1; Q_3]. The Mann–Whitney test was used to compare independent samples when the number of groups was equal to 2. The Kruskal–Wallis test was used to compare the values when the number of groups was >2. The critical level of significance for statistical hypothesis testing in the study was $p < 0.05$.

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RESULTS AND DISCUSSION

In the study, the bioflavonoid concentration in the NBC was determined to be as follows: curcumin, 13.6 ± 0.3 mg/g; piperine, 7.2 ± 0.1 mg/g; soy isoflavonoids, 15.5 ± 0.4 mg/g; epigallocatechin 3-gallate, 72.7 ± 0.8 mg/g; triterpene saponins, 8.8 ± 0.1 mg/g; β-carotene, 0.4 ± 0.02 mg/g.

When evaluating the alcoholic motivation of chronically alcoholized animals after the course of NBC, a lower average daily consumption of 10% ethanol by animals in the experimental group was found compared to the control group of chronically alcoholized mice: 4.9 [4.5; 5.1] mL/(day × mouse) in the control group and 1.9 [1.7; 2.2] mL/(day × mouse) in the experimental group, $p = 0.038$, Mann–Whitney *U* test. Meanwhile, the water consumption of mice under free-choice conditions after the NBC administration was significantly higher at 3.2 [2.9; 3.5] mL/(day × mouse) compared to that in the control group, 0.4 [0.0; 0.4], $p = 0.028$, Mann–Whitney *U* test.

In the study of OEB in the open field test, a stimulation of behavioral activity was found in animals injected with the NBC, which was expressed as an increase in the motor behavior indices (horizontal motor activity: experimental group: 75.2 [73.1; 77.8] for peripheral activity, 2.4 [2.1; 2.7] for central activity, 77.8 [75.0; 79.4] for total activity; control group of chronically alcoholized mice: 46.8 [45.1; 47.9] for peripheral activity, $p = 0.017$, Mann–Whitney *U* test, 1.3 [1.2; 1.5] for central activity, $p = 0.024$, Mann–Whitney *U* test, 48.9 [46.5; 49.7] for total activity, $p = 0.014$, Mann–Whitney *U* test) and the exploratory behavior component (vertical rearing: experimental group, 0.0 [0.0; 0.1] for unsupported rearing, 4.5 [4.3; 4.7] for wall-supported rearing, 4.4 [4.3; 4.7] for total activity; control group of chronically alcoholized mice: 0.0 [0.0; 0.1] for unsupported rearing, $p = 0.012$, Mann–Whitney *U* test, 2.3 [2.1; 2.4] for wall-supported rearing, $p = 0.026$, Mann–Whitney *U* test, 2.3 [2.1; 2.4] for total activity, $p = 0.024$, Mann–Whitney *U* test). Under the effect of curcumin, the motor activity indices changed (horizontal: 64.3 [47.2; 67.8] for peripheral activity, $p = 0.051$, Mann–Whitney *U* test, 2.1 [1.8; 2.3] for central activity, $p = 0.062$, Mann–Whitney *U* test, 67.3 [45.9; 69.1] for total activity, $p = 0.059$, Mann–Whitney *U* test, compared to the performance in the animals that were administered the NBC); and the exploratory behavior component (vertical rearing: 0.0 [0.0; 0.2] for unsupported rearing, $p = 1.0$, Mann–Whitney *U* test, 4.0 [3.3; 4.5] for wall-supported rearing, $p = 0.069$, Mann–Whitney *U* test, 4.4 [4.3; 4.7] for total activity, $p = 0.084$, Mann–Whitney *U* test).

The neuroinflammation that is typical of chronic alcohol abuse is due to both the direct interaction of ethanol with neuronal and immune cells in the brain and the induction of inflammation in the periphery. It is known that chronic ethanol exposure leads to increased production of proinflammatory cytokines IL-1β, IL-6, IL-12, TNF-α, IFN-γ and neuroinflammation-induced increase in the blood-brain barrier permeability [36].

When studying the effect of the NBC on the quantitative concentration of some cytokines that are pathogenetically significant for chronic alcohol abuse in the brain structures of chronically alcoholized mice, a decrease in the levels of IL-1β, IL-6, IFN-γ, TNF-α in the prefrontal cortex, hypothalamus, hippocampus and striatum was registered, along with an increase in the content of IL-10 in the hypothalamus and hippocampus (see Table 1).

According to the data summarized in Table 1, the most pronounced changes in the concentration of proinflammatory cytokines were found in the hippocampus. Considering that ethanol consumption causes prolonged activation of microglia mainly in the hippocampus, mediated by TLR [37], we can assume the influence of the NBC on the activity of microglia, acting as a source of neuroinflammatory signals, which is expressed in the reduced neuroinflammation. Studies in animal models have shown that neuroinflammation contributes to the maintenance of alcohol dependence [36, 38]. Pro-inflammatory cytokines are also triggers of depression-like behavior in alcoholism. This study revealed a reduction in the levels of proinflammatory cytokines in the brain structures pathogenetically relevant in alcohol abuse, indicating a decrease in neuroinflammation, which may also be one of the mechanisms of the above-demonstrated positive effects of the NBC on alcoholic motivation and motor activity in chronically alcoholized mice.

Recent studies show that dietary flavonoid intake exerts neuroregulatory effects through a variety of direct (local) and indirect (systemic) mechanisms, schematically presented in Fig. 2. Flavonoids can penetrate the blood-brain barrier and cumulate in the central nervous system, counteracting the accumulation of reactive oxygen species, promoting neuron survival and proliferation by inhibiting neuroinflammatory and oxidative stress responses. Moreover, the gut microbiota is also involved in the regulation of brain function and behavior through the production of bioactive metabolites. Flavonoids can form the composition of the gut microbiota by acting as carbon substrates, promoting the growth of probiotic flora that produce neuroprotective metabolites. By influencing the microbiota-gut-brain axis, flavonoids mediate effects on brain function.

As already mentioned, the immune system plays a significant role in the development and maintenance of alcohol dependence. Therefore, there is a growing interest in the development of methods of immunotherapy of alcoholism. We investigated the effects of a course of NBC on the main players of the immune response in chronically alcoholized mice. The level of development of the DHS response was found to be significantly reduced in the group of chronically alcoholized mice (control group 1), which corresponds to the literature data on

Table. Cytokine content in the brain structures of chronically alcoholized male mice (CBA × C57Bl/6)F1 after a course of intragastric administration of the novel bioflavonoid composition, *Me* [Q_1; Q_3]

Таблица. Содержание цитокинов в структурах головного мозга длительно алкоголизированных мышей-самцов (CBA×C57Bl/6)F1 после курсового внутрижелудочного введения инновационной композиции биофлавоноидов, *Me* [Q_1; Q_3]

Group of animals	Cytokine concentration, pg/mL of tissue			
	Prefrontal cortex	Hypothalamus	Hippocampus	Striatum
		IL-1β		
Control	165.2 [151.8; 179.3]	180.2 [172.1; 192.5]	206.1 [196.0; 224.3]	124.9 [114.7; 135.0]
Experimental	82.3 [77.1; 89.2]*, p = 0.001	183.0 [172.7; 193.1], p = 0.074	205.5 [195.3; 215.6], p = 0.082	83.6 [73.4; 93.7]*, p = 0.001
		IL-6		
Control (n = 30)	230.9 [215.8; 266.1]	172.0 [157.2; 179.1]	308.2 [298.0; 319.4]	325.9 [315.7; 346.0]
Experimental (n = 30)	235.4 [215.3; 255.7], p = 0.057	153.3 [144.0; 163.4], p = 0.055	214.0 [193.8; 227.2]*, p = 0.001	326.0 [315.9; 346.1], p = 0.234
		IL-10		
Control (n = 30)	176.1 [132.9; 193.3]	128.7 [101.4; 152.5]	352.6 [324.5; 373.4]	249.5 [229.2; 259.8]
Experimental (n = 30)	173.6 [131.3; 181.9], p = 0.095	236.4 [226.2; 248.7]*, p = 0.001	413.9 [404.5; 428.1]*, p = 0.002	230.8 [223.3; 250.9], p = 0.120
		IFN-γ		
Control (n = 30)	49.3 [44.0; 54.9]	93.9 [81.2; 99.3]	105.1 [94.7; 124.2]	47.5 [34.9; 55.4]
Experimental (n = 30)	28.0 [27.7; 34.1]*, p = 0.030	97.8 [83.4; 97.9], p = 1.000	64.5 [53.3; 72.8]*, p = 0.030	54.9 [44.6; 63.3], p = 0.098
		TNF-α		
Control (n = 30)	241.5 [231.2; 252.8]	238.8 [218.5; 249.0]	247.1 [236.8; 257.4]	150.9 [142.4; 163.1]
Experimental (n = 30)	184.8 [171.6; 195.0]*, p = 0.040	230.1 [219.8; 240.3], p = 0.20	248.5 [228.2; 258.8], p = 0.450	153.0 [132.7; 165.1], p = 0.150

*Significant difference (p < 0.05) between the corresponding parameters in the samples from the control group (chronically alcoholized mice) and the experimental group (chronically alcoholized mice that received the novel bioflavonoid composition).
*Достоверные различия (p < 0,05) между соответствующими показателями в образцах контрольной группы (длительно алкоголизированные мыши) и экспериментальной группы (длительно алкоголизированные мыши, получавшие инновационную композицию биофлавоноидов).

immunosuppression induced by chronic ethanol exposure [40]. After administration of the NBC, the level of DHS in chronically alcoholized mice was close to that seen in the intact group and exceeded this index in the group of chronically alcoholized mice which was administered only curcumin (control group 2; Fig. 3), suggesting that the NBC stimulates the cellular immune response.

After administration of the NBC, a significant stimulation of the humoral immune response was also observed, assessed by the relative number of spleen AFCs, which, as expected, was significantly reduced in control group 1 (chronically alcoholized mice). Moreover, the intensity of humoral immune response under the influence of the NBC also exceeded that under curcumin administration (control group 2), which indicates the synergism of bioflavonoid effects in the NBC (Fig. 4).

The obtained results allow us to reasonably declare the presence of immunostimulatory properties of the NBC.

Bioflavonoids with a wide range of biological activity were included in the composition of the NBC used in the experiments. Thus, turmeric, a product from the rhizomes of the *Curcuma longa* L. plant belonging to the ginger family, is considered to be one of the most active spices due to a high content of hydrophobic polyphenols of the curcuminoid family [41]. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione) is considered one of the most active components of this group of compounds [42, 43]. The ability of curcumin to interact with various proteins and modulate signal transduction functions is associated with its effects on many acute and chronic pathological processes. Studies have shown that curcumin modulates a variety of molecules in the cellular signal transduction pathway including PI3K, Akt, mTOR, ERK5, AP-1, TGF-β, Wnt, β-catenin, Shh, PAK1, Rac1, STAT3, PPARγ, EBPα, NLRP3 inflammasome, p38MAPK, Nrf2, Notch-1, AMPK, TLR4 and MyD-88. Curcumin has also been shown to inhibit Th17 cell proliferation and reduce the production of inflammatory cytokines

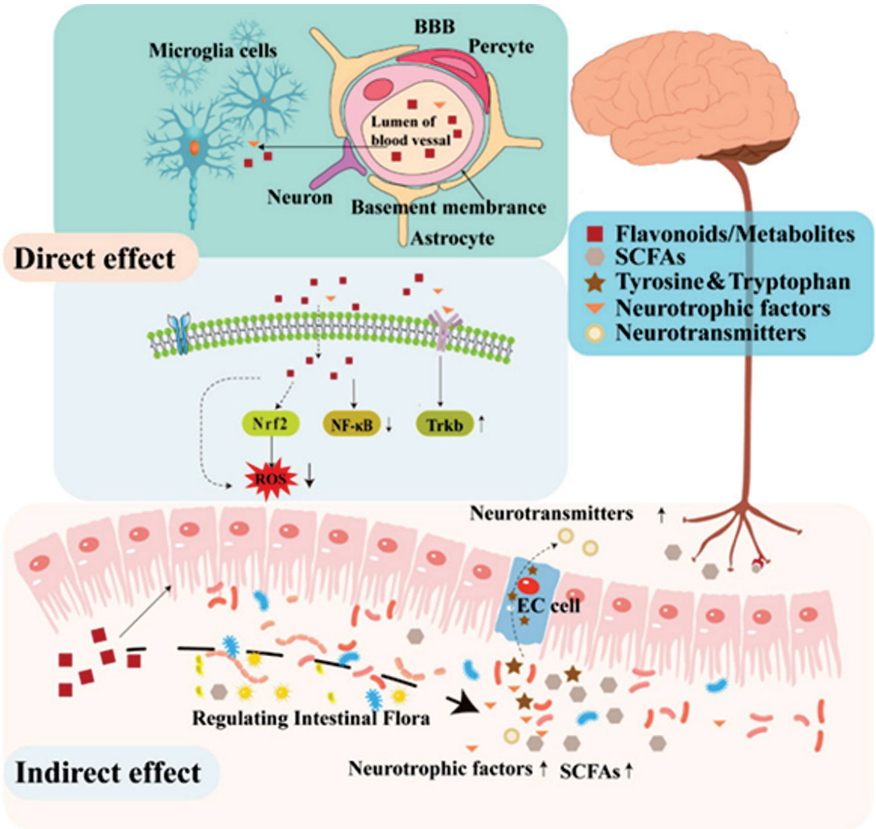

Fig. 2. The neuroregulatory effects of flavonoids (according to Wang H. et al. [39]). BBB, Blood-brain barrier; Nrf2, Nuclear erythroid 2-related factor 2; NF-κB, nuclear transcription factor κB; Trkb, Tropomyosin receptor kinase B; ROS, Reactive oxygen species; ES cell, human embryonic stem cells; SCFAs, Short-chain fatty acids

Рис. 2. Нейрорегуляторное действие флавоноидов (по: Wang H. и соавт., 2023 [39]). Direct effect — прямое действие; Indirect effect — непрямое действие; BBB (Blood-brain barrier) — гематоэнцефалический барьер; Nrf2 (Nuclear erythroid 2-related factor 2) — ядерный эритроидный фактор 2; NF-κB (nuclear transcription factor κB) — ядерный фактор транскрипции κB; Trkb (Tropomyosin receptor kinase B) — тропомиозиновый тирозинкиназный рецептор; ROS (Reactive oxygen species) — активные формы кислорода; ES cell (human embryonic stem cells) — эмбриональные (стволовые) клетки человека; SCFAs (Short-chain fatty acids) — короткоцепочечные жирные кислоты; Microglia cells — клетки микроглии; Neuron — нейрон; Percyte — перициты; Lumen of blood vessal — просвет кровеносного сосуда; Basement membrane — базальная мембрана; Astrocyte — астроцит; Regulating intestinal Flora — регулирующая флора кишечника; Neurotrophic factors — нейротрофные факторы; Neurotransmitters — нейротрансмиттеры

including IL-1β, TNF-α, IL-22 and IL-17, which, in turn, reduces the severity of systemic inflammation [43, 44]. The neuroprotective properties of curcumin are realized through several mechanisms. Curcumin can neutralize free radicals and enhance the activity of antioxidant enzymes (superoxide dismutase, SOD; catalase, CAT; glutathione peroxidase, GPx), protecting neurons from oxidative stress. Curcumin has an anti-inflammatory effect by inhibiting inflammatory markers, such as TNF-α, IL-1β and IL-6, thereby reducing the severity of inflammatory reaction in the brain tissue [45]. In addition, this bioflavonoid inhibits the activity of pro-inflammatory enzymes (COX 2 and iNOS), resulting in decreased levels of prostaglandins and nitric oxide, modulates the signaling pathways of NF-κB, a key transcription factor, involved in the regulation of inflammatory responses, along with Wnt5 (a member of the Wnt5A family) and JNK1 (N-terminal c-Jun kinases), which are crucial for neuronal activity, cell survival, inflammation, and apoptosis [46].

The efficacy of curcumin has been demonstrated in neurodegenerative diseases [47–49], depression. According to numerous non-clinical studies, curcumin has antidepressant effects in animal models, with effects resembling those of antidepressants such as fluoxetine and imipramine [50, 51]. Another antidepressant mechanism of action of curcumin is related to the inhibition of nuclear factor transcriptional signaling pathways, reducing neuroinflammation [52]. In addition, curcumin increases brain-derived neurotrophic factor (BDNF) levels, which are reduced in depression [53]. The results of a meta-analysis on people with depression also showed that curcumin reduces the severity of symptoms of depression and anxiety [54], which opens the possibility of its use in the treatment of depressive disorders.

Curcumin has also been found to be effective in alcoholism. It is assumed that curcumin acts as a neuroprotective agent in alcohol abuse due to activation of the CREB–BDNF signaling pathway [6]. In addition, in mice

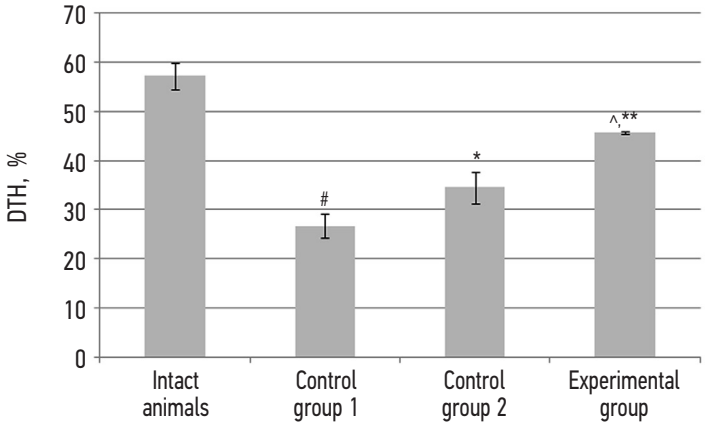

Fig. 3. The severity of a delayed-type hypersensitivity (DTH) response in chronically alcoholized mice (CBA × C57Bl/6)F1 after a course of intragastric administration of the novel bioflavonoid composition. *n* = 30 in each group; $^{\#}p$ = 0.002 between the values in intact animals and in the control group 1 (alcoholized animals); $^{*}p$ = 0.061 between the values in the control group 1 (alcoholized animals) and the control group 2 (alcoholized animals receiving curcumin); $^{\wedge}p$ = 0.011 between the values in the control group 2 (alcoholized animals receiving curcumin) and the experimental group (alcoholized animals receiving the novel bioflavonoid composition); $^{**}p$ = 0.054 between the parameters in the control group 2 (alcoholized animals) and the experimental group (alcoholized animals receiving the novel bioflavonoid composition)

Рис. 3. Выраженность реакции гиперчувствительности замедленного типа (ГЗТ) у длительно алкоголизированных мышей (CBA×C57Bl/6)F1 после курсового внутрижелудочного введения инновационной композиции биофлавоноидов. *n* = 30 — в каждой группе; $^{\#}p$ = 0,002 между показателями у интактных животных и в контрольной группе 1 (алкоголизированные животные); $^{*}p$ = 0,061 между показателями в контрольной группе 1 (алкоголизированные животные) и контрольной группе 2 (алкоголизированные животные, получавшие куркумин); $^{\wedge}p$ = 0,011 между показателями в контрольной группе 2 (алкоголизированные животные, получавшие куркумин) и экспериментальной группе (алкоголизированные животные, получавшие инновационную композицию биофлавоноидов); $^{**}p$ = 0,054 между показателями в контрольной группе 2 (алкоголизированные животные) и экспериментальной группе (алкоголизированные животные, получавшие инновационную композицию биофлавоноидов)

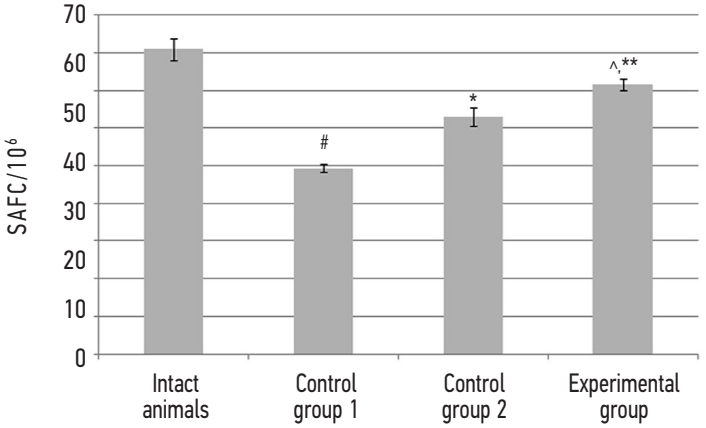

Fig. 4. Splenic antibody-forming cells (SAFC) count in alcoholized mice (CBA × C57Bl/6)F1 after a course of intragastric administration of the novel bioflavonoid composition. *n* = 30 in each group; $^{\#}p$ = 0.003 between the values in intact animals and in the control group 1 (alcoholized animals); $^{*}p$ = 0.041 between the values in the control group 1 (alcoholized animals) and the control group 2 (alcoholized animals receiving curcumin); $^{\wedge}p$ = 0.047 between the values in the control group 2 (alcoholized animals receiving curcumin) and the experimental group (alcoholized animals receiving the novel bioflavonoid composition); $^{**}p$ = 0.0006 between the parameters in the control group 1 (alcoholized animals) and the experimental group (alcoholized animals receiving the novel bioflavonoid composition)

Рис. 4. Количество антителообразующих клеток селезенки (АОК) алкоголизированных мышей (CBA×C57Bl/6)F1 после курсового внутрижелудочного введения инновационной композиции биофлавоноидов. *n* = 30 — в каждой группе; $^{\#}p$ = 0,003 между показателями у интактных животных и в контрольной группе 1 (алкоголизированные животные); $^{*}p$ = 0,041 между показателями в контрольной группе 1 (алкоголизированные животные) и контрольной группе 2 (алкоголизированные животные, получавшие куркумин); $^{\wedge}p$ = 0,047 между показателями в контрольной группе 2 (алкоголизированные животные, получавшие куркумин) и экспериментальной группе (алкоголизированные животные, получавшие инновационную композицию биофлавоноидов); $^{**}p$ = 0,0006 между показателями в контрольной группе 1 (алкоголизированные животные) и экспериментальной группе (алкоголизированные животные, получавшие инновационную композицию биофлавоноидов)

with ethanol-induced tissue damage, oral administration of curcumin reduced the severity of oxidative stress and protected the gastric mucosa [55]. As mentioned above, we have also previously shown the effects of curcumin on behavioral and immunological parameters in experimental alcoholism.

Among the methods aimed at increasing the bioavailability of curcumin, the combination of curcumin with piperine was demonstrated to be effective [43]. As shown in this study, in addition to curcumin, the NBC also contains piperine, which increases curcumin bioavailability by inhibiting its glucuronidation and increasing its transport into plasma; piperine also has antioxidant, antitoxic, and anticarcinogenic properties [24, 43]. Soy isoflavonoids, which are present in the NBC. are characterized by high antioxidant activity and anti-inflammatory properties (decreased IL-18 levels) [24, 56]. Epigallocatechin 3-gallate, a green tea flavonoid, can neutralize the damaging effect of high concentrations of cytokines that occur during inflammation, and in the presence of IL-1β it inhibits MAPKs, degradation of IRAK-1 and reduces the activity of NF-κB, p38 and JNK effectors, which play a key role in the transcription of inflammatory response genes in cells [57]. Saponins, complex organic compounds of plant glycosides with surfactant properties, are present in the rhizomes of *Hedysarum*. The chemical properties of saponins are due to the aglycon structure, the presence of distinct functional groups and glycosidic linkage. Saponins from various plants also increase the bioavailability of curcumin while possessing neurotrophic, hypotensive, hypocholesterolemic, diuretic, adaptogenic and sedative properties [58]. β-Carotene is the most abundant carotenoid of the terpenoid group, it is a potent antioxidant, which also has immunostimulatory and adaptogenic properties [59].

Thus, the study demonstrated that combination of curcumin with the mentioned bioflavonoids in the NBC in pharmacologically significant concentrations leads to synergism of their effects, leading to a significant reduction in the severity of neuro- and immunotoxic effects of chronic ethanol consumption, which allows us to consider the potential of using this composition as an immunomodulatory and neurotropic agent in the complex therapy of chronic alcoholism.

CONCLUSIONS

1. The novel bioflavonoid composition analyzed in this study contains a complex of biologically active components, including curcumin, piperine, soy isoflavonoids, epigallocatechin 3-gallate, triterpene saponins, and β-carotene in pharmacologically significant amounts.

2. Administration of this composition along with chronic ethanol use has a positive effect aimed at reducing the severity of changes in the functional activity of the nervous system caused by chronic toxic influence (reduction in alcoholic motivation, stimulation of orientation and research behavior, modulation of the level of pro-inflammatory cytokines in the central nervous system, indicating a decrease in neuroinflammation) and the immune system (stimulation of humoral and cellular immune response).

ADDITIONAL INFO

Author's contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of the authors: I.A. Goldina — concept and design of the study, literature review, data analysis, writing the text, making final edits; E.V. Markova — head of the research topic «Experimental substantiation of the development of new technologies for immunotherapy of behavioral and addictive disorders in models of stress-induced depression/aggression and alcoholism», study concept and design, literature review, data analysis, text writing, making final editing; I.V. Savkin — modeling of chronic alcoholism, data analysis, chromatographic research; O.S. Anikeeva, A.V. Smyk — conducting experiments on the bioflavonoides influence on long-term alcoholized animal's alcohol motivation and behavior in the "Open Field" test; E.V. Serenko — conducting experiments on the bioflavonoids effect on the cytokines content in brain structures and the immune response intensity; T.V. Shushpanova — consultant for the chemical part of the study; M.A. Knyazheva — conducting experiments on the bioflavonoids effect on the cytokines content in brain structures and the immune response intensity.

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Competing interests. The authors declare that they have no competing interests.

Ethics approval. The protocol of the study was approved by the local Ethics Committee of the Federal State Budgetary Scientific Institution "Research Institute of Fundamental and Clinical Immunology" (No. 139 of 2022 May 30).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Личный вклад каждого автора: И.А. Гольдина — концепция и дизайн исследования, обзор литературы, обработка данных, написание текста, внесение окончательной правки; Е.В. Маркова — руководитель темы НИР «Экспериментальное обоснование разработки новых технологий иммунотерапии поведенческих и аддиктивных расстройств

в моделях стресс-индуцированной депрессии/агрессии и алкоголизма», концепция и дизайн исследования, обзор литературы, обработка данных, написание текста, внесение окончательной правки; И.В. Савкин — моделирование хронического алкоголизма, обработка данных, хроматографическое исследование; О.С. Аникеева, А.В. Смык — проведение экспериментов по влиянию ИНС на алкогольную мотивацию и поведение длительно алкоголизированных животных в тесте «открытое поле»; Е.В. Серенко — проведение экспериментов по влиянию биофлавоноидов на содержание цитокинов в структурах мозга и интенсивность иммунного ответа; Т.В. Шушпанова — консультант по проведению химической части исследования; М.А. Княжева — проведение экспериментов по влиянию биофлавоноидов на содержание цитокинов в структурах мозга и интенсивность иммунного ответа.

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Конфликт интересов. Авторы заявляют об отсутствии потенциального конфликта интересов, требующего раскрытия в данной статье.

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