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## Effect of *Salvia officinalis* and *S. sclarea* on rats with a high-fat hypercaloric diet

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Phytotherapy for the correction of excess body weight is widely used. However, a comprehensive study of herbal preparations on the organism of model animals has been carried out only for a few plant species. Supplementing the diet of rats with closely related sage species (*Salvia officinalis* L. and *S. sclarea* L.) against the background of high-fat hypercaloric diet triggered multidirectional changes in their metabolism. The addition of crushed dry shoots of *S. officinalis* to the diet of animals led to a sharp increase in their body weight (up to 130.8% of the initial one in 30 days of the experiment). The body weight of the rats treated with *S. sclarea* for 30 days increased only up to 103.8% of their initial weight and was lower than in the control group. Addition of *S. officinalis* caused an increase in daily weight gain up to 253.1% of the control group, and *S. sclarea* – its decrease to 27.8% of the daily weight gain in the control group. In the *S. officinalis* group, the relative weight of the brain, spleen, and thymus decreased, while in the *S. sclarea* group, the relative weight of the thymus decreased and that of the colon increased. Under the influence of *S. officinalis*, the concentration of urea, total bilirubin, and triglycerides in the blood plasma of male rats decreased and the concentration of total protein and the activity of alkaline phosphatase increased. While consuming *S. sclarea* shoots, there was an increase of alkaline phosphatase activity in the rats' blood, but atherogenic index (23.1% of the level of the control group) sharply dropped due to an increase in the concentration of high-density lipoprotein cholesterol (286.9% of the control) and a decrease in the concentration of low-density lipoprotein cholesterol (67.7% of control). In rats feeding on *S. sclarea* shoots, we observed a decrease in the concentration of triglycerides in the blood (39.9% of the control), a decrease in the activity of gamma-glutamyl transferase (62.8%), and an increase in the Ca/P ratio (132.5% of the control group). No significant changes were observed in CBC and WBC differential of male rats when eating *S. officinalis* and *S. sclarea* shoots. According to the results of the open field test, the physical and orientational activity of male rats under the influence of *S. officinalis* significantly decreased by the end of the experiment. Emotional status of rats, on the contrary, decreased when they ate dry crushed shoots of *S. sclarea* in the composition of the food. Thus, excess body weight of rats in the conditions of hypercaloric diet led to more pronounced deviations from the norm while consuming dry crushed shoots of *S. officinalis*. The addition of *S. sclarea* dry crushed shoots to the animals' diet normalized the body weight in comparison with the control group, reduced the negative manifestations of obesity at the biochemical and organismal levels. In this regard, the substances that contain *S. sclarea* should be carefully studied for anti-atherosclerotic activity, and tea supplemented with *S. sclarea* shoots can be recommended as a corrective supplement in the diet of overweight people.

**Keywords:** relative mass of the organs; increase in the body weight; high-fat diet; garden sage; clary sage; phytotherapy; obesity correction.

### Introduction

Aromatic plant species of the genus *Salvia* are important medicinal herbs that are highly recommended because of their therapeutic properties: antiseptic, antispasmodic, antimicrobial, antirheumatic, antidiabetic and flatus-relieving (Pop et al., 2016; Jakovljević et al., 2019; Ghowsi et al., 2020). Species of the *Salvia* genus have significant antioxidant and anti-proliferative properties against tumour cells (Loizzo et al., 2014). Sage antioxidant features are explained by a high level of phenolic compounds (Hudz et al., 2019).

Abietane diterpenoids (ADs) – compounds synthesized from the roots of various species of *Salvia* – contain aethiopinone, 1-oxoaethiopinone, salvipisone, and ferruginol, which displayed promising cytotoxic activity toward several lines of human tumour cells, e.g., the breast adenocarcinoma MCF7, HeLa, epithelial carcinoma, prostate adenocarcinoma PC3, and human melanoma A375 (Vaccaro et al., 2020). Aethiopinone, an o-naphtho-quinone diterpene, produced from the roots of various *Salvia* plants, exerted selective cytotoxicity against the A375 melanoma cell line (Vaccaro et al., 2019). Such compounds as ferruginol, salvipisone, and carnosic acid also showed antiproliferative activity (Vaccaro et al., 2019). The antioxidant activity of these extracts was evaluated *in vitro* using

DPPH (alpha, alpha-diphenyl-beta-picrylhydrazyl), FRAP (ferric reducing antioxidant power) and HAPX (haemoglobin / ascorbate peroxidase activity inhibition) methods (Hanganu et al., 2019). The polyphenolic profile of some *Salvia* species (*S. aetiopsis*, *S. austriaca*, *S. sclarea*, *S. mutans*, *S. verticillata* and *S. nemorosa*) was found to have some common elements (caffeic acid, p-cumaric acid, isoquercitrin, hyperoside, luteolin, apigenin) and other rare compounds (chlorogenic acid, caftaric acid, ferulic acid, quercitrin, rutin, quercetin, kaempferol). All studied species of the *Salvia* genus were confirmed to contain significant amounts of polyphenolic compounds (22.25–118.75 mg GAE/g dry weight material plant) and could be used as a valuable resource of natural antioxidants together with *S. officinalis*, the most known one (Francik et al., 2020).

It was found that extracts from collected plants were effective antioxidants in three different *in vitro* assays (DPPH, ABTS, FRAP and superoxide anion scavenging activity) (Vergine et al., 2019). Therefore, they can be used as natural ingredients in herbal medicines, functional foods, or as bioactive molecules sources.

Common sage (*S. officinalis* L.) is a well-known medicinal plant that is cultivated in several European countries. In sage, leaves or flowering tops are used as raw materials. The value of sage as a medicinal herb lies in its essential oil, which contains D- $\alpha$ -pinene, cineole (about 15%),  $\alpha$ - and

$\beta$ -thujone, D-borneol and D-camphor. The leaves also contain alkaloids, flavonoids, tannins, oleanolic and ursolic acids, and the fruits contain 19–25% fatty oil, represented mainly by linoleic acid glycerides. Having confirmed antioxidant properties, *S. officinalis* was used as a reference plant (Miliauskas et al., 2004). Free radical bounding capacities of extracts and their total content of phenolic compound were observed to correlate.

Clary sage (*S. sclarea* L.) is an equally important medicinal herb of this genus. It is a widespread field crop used for essential oil production (Cui et al., 2015; El-Gohary et al., 2020; Grigoriadou et al., 2020; Tutto-lomondo et al., 2020). Essential oil of clary sage is isolated from the flowers and leaves. The plant is cultivated in Moldova, Russia, Bulgaria, France, Germany and other countries. Currently, there are micropropagation techniques to industrially produce clonally stable clary sage plants that would be used for commercial purposes (Erisen et al., 2020).

The essential oils of *S. sclarea* have been known since Ancient Greece (Pitarokili et al., 2002). Sixty six compounds have been identified, which is 93.3–98.2% of oils, their main compounds are linalyl acetate (19.8–31.1%), linalool (18.5–30.4%), geranyl acetate (4.5–12.1%), and  $\alpha$ -terpineol (5.1–7.6%). There are two types of aromatic products – sage concrete and sage absolute. The essential oil of varies in composition depending on the sage's growing conditions and is determined by a wide variety of environmental factors (Dogana, 2020). It was found that the rate of essential oil in the plant grown without boron was 0.11%, while in the plant grown with pure boron it was 0.44% (Karayel, 2020). Therefore, pure boron has a positive effect on the ratio of essential oil and components of clary sage.

The volatile oil compounds of *S. sclarea* and *S. officinalis* were identified to be relatively richer in terpenes but the amount of volatile oil depended on ecological factors (Karayel & Akcura, 2019).

While seed oil of *S. officinalis* could be categorized as oleic-linoleic oil, the fatty acid prevailing in *S. sclarea* was linolenic acid (around 54%). In both seeds and oils, main isomers among tocopherols were  $\gamma$ -tocopherol and  $\alpha$ -tocopherol. The concentration of carotenoids accounted for about 0.75 mg/100 g of seeds and 0.16 mg/100 g of oils, lutein being prevalent. Antioxidant potential exerted by oil from *S. officinalis* and its seeds was greater than such of investigated samples of *S. sclarea*, possibly because of larger amounts of overall vitamin E and carotenoids (Zivkovic et al., 2017).

Effects of essential oil from *S. sclarea* on pulse, blood pressure and mood were analyzed on healthy female and male humans (Mitic et al., 2020). The pulse rate decreased more significantly in women than in men. In general, these effects may depend on the method of application (inhalation or dermal application) and sex. Clinical studies confirmed that oil from *S. sclarea* is effective in reducing stress, depression and as analgesic agents in primary dysmenorrhea (Mahboubi, 2020). Studies have confirmed that clary sage has antioxidant, antimicrobial, cytotoxic and anti-inflammatory effects.

By applying *S. sclarea* topically as part of aromatherapy, the severity of menstrual cramps was effectively reduced (Han et al., 2006). Therefore, women who experience menstrual cramps or dysmenorrhea may be offered aromatherapy as part of their nursing care (Han et al., 2006). In aromatherapy, oil from clary sage is used for women during their menstrual cycle, childbirth and menopause (Mahboubi, 2020).

Essential oil from *S. sclarea* damages the cell membrane and changes its permeability, thereby leading to the release of macromolecular substances of cytoplasm such as ATP and DNA. The antimicrobial effect of essential oil from *S. sclarea* is a result of a series of events occurring on the cell surface and within the cytoplasm (Cui et al., 2015).

Abietane diterpenoids isolated from culture of *S. sclarea* transformed roots inhibited pathogenic microorganisms as *Acanthamoeba* spp. (Kuzma et al., 2015). Microorganisms of the *Acanthamoeba* genus are well known pathogens of different diseases like granulomatous amoebic encephalitis (GAE), chronic progressive disease of the central nervous system, amoebic keratitis (AK), chronic eye infection, amoebic pneumonitis (AP), chronic lung and skin infections. The activity of *Acanthamoeba* was notably inhibited by ferruginol. This component produced 72% growth inhibition of *Acanthamoeba* in a 3-day exposure period ( $IC_{50}$  17.45  $\mu$ M), whereas such activity of aethiopinone and 1-oxo-aethiopinone was only at the level of 55–56% (Kuzma et al., 2015). Essential oil of *S. sclarea* was observed to have notable antifungal activity (Fratemale et al., 2005). 2,3-Dehyd-

rosalvipisone, sclareol, manool, 7-oxoroyleanone, spathulenol and caryophyllene oxide were active against *Staphylococcus aureus*, the first and third components exerted significant action toward *Candida albicans*, while the last compound was active against *Proteus mirabilis* (Ulubelen et al., 1994). Lately, the antimicrobial and fungicidal effects of *S. sclarea* essential oil has found application in other areas of life. Results of the recent studies showed high fungicidal efficacy of *S. sclarea* for the packaging materials (Kostova et al., 2020). During the investigated shelf life period, inhibition of *Candida albicans* accounted for around 100%. Suppression of *C. albicans* during the investigated shelf life of the package accounted for 100%. Recycled paper showed a high efficiency against *Aspergillus brasiliensis* (81.9–99.2%). Bactericidal effect of the studied packaging materials processed with sage oils was higher against *Escherichia coli* and lower against Gram-negative bacterium *Salmonella abony* (Kostova et al., 2020). Therefore, clary sage essential oil could be used as an antimicrobial agent in the food industry because of its good antimicrobial features so as to improve products' quality and extend their shelf life.

After the essential oil is obtained from the raw material of clary sage, sclareol is isolated from the green parts of the plant – diterpene alcohol, a representative of terpenoids. Methanol was experimentally selected as the optimal solvent for ultrasound-assisted extraction of phenolic compounds from these plants (Jasicka-Misiak et al., 2018). In glandular trichomes of *S. sclarea*, bicyclic diterpene (-)-sclareol is accumulated (Schmiderer et al., 2008). In the flavours and fragrances industry, it is also used as the raw material for synthesis of Ambrox, a synthetic analogue of ambergris (Gunnewich et al., 2013).

Acetone extract of *S. sclarea* contains nine diterpenes: sclareol, manool, salvipisone, ferruginol, microstegiol, candidissiol and 7-oxoroyleanone, 2,3-dehydrosalvipisone and 7-oxoferruginol-18-al. Furthermore, the plant was found to contain two sesquiterpenes, caryophyllene oxide, spathulenol, alpha-amyrin, beta-sitosterol and the flavonoids apigenin, luteolin, 4-methylapigenin, 6-hydroxyluteolin-6,7,3',4'-tetramethyl ether, 6-hydroxyapigenin-7,4'-dimethyl ether (Ulubelen et al., 1994).

The methanol extracts of *S. sclarea* inhibited the growth of all tested bacterial strains, also this plant had a prominent antioxidant activity (Firuzi et al., 2013). Sclareol caused inhibition of prostaglandin (PG) F-2 alpha-, oxytocin-, acetylcholine-, carbachol-, KCl-, and Bay K 8644-induced uterine contraction and led to an analgesic effect in the writhing test (Wong et al., 2020). Sclareol takes effect on  $Ca^{2+}$  level and mediates oxytocin receptor (OXTR), myosin light chain kinase (MLCK), extracellular signal-regulated kinase, p-p38, cyclooxygenase-2 (COX-2), and phosphomyosin light chain 20 (p-MLC20) protein expression. Summarizing these results, sclareol is a promising alternative supplement in treatment of dysmenorrhea (Wong et al., 2020).

The strongest antioxidant capacity among 5 studied species of *Salvia* was exhibited by extract from *S. officinalis* (Pop et al., 2016). Extracts from *S. sclarea* and *S. officinalis* displayed antibacterial activity toward *Bacillus cereus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Nonetheless, research has revealed resistance of *Salmonella typhimurium* to extract of *S. sclarea* and resistance of *Escherichia coli* to the extract of *S. officinalis* (Pop et al., 2016; Zazharskyi et al., 2019).

Intraperitoneally injected sclareol was studied for its effects that reduce the tumour volume and shift the cytokine profile. Also, there has been an investigation of whether injection of sclareol intraperitoneally can improve the outcome of cancer therapy by suppressing the regulatory T-cells (Noori et al., 2013). The results demonstrated significant decrease in tumour size. Moreover, in the group that was intraperitoneally injected with sclareol, the level of IL-4 significantly dropped and the level of IFN-gamma increased. An assay of cell proliferation also revealed that the splenocytes of the experimental animals significantly increased. Noori et al. (2013) proposed that sclareol can enhance cancer therapy as an immunostimulator by reducing regulatory T-cells ( $T_{regs}$ ) frequency and size of tumour. Sclareol also demonstrated immuno-therapeutic efficacy after direct intra-tumoral injection.

According to Fiore et al. (2006), there was potential antitumoral activity of *S. sclarea* extracts, determined by MTT test, on nine human cancer cell lines: glioblastoma (DBTRG-05MG, T98G, U-87MG), colorectal adenocarcinoma (WiDr and HT-29), prostate adenocarcinoma (MDA Pca2b), choriocarcinoma (JEG-3), endometrium adenocarcinoma (HEC-1A) and

B lymphoblast (CIR). Extracts of *S. sclarea* also demonstrated cytotoxic activity to various degrees depending on the type of cell line (Fiore et al., 2006). The results confirmed that *Salvia* may be considered as a natural source of potential antitumor agents (AlMotwaa et al., 2020).

There were four diterpenoids isolated from transformed roots of *S. sclarea*, namely ferruginol, salvipinone, aethiopinone and 1-oxoaethiopinone (Rozalski et al., 2006). Determining caspase-3 activity showed that salvipinone and aethiopinone could induce apoptosis in time- and concentration-dependent ways. Thus, aethiopinone and salvipinone diterpenoids from *S. sclarea* could be useful in treating human cancers, specifically in the drug-resistant cases (Rozalski et al., 2006).

The lectin isolated from seeds of *S. sclarea* (SSL) recognizes the Tn-antigen (GalNAc alpha 1 -> Ser/Thr), which is expressed in some human carcinomas (Wu, 2005). This was confirmed by Medeiros et al. (2000), whose studies found that SSL from *S. sclarea* seeds recognized the Tn-antigen (GalNAc alpha-O-Ser/Thr), a specific marker of many human carcinomas. SSL is an acidic (pI 5.5), 60–61 kDa dimeric glycoprotein that is composed of identical subunits, interlinked by a single disulfide bond.

Specificity of lectin from *S. bogotensis* seeds and its high affinity for the Tn-antigen, commonly found in tumour cells, is making this protein a useful element for immunohistochemical and cellular studies (Vega & Perez, 2006).

The antiviral effect of sclareol also has a significant potential. It is well known that filoviruses can trigger severe hemorrhagic fever in humans. So far, the most contagious filovirus is Ebola virus (EBOV). Sclareol and sclareolide exerted inhibitory activity toward all tested filoviruses, indicating their broad range of activities against filoviruses (Chen et al., 2020).

Inhibitory effect of sclareol was investigated on osteoclastogenesis and progression of postmenopausal osteoporosis (Jin et al., 2019). Sclareol was seen to have a protective effect against bone loss in the conditions of ovariectomy-induced mouse model. Jin et al. (2019) results suggested that sclareol is a potentially valuable therapeutic agent during postmenopausal osteoporosis.

Traditionally, *S. sclarea* is used as an agent against gingivitis, stomatitis and aphthae (Kosti et al., 2017). Treatment with *S. sclarea* extract significantly lowered the inflammation process by decreasing the levels of IL-1 beta, IL-6 and TNF-alpha, reducing lesions in the gingival tissue and preserving alveolar resorption of the bone, compared with the untreated group of the rats (Kosti et al., 2017). Extract from *S. sclarea* showed an anti-inflammatory effect in periodontitis induced by *E. coli* lipopolysaccharide, suggesting that it could be used as a therapeutic agent in treating periodontal diseases. There was increase in the inhibition depending on time of contact. Essential oils from *S. sclarea* can demonstrate better results when used in bioadhesive formulations that would take peripheral analgesic and anti-inflammatory actions on a local level (Peana et al., 1999).

Diffusion of essential oil of *S. sclarea* and its infiltration through porcine buccal mucosa has been considered useful in stomatology. Compared to the other compounds, the ones having terpenic structure penetrated through the porcine buccal mucosa best (Ceschel et al., 1998).

*Strongyloides papillosus* (Wedl, 1856) is a common nematode of ruminants, and 24 hour-influence of *S. sclarea* at different doses had significant effects on the survival of invasive and noninvasive types of larvae (Boyko & Brygadyrenko, 2016). Aqueous extracts of *S. sclarea* inflorescences killed 50% of *S. papillosus* invasive larvae in 464 +/- 192 mg/L concentration and non-invasive larvae in 327 +/- 186 mg/L concentration (Palchykov et al., 2019).

*Salvia sclarea* is a rich source of terpenoid compounds and may be used as a bio-based pesticide in nature (Bozok & Ulukanli, 2016). In the phytotoxicity assay, essential oil from *S. sclarea* showed significant dose dependent potential toxicity on *Lactuca sativa* L., *Lepidium sativum* L. and *Portulaca oleracea* L. (Bozok & Ulukanli, 2016).

Therefore, the objective of the study was the effect of the herbs on the organism of laboratory rats on a high-fat diet during a 30-day experiment.

## Materials and methods

The choice of animals for the experiment, research protocols, withdrawal of animals from the experiment were approved by the local ethical

committee of the Dnipro State Agrarian and Economic University. The maintenance, nutrition, care for animals and their withdrawal from the experiment were carried out in compliance with the principles described in the "European Convention for the Protection of Vertebrate Animals used for Experiments and for Other Scientific Purposes" (Strasbourg, March 18, 1986, ETS No. 123) and in the order No. 3447-IV from February 21, 2006 "About protection of animals from cruel treatment" (Ukraine).

A control group and two experimental groups of 8 animals in each were formed from 24 adult white outbred male laboratory rats weighing  $200 \pm 10$  g. The rats were housed in polycarbonate cages with steel lattice lids and a stern recess, 4 rats per cage. Rats were kept in a room with a temperature of 20–22 °C and a relative humidity of 50–65%. The light regime was 12 hours of light and 12 hours of darkness. Ventilation was carried out according to the regime. The animals received water ad libitum. The duration of the experiment was 30 days.

The control group of animals was fed a high-fat diet (3600 kcal/kg), which was based on the standard diet (75% grain mixture (corn, sunflower seeds, wheat, barley, soybeans), 8% roots (potatoes, carrots), 2% meat and bone flour, 2% mineral-vitamin complex) with the addition of 15% sunflower oil. Animals in the experimental groups received semi-synthetic high-fat diets supplemented with 5% of medicinal plants. To the diet of the first experimental group, we added 5% of dry shredded shoots of *S. officinalis*, and the second experimental group was given 5% of dry shredded *S. sclarea* shoots. Herbal raw material was collected manually, dried without access to direct sunlight in the room temperature. The main ingredients of the diet were ground in a mill (grain, meat and bone meal, mineral-vitamin complex, dry shoots of medicinal plants) and mixed, then sunflower oil was added and granules were made at the rate of 4.200 g for each group for the entire experiment period (30 days). Fresh root crops were additionally given in an appropriate amount every day. The animals had free access to the food. During the experiment, we monitored the amount of food consumed by each group per day and the total amount for the entire period of the experiment.

Morphometric parameters (body weight, abdominal circumference) were determined on the first day and the 30th day of the experiment. The total increase in animal weight and the daily increase in live body weight were calculated (Bilan et al., 2019; Brygadyrenko et al., 2019; Lieshchova et al., 2018, 2019, 2020). The locomotor activity and the emotional status in the experimental rats were studied in the open field test. We used an installation consisting of a square area of 1 m<sup>2</sup>, divided into 16 squares and bounded by an opaque wall 20 cm high. The experiment was carried out in complete silence with intense illumination of the field itself. An experimental rat, was taken from a cage in a previously darkened room, and was placed in the center of the field. The exposure time was 2 minutes. The animals were tested for four days (1–4 days) at the beginning of the experiment and four days at the end (26–30 days). The number of squares that rats crossed was counted: peripheral and central ones – motor activity was assessed; peripheral (with support on the wall) and central (without support on the wall) standings upright squares – orientational activity; the number of acts of grooming, defecation and urination – emotional status (Lieshchova et al., 2021).

The animals were euthanized on the 30th day of the experiment under anaesthesia (80 mg/kg ketamine and 12 mg/kg xylazine, intraperitoneally) by blood withdrawal with cardiac puncture. After autopsy, the state of the internal organs was visually assessed for the presence of pathological changes. The sampling of organs and tissues (heart, liver, lungs, thymus, spleen, stomach, small and large intestines, kidneys, brain) was performed with surgical instruments and they were weighed. The mass of internal organs was determined with the accuracy of 0.01 g.

Blood samples that we collected during euthanasia were subjected to biochemical and morphological studies. Biochemical parameters were determined using an automatic analyzer Miura 200 (I.S.E. Srl, Italy) and with High Technology reagent kits (USA), PZ Cormay S.A. (Poland) and Spinreact S.A. (Spain). The erythrocytes and white blood cells (WBC) count in the rats' stabilized blood was determined using an automatic hematological analyzer BC-2800Vet and Mindray (Lieshchova et al., 2018, 2019, 2020; Brygadyrenko et al., 2019). For the white blood cell differential, blood smears were prepared by Pappenheim method with their further staining according to Romanowsky-Giemsa. The total protein was deter-

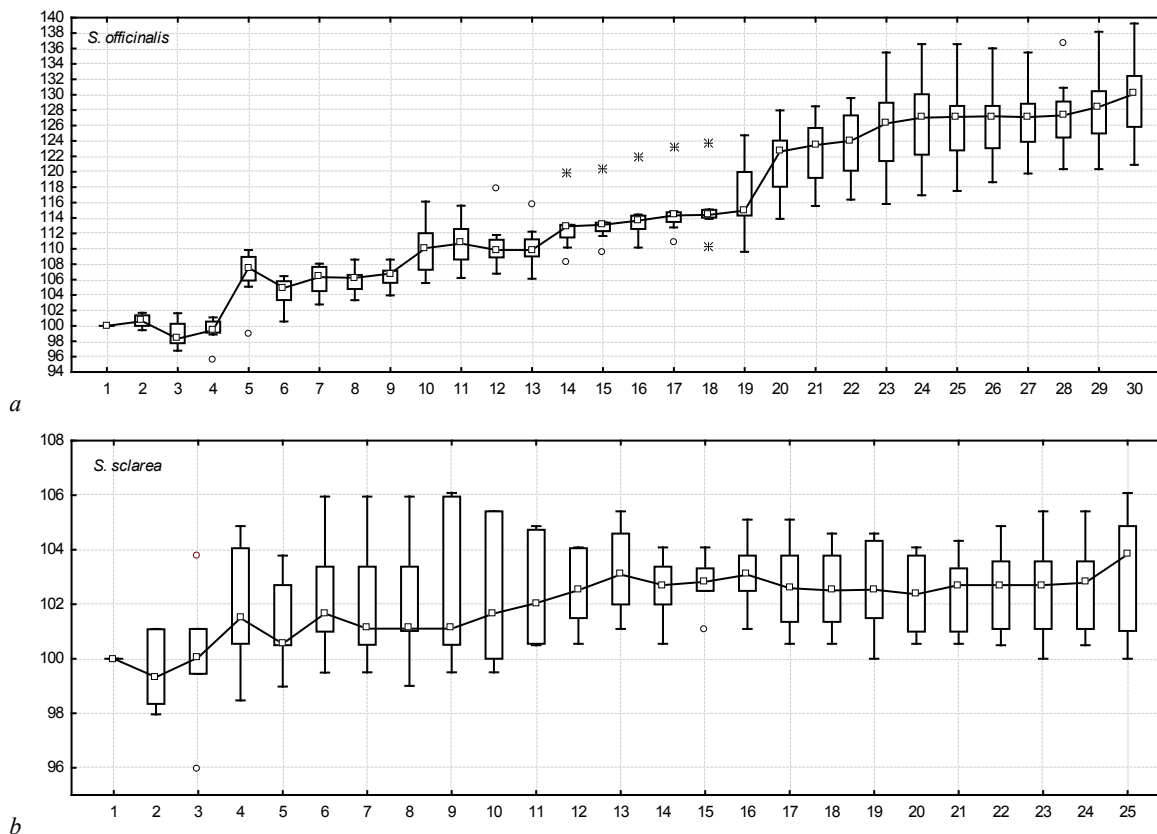
mined using the biuret method; globulins and protein coefficient – calculated; albumin – by reaction with bromocresol green; the activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) – kinetic, based on the optical Warburg test; alkaline phosphatase – enzymatic with n-nitrophenyl phosphate; glucose – by glucose oxidase method; urea – enzymatic, kinetic using urease and glutamate dehydrogenase; creatinine – by the modified Jaffe method without deproteinization; total bilirubin – by a method based on oxidation in the presence of vanadate as an oxidizing agent; total calcium – by colorimetric method with Arsenazo III, inorganic phosphorus – by direct phosphomolybdate method without deproteinization, gamma-glutamyl transferase – kinetic method with L-gamma-glutamyl-3-carboxy-4-nitroanilide. The concentration of total cholesterol was determined using the colorimetric, enzymatic method with esterase and cholesterol oxidase; triglycerides – by colorimetric, enzymatic methods with glycerophosphoric oxidase; HDL and LDL – by direct enzymatic method, the atherogenic index were calculated. From biochemical markers of inflammation, C-reactive protein was determined by the method of highly sensitive latex-enhanced immunoturbidimetry.

All the data were analysed using Statistica 8.0 software (StatSoft Inc., USA). Results in the tables are demonstrated as  $\bar{x} \pm SD$  (mean  $\pm$  standard deviation). Differences between the control and experimental groups values were determined using the Tukey test (with consideration of Bonferroni's correction), where the differences were considered significant at  $P < 0.05$ .

## Results

The addition of *S. officinalis* dry shoots to the male rats' diet notably increased the body weight of the animals compared with the control group: the body weight in the control group increased to 111.5% of the initial, and in the *S. officinalis* group – up to 130.8% in 30 days of the experiment (Fig. 1a). The body weight of rats that had consumed diet supplemented with dry crushed shoots of *S. sclarea* was only 103.8% of their initial weight (Fig. 1b), that is, it was significantly lower than in the control group.

Rats that consumed dry crushed shoots of *S. officinalis* were observed to have insignificantly (at the tendency level,  $P > 0.05$ ) reduced food intake to 85.3% of the control group level (Table 1). Animals that were fed on diet supplemented with *S. sclarea* shoots did not change feed intake, but increased water intake at the level of the trend to 116.9% of the level of the control group. With a change in the daily body weight gain in animals, there were multidirectional changes as compared with the control group (Table 1): *S. officinalis* caused an increase in weight gain up to 1771  $\mu\text{g}/\text{day}$  (253.1% of the control group), and *S. sclarea* – a decrease in body weight gain to 194  $\mu\text{g}/\text{day}$  (27.8% of the control group). Moreover, such abrupt changes in body weight in animals did not affect the abdominal circumference, which did not differ from the control group.



**Fig. 1.** Change in the rats' body weight when chopped shoots of *Salvia officinalis* L. (a) and *S. sclarea* L. (b) were added to their diet: the abscissa is the day of the experiment, the ordinate is the body weight of the animals (% relative to the initial body weight before the start of the experiment, taken as 100% for each of the experimental animals); small square – median, upper and lower borders of the rectangle – 25% and 75% quartiles, vertical line – minimum and maximum values, circles – outliers;  $n = 8$

**Table 1**

Change in the body weight and food consumption of young male rats under the influence of *Salvia officinalis* L. and *S. sclarea* L. addition to their diet ( $\bar{x} \pm SD$ ,  $n = 8$ , duration of experiment 30 days)

Parameter	Control	<i>S. officinalis</i>	<i>S. officinalis</i> compared to the control, %	<i>S. sclarea</i>	<i>S. sclarea</i> compared to the control, %
Food consumption by rats, g/day	20.09	17.14	85.3	19.97	99.4
Water consumption by rats, g/day	18.42	17.21	98.9	21.53	116.9
Body weight change, $\mu\text{g}/\text{day}$	$700 \pm 271$	$1771 \pm 373^{***}$	253.1	$194 \pm 127^{***}$	27.8
Body weight change, %/day	$13.6 \pm 5.9$	$29.3 \pm 5.8^{***}$	215.0	$3.3 \pm 2.1^{***}$	24.3
Abdominal circumference, cm	$14.00 \pm 0.46$	$13.79 \pm 0.79$	98.5	$13.83 \pm 1.11$	98.8

Note: different letters indicate values that differed one from another reliably within one line of the table according to the results of comparison using the Tukey test with Bonferroni correction.

The overall increase in the body weight in the group consuming *S. officinalis* led (Table 2) to a significant decrease in the relative weight of the brain (to 77.7% compared with the control group), spleen (to 80.4%) and thymus (to 59.1%). After consumption of *S. sclarea*, the relative weight of the thymus in male rats also reduced (to 43.4% of the control), but, at the same time, there was a significant increase in their relative weight of the colon (up to 159.7% compared with the control group, Table 2). No other significant changes in the relative mass of the organs in animals from experimental groups were recorded.

Change in blood biochemical parameters of male rats fed on *S. officinalis* manifested itself in a decrease of the urea concentration (78.3% of control), total bilirubin (up to 59.5%), triglycerides (up to 67.1%), a moderate increase of the total protein in blood plasma (up to 109.8%) and a drastic increase in alkaline phosphatase activity (up to 435.1% of control, Table 3). There were no significant changes compared to the control group in other biochemical blood parameters that we studied in the *S. officinalis* group.

Consuming *S. sclarea* shoots in the composition of feed by rats also caused an increase in the alkaline phosphatase activity in blood plasma (however, weaker than in the previous group – only up to 276.5% of control, Table 3). More prominent changes in the group of animals eating *S. sclarea* were observed in fat metabolism: the index of atherogenicity decreased sharply – to 23.1% of the control group level (Table 3). This was due to a sharp increase in the concentration of high density lipoprotein cholesterol (up to 286.9% of the level of the control group) and an insigni-

ficant (at the tendency level,  $P > 0.05$ ) decrease in the concentration of low density lipoprotein cholesterol (up to 67.7% of the level of the control group). Also, in the group of rats that were feeding on *S. sclarea*, an increase in the concentration of cholesterol (up to 128.5% of the control group) and a strong decrease in the concentration of triglycerides (up to 39.9% of the control, more pronounced than in the group of *S. officinalis*) were recorded. In addition, there was a decrease in gamma-glutamyl transferase activity in the blood of animals that consumed *S. sclarea* (up to 62.8% of the control group) and an increase in the Ca/P ratio (up to 132.5% of the control group). Other investigated blood biochemical parameters in the group of animals that consumed *S. sclarea* did not show significant differences (Table 3).

Under the influence of the *S. officinalis* and *S. sclarea* chopped shoots added to the diet of rats, there were no significant changes in complete blood count (CBC) and white blood cell (WBC) differential of male rats (Table 4).

Physical activity (Fig. 2a) in male rats fed *S. officinalis* significantly decreased by the end of the experiment; the addition of *S. sclarea* to the diet of animals caused an insignificant decrease (at the tendency level,  $P > 0.05$ ) in the physical activity of rats. The effect of *S. officinalis* also significantly decreased the orientational activity in animals (Fig. 2b). On the other hand, the emotional status (Fig. 2c) of rats on the diet with *S. officinalis* did not significantly change, while eating dry crushed shoots of *S. sclarea* as part of the compound feed significantly reduced the emotional status of experimental animals.

**Table 2**

Change in organs' relative mass (%) of male rats under the influence of *Salvia officinalis* L. and *S. sclarea* L. supplementation to their diet ( $\bar{x} \pm SD$ ,  $n = 8$ , duration of experiment 30 days)

Organ	Control	<i>S. officinalis</i>	<i>S. officinalis</i> compared to the control, %	<i>S. sclarea</i>	<i>S. sclarea</i> compared to the control, %
Heart	0.352 ± 0.023	0.350 ± 0.026	99.6	0.375 ± 0.027	106.6
Liver	4.08 ± 0.17	4.04 ± 0.31	99.1	4.25 ± 0.28	104.2
Lungs	0.979 ± 0.169	0.836 ± 0.128	85.4	1.056 ± 0.114	108.0
Thymus	0.285 ± 0.046	0.168 ± 0.038***	59.1	0.124 ± 0.101**	43.4
Spleen	0.370 ± 0.036	0.298 ± 0.037*	80.4	0.382 ± 0.067	103.3
Stomach	0.699 ± 0.060	0.786 ± 0.165	112.4	0.955 ± 0.335	136.6
Small intestine	2.58 ± 0.52	2.38 ± 0.52	92.1	2.21 ± 0.36	85.7
Caecum	0.509 ± 0.176	0.457 ± 0.068	89.8	0.487 ± 0.117	95.7
Colon	0.374 ± 0.085	0.430 ± 0.205	115.1	0.596 ± 0.082***	159.7
Rectum	0.398 ± 0.073	0.276 ± 0.068	69.2	0.359 ± 0.095	90.2
Right kidney	0.358 ± 0.031	0.394 ± 0.177	110.1	0.345 ± 0.045	96.3
Left kidney	0.372 ± 0.040	0.381 ± 0.167	102.4	0.336 ± 0.039	90.4
Brain	0.867 ± 0.052	0.673 ± 0.079***	77.7	0.901 ± 0.096	104.0

Note: see Table 1.

**Table 3**

Change in blood biochemical parameters of male rats under the influence of *S. officinalis* L. and *S. sclarea* L. ( $\bar{x} \pm SD$ ,  $n = 8$ , duration of experiment 30 days)

Parameters	Control	<i>S. officinalis</i>	<i>S. officinalis</i> compared to the control, %	<i>S. sclarea</i>	<i>S. sclarea</i> compared to the control, %
Total protein, g/L	77.0 ± 4.9	84.6 ± 1.8*	109.8	82.7 ± 4.9	107.4
Albumins, g/L	39.6 ± 2.6	43.0 ± 1.1	108.7	42.0 ± 2.0	106.1
Globulins, g/L	37.4 ± 3.9	41.6 ± 1.3	111.1	40.7 ± 3.2	108.7
Protein coefficient, U	1.100 ± 0.151	1.029 ± 0.045	93.5	1.050 ± 0.050	95.5
Urea, mmol/L	6.8 ± 1.0	5.4 ± 0.6*	78.3	6.1 ± 1.1	88.9
Blood urea nitrogen (BUN), mg/100 g	13.1 ± 2.0	10.2 ± 1.1	78.3	11.6 ± 2.1	89.1
Creatinine, μmol/L	63.0 ± 4.4	67.1 ± 5.8	106.6	65.8 ± 9.6	104.5
Aspartate aminotransferase (AST), U/L	186 ± 61	187 ± 38	100.5	210 ± 25	112.9
Alanine aminotransferase (ALT), U/L	131 ± 41	123 ± 21	94.0	109 ± 28	83.6
De Ritis ratio (AST/ALT), U	1.63 ± 0.78	1.51 ± 0.19	93.0	2.05 ± 0.59	125.9
Alkaline phosphatase, U/L	129 ± 64	561 ± 243***	435.1	357 ± 81***	276.5
Total bilirubin, μmol/L	6.07 ± 1.67	3.61 ± 0.88*	59.5	8.22 ± 1.32	135.3
Glucose, mmol/L	7.39 ± 1.04	6.57 ± 0.76	89.0	6.17 ± 0.55	83.5
Total calcium, mmol/L	2.53 ± 0.09	2.69 ± 0.20	106.2	2.67 ± 0.14	105.5
Non-organic phosphorus, mmol/L	3.07 ± 0.58	3.43 ± 0.25	111.6	2.47 ± 0.42	80.3
Ca/P	0.843 ± 0.129	0.800 ± 0.076	94.9	1.117 ± 0.195*	132.5
Gamma-glutamyl transferase (GGT), U/L	9.29 ± 2.60	7.86 ± 2.17	84.6	5.83 ± 0.69**	62.8
Cholesterol, mmol/L	1.27 ± 0.14	1.41 ± 0.14	111.2	1.63 ± 0.11***	128.5
Triglycerides, mmol/L	2.129 ± 0.547	1.429 ± 0.306*	67.1	0.850 ± 0.299***	39.9
HDL, mmol/L	0.650 ± 0.128	0.843 ± 0.243	129.6	1.865 ± 0.115***	286.9
LDL, mmol/L	0.517 ± 0.290	0.605 ± 0.149	117.0	0.350 ± 0.064	67.7
Atherogenic index of plasma (AIP), U.	1.04 ± 0.45	0.86 ± 0.49	82.2	0.24 ± 0.18***	23.1
C-reactive protein (CRP), mg/L	12.5 ± 5.4	15.5 ± 4.6	123.6	9.3 ± 1.9	74.3

Note: see Table 1.

**Table 4**Change in CBC and WBC differential of male rats under effect of addition to *S. officinalis* L. and *S. sclarea* L. ( $\bar{x} \pm SD$ ,  $n = 8$ , duration of experiment 30 days)

Parameter	Control	<i>S. officinalis</i>	<i>S. officinalis</i> compared to the control, %	<i>S. sclarea</i>	<i>S. sclarea</i> compared to the control, %
Hemoglobin, g/L	126.8 ± 7.0	133.8 ± 9.5	105.5	112.7 ± 12.0	88.8
Hematocrit, %	40.5 ± 2.7	43.0 ± 3.3	106.3	35.4 ± 3.9	87.3
Erythrocytes, 10 <sup>12</sup> /L	6.93 ± 0.29	7.74 ± 0.46	111.7	6.22 ± 0.55	89.7
Erythrocyte sedimentation rate (ESR), mm/h	1.17 ± 0.39	1.00 ± 0.00	85.7	1.00 ± 0.00	85.7
Thrombocytes, 10 <sup>9</sup> /L	339 ± 66	349 ± 41	103.1	283 ± 40	83.6
WBC, 10 <sup>9</sup> /L	8.6 ± 1.6	11.1 ± 3.4	129.0	9.4 ± 3.3	109.7
WBC differential					
Basophils, %	0.0 ± 0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0
Eosinophils, %	1.50 ± 0.76	0.83 ± 0.90	55.6	1.00 ± 0.58	66.7
Eosinophils, %:	0.0 ± 0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0
Neutrophils, %:					
– young	0.0 ± 0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0
– band	1.17 ± 0.69	0.67 ± 0.47	57.1	0.17 ± 0.37	14.3
– with segmented nuclei	23.0 ± 8.2	18.8 ± 3.8	81.9	21.7 ± 6.2	94.2
Lymphocytes, %	68.8 ± 8.6	73.0 ± 3.8	106.1	73.2 ± 8.0	106.3
Monocytes, %	5.50 ± 1.26	6.67 ± 0.94	121.2	4.00 ± 1.83	72.7

Note: no statistically significant changes were found between samples.

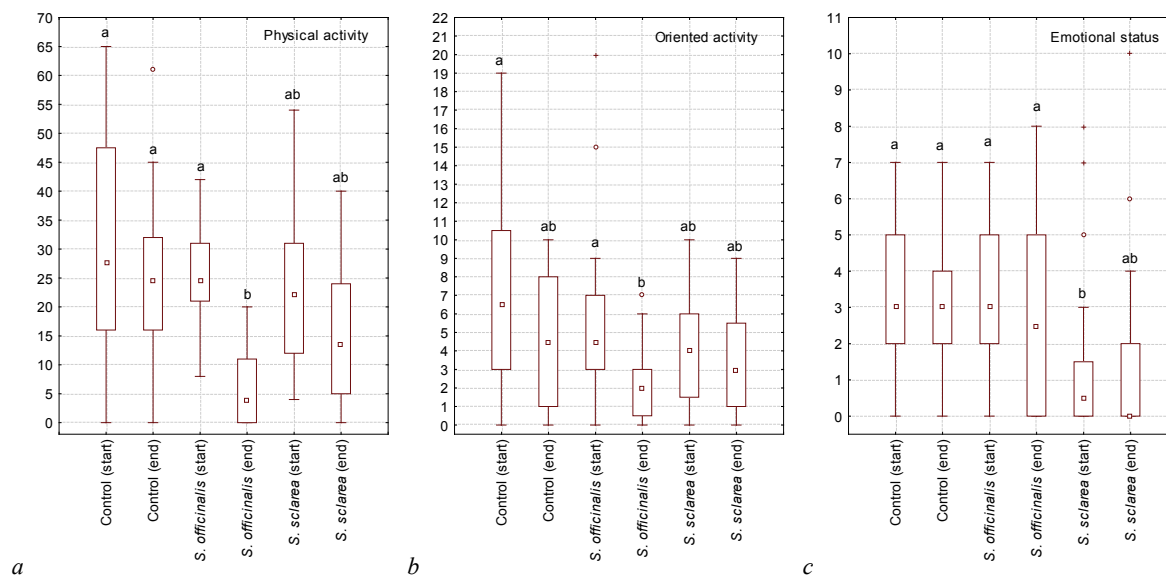
There were no significant changes in the open field test between the groups and within groups at the beginning and the end of the experiment (Table 5), except for the group of rats that ate dry shoots of *S. officinalis* according to the number of peripheral squares that they visited (decrease from 24.9 ± 7.8 to 6.1 ± 6.6).

## Discussion

In modern scientific medicine, sage herb is used very broadly. Scientific studies have revealed antitumour, anti-inflammatory, analgesic, antioxidant, antibacterial, antimutagenic, hypoglycemic, neuroprotective, hypolipidemic properties of sage extracts (Hamidpour et al., 2014; Monsefi et al., 2015, 2017). Sage contains essential oil, coumarins, alkaloids, flavonoids, saponins, sclareol, rosmarinic acid, dihydroquercetin, rutin, coumarin, umbelliferone, gallic, chicoric and ferulic acids, salts of K, Ca, Fe, Mn, Zn, Li, Sn, and also identified polyphenols, phenolic and flavonoid glycosides. Of the phenolic substances, glycosides of luteolin (42%) and apigenin (27%) were identified, the main volatile compounds of the extract

were  $\alpha$ -thujone (32.3%), camphor (29.7%), 1,8-cineole (6.2%) and humulene (5.1%).

Bioactive hydrophobic diterpene in the composition of the essential oil from *S. sclarea* is sclareol, it is broadly studied for its anti-inflammatory and antioxidant effects (Cerri et al., 2019). Cerri et al. (2019) did a very similar study to the one we did, where one of the randomly composed groups of Swiss male mice was fed standard diet (STD) and the other one received high-fat diet (HFD). After obesity in the mice had been induced, three treatment groups were made out of each of the two: free sclareol (Sc), sclareol-loaded lipid nanoparticle (L-Sc) and empty lipid nanoparticle (L). Treatments were conducted every day for the period of 30 days. The study revealed that L-Sc had positive effects on metabolic profiles in obese mice by decreasing adiposity, improving insulin sensitivity, tolerance to the glucose and increasing the HDL plasma levels. Furthermore, L-Sc caused decreases in the expressions of NF-KB, MCP-1 and SERBP-1. Combination treatment using sclareol and lipid nanocarriers, which can reduce adipose tissues, could be effective against metabolic disorders.



**Fig. 2.** Changes in the motor (a) and orientational activity (b), as well as the emotional status (c) of male rats when *Salvia officinalis* L.

and *S. sclarea* L. chopped shoots were added to their diet: on the abscissa – groups of animals ( $n = n_1 * n_2 = 32$ :  $n_1 = 8$  animals,  $n_2 = 4$  experiments with each animal) on a high fat diet with and the addition of shredded herbal shoots (the days after the start of the experiment are indicated in parentheses: 1–4th or 26–30th), on the ordinate axis – the absolute number of markers of this behaviour type in 120 seconds of the experiment: for physical activity – the number of visited squares of the open field, for orientational activity – the number of standings upright, for emotional status – the number of grooming actions, defecation and urination; small square – median, upper and lower borders of the rectangle – 25% and 75% quartiles, vertical line – minimum and maximum values, circles – outliers; different letters within each figure indicate significant differences between groups ( $P < 0.05$ ) according to the results of the Tukey test

In our study, the two sage species showed the opposite effect on weight gain rats that received high-fat diet. Thus, the addition of *S. officinalis* dry crushed shoots led to sharp increase in the rats' body weight during the 30-day experiment, while the addition of *S. sclarea*, on the contrary, slowed down the weight gain both in comparison with the control and the first experimental group. This fact is of interest, since at the same time a decrease in food intake was observed in the group of rats that consumed *S. officinalis*, in comparison with the control group and animals that consumed *S. sclarea*.

An indicator that is often used as a sensitive index for assessing the toxic effects of various substances, including medicinal ones, is the mass of the organs (Balogun et al., 2014; Varcholyak & Gutyi, 2019). Increase in the total body weight against the background of high-fat diet is accompanied by increase in the absolute mass of the internal organs, while the relative mass may not always increase. In our experiment, the intake of

sage led to significant decrease in the relative mass of the immune system organs (thymus and spleen), but no changes in the composition of the blood (WBC count, WBC differential) were found. In the studies by Tkachuk & Shapoval (1987), it was also indicated that *S. sclarea* essential oils affects the immune system, as well as the fermentative activity of the blood. In our experiment, we also observed change in the enzymatic activity of the rats' blood when chopped sage was added to the high-fat diet. Thus, the consumption of *S. officinalis* caused a strong increase in the activity of alkaline phosphatase, and consumption of *S. sclarea* caused moderate increase, while the activity of AST and ALT did not significantly differ from those of the control animals. Also, in comparison with the control group, the rats of the first experimental group were observed to have insignificant decrease in the activity of gamma-glutamyl transferase, whereas in the second group this parameter significantly and reliably decreased; this indicator was within the reference values in all the groups.

**Table 5**

Change in behavioural characteristics of three rats groups during 2 minutes of the experiment, in which diet *Salvia officinalis* L. and *S. sclarea* L. was added ( $x \pm SD$ ,  $n = 32$ , duration of the experiment was 30 days)

Feature	Control, 1–4th days	Control, 26–30th days	<i>S. officinalis</i> , 1–4th days	<i>S. officinalis</i> , 26–30th days	<i>S. sclarea</i> , 1–4th days	<i>S. sclarea</i> , 26–30th days
Number of visited peripheral squares	28.1 ± 18.0 <sup>a</sup>	24.3 ± 14.5 <sup>a</sup>	24.9 ± 7.8 <sup>a</sup>	6.1 ± 6.6 <sup>b</sup>	22.0 ± 12.3 <sup>ab</sup>	15.4 ± 11.7 <sup>ab</sup>
Number of visited central squares	1.000 ± 2.341	0.292 ± 1.042	0.500 ± 2.134	0.000 ± 0.000	0.542 ± 1.285	0.167 ± 0.565
Number of upright stands in peripheral squares	5.58 ± 4.53	3.79 ± 3.13	4.50 ± 2.89	1.96 ± 1.67	2.79 ± 1.74	2.29 ± 1.71
Number of upright stands in central squares	1.292 ± 1.429	0.708 ± 0.999	1.143 ± 1.533	0.071 ± 0.378	1.250 ± 1.294	1.042 ± 1.233
Number of grooming acts	0.583 ± 0.830	0.583 ± 0.929	1.214 ± 1.475	0.143 ± 0.356	0.833 ± 1.761	0.792 ± 1.560
Number of faecal bolus	2.250 ± 2.027	2.375 ± 1.555	2.036 ± 1.795	2.536 ± 2.646	0.500 ± 0.722	0.542 ± 1.021
Number of urinations	0.333 ± 0.482	0.375 ± 0.495	0.071 ± 0.262	0.107 ± 0.315	0.042 ± 0.204	0.042 ± 0.204

Note: there were no significant differences between the groups for most of the parameters studied; differences in the number of visited peripheral squares are indicated by different Latin letters ( $P < 0.05$ ) according to the Tukey test results with Bonferroni correction.

In studies that were carried out on broiler chickens, sage powder of *S. officinalis* was added to the diet in the doses of 4 and 8 g/kg, its effect on the immune organs and blood biochemical parameters was indicated. Such a diet did not affect the ratio of albumin and globulins and the ratio of granulocytes and blood lymphocytes, as well as the concentration of cholesterol, HDL and LDL. At the same time, a high concentration of the sage powder (8 g/kg) significantly increased the relative mass of the cloacal bursa in poultry, and also led to a decrease in the concentration of total protein and triglycerides in the blood serum (Toghyani et al., 2012).

A study by Ekin et al. (2019) focused on antialzheimer, antidiabetic, antioxidant and antiobesity activities of ethanol extracts from *S. sclarea*. Leaf extract of *S. sclarea* significantly inhibited butyrylcholinesterase (51.76 ± 1.04%). The *Salvia* species demonstrated the highest total antioxidant activity. Extracts from flowers of *S. sclarea* (1.34 ± 0.08) and leaves (1.34 ± 0.08) exhibited high ferric-reducing antioxidant power. Extracts of *S. sclarea* displayed notable inhibitory activity and are considered possible sources of alpha-glucosidase inhibitors (Ekin et al., 2019).

The most active chemotype of *S. sclarea* was determined by monitoring the acute and subchronic antidiabetic activities of essential oils along with linalool and linalyl acetate. Plants of chemotypes 1 (linalool content), which grow on low altitudes in Lebanon and Poland, was seen to have significantly higher acute and subchronic antidiabetic activities compared with chemotype 5 (high linalyl acetate content). Essential oils from *S. sclarea* demonstrated potential antidiabetic activities, and may be used as a complementary or alternative treatment of diabetes and complications that accompany it (Raafat & Habib, 2018; Pereira et al., 2019; Salehi et al., 2020; Abu-Odeh & Talib, 2021).

In studies by Agadzhanian (2015) on human blood serum with a glucose concentration of 10.0 mmol/L and a total cholesterol level of 8.2 mmol/L *in vitro*, the hypoglycemic and hypolipidemic activity of *S. officinalis* leaf extracts was investigated. The results revealed both aqueous and alcoholic extracts of the studied plant being effective in reducing glucose concentration and serum cholesterol levels (Bassil et al., 2015). In studies on mice with diet-induced obesity, ethanolic sage extract caused rosiglitazone-like effect, improved insulin sensitivity, inhibited adipocyte lipogenesis, and reduced inflammation (Ben Khedher et al., 2018).

In our study, in rats on a high-fat diet, the glucose level was at the upper level of the reference range, and the addition of sage to the feed led to a

slight and insignificant decrease in the blood glucose. At the same time, the indicators of fat metabolism in animals were significantly altered by the consumption of *S. sclarea*. Thus, in comparison with the control group, the rats of the second experimental group (that consumed *S. sclarea*) had an increase in cholesterol levels, a sharp increase in the concentration of high-density lipoproteins and a decrease in low-density lipoproteins, which led to a sharp significant decrease of the atherogenic index.

In our previous study (Zazharskyi et al., 2019), we observed a high activity of an alcoholic tincture of the *S. sclarea* against *Escherichia coli* and *Proteus vulgaris*, and, at the same time, a very low activity against *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Corynebacterium xerosis* and fungus *Candida albicans*.

A study (Yang et al., 2014) of efficiency of *S. sclarea* in treatment of endothelial dysfunction induced by chronic immobilization stress in rats demonstrated that treatment with 5%, 10%, and 20% *S. sclarea* significantly decreased systolic blood pressure. Treatment with 20% *S. sclarea* also significantly reduced the heart rate compared with the group that had chronic immobilization stress (Yang et al., 2014). Also, *S. sclarea* caused decreases in corticosterone (10% and 20%) and malondialdehyde (10%, 20%) in serum. Similar results were observed with nifedipine. Moreover, 20% *S. sclarea* provoked significant increases in nitric oxide production and eNOS expression level and relaxed aortic rings in rats suffering stress from chronic immobilization (Yang et al., 2014). By increasing production of NO and eNOS level, as well as decreasing oxidative stress, treatment of rats that were under immobilization stress with *S. sclarea* led to their recovery from endothelial dysfunction. Therefore, treatment of endothelial dysfunction with appropriate *S. sclarea* concentration could lead to recovery. These data indicate that oil from *S. sclarea* may be efficient in prophylaxis and treatment of stress-induced cardiovascular diseases (Yang et al., 2014).

In studies by El-Shafeial et al. (2013), against the background of pathological and toxic changes in the body of mice caused by the action of carbon tetrachloride, the use of *S. officinalis* oil before and after carbon tetrachloride had a levelling effect on the state of the liver and kidneys, and there was also a tendency towards restoration of their functions. At the same time, the preventive use of oils was less effective. Essential oil isolated from *S. sclarea* inhibited growth of HeLa cells with an IC<sub>50</sub> of 80.69 ± 0.01 µg/mL. Staining with propidium iodide (PI) showed the

presence of apoptosis in cells that were treated with oil (Durgha et al., 2016). Treatments with essential oil from *S. sclarea* in different concentrations reduced inflammation (Durgha et al., 2016). However, histopathological assay of the liver tissue treated with 1.5 µg lipopolysaccharide (LPS)/30 g body weight of BALB/c mice revealed severe inflammation and necrosis. Hepatocytes' necrosis and infiltration were barely seen after using 100 µg of essential oil of *S. sclarea* (Durgha et al., 2016).

The influence of sage and medicinal preparations made with it on the nervous system attracts considerable interest of researchers (Cavalcante et al., 2018; Dinel et al., 2020). Their study revealed significant neuroprotection in the MTT assay by 39.5% and inhibition of intracellular ROS by 61.4% caused by eighty percent methanol extracts of *S. sclarea* in 100 µg/mL concentration (Tavakkoli et al., 2014). In the future, researchers may discover new natural therapeutic agents for treating disorders such as Alzheimer and Parkinson diseases (Tavakkoli et al., 2014). A group of female patients exposed to vapours of *S. sclarea* essential oil were observed to have a significant decrease in systolic blood pressure, diastolic blood pressure and respiratory rate compared with the control (Seol et al., 2013). Inhaling *S. sclarea* essential oil statistically significantly reduced the respiratory rate.

*Salvia sclarea* oil contains two times more omega-3 fatty acids than other *Salvia* species, which take part in eicosanoid synthesis and contain significant levels of monoterpane linalool, a psychoactive ingredient (Gross et al., 2013). In dominant mice, pregnant mothers of which received *S. sclarea* oil-enriched food from the date of conception, dominant and anxiety behaviour significantly decreased, compared with their counterparts treated with sunflower oil. A similar tendency and a prominent reduction in blood corticosterone levels were seen in submissive mice treated with *S. sclarea* oil (Gross et al., 2013). These data and findings confirm the hypothesis that *S. sclarea* oil has anxiolytic properties.

In the study, where rats were intraperitoneally injected or inhaled essential oils (Seol et al., 2010), 5% (v/v) *S. sclarea* oil had the strongest anti-stress effect in rats during the forced swim test. However, pre-treatment with buspirone (a 5-HT<sub>1A</sub> agonist), SCH-23390 (a D-1 receptor antagonist) and haloperidol (a D-2, D-3, and D-4 receptor antagonist) significantly blocked the anti-stress effect of *S. sclarea* oil (Seol et al., 2010). The antidepressant-like effect taken by oil from *S. sclarea* oil is related to the modulation of the dopaminergic pathway.

In our study, the behavioural responses of rats from the experimental groups which consumed dry crushed sage shoots with high-fat diet had changed by the end of the experiment compared with the control group. Thus, consuming *S. officinalis* caused only significant decrease in rats' physical activity. At the same time, *S. sclarea* caused decrease of physical activity at the level of tendency, significant decrease in orientational activity, and decrease in the emotional status of experimental animals.

Therefore, further research will be aimed at studying the effects of different doses of extracts from these medicinal plants (*S. officinalis* and *S. sclarea*) on the organism of laboratory animals during various metabolic disorders at the tissue, cellular and subcellular levels.

## Conclusions

The addition of closely related sage species from the same genus (*Salvia officinalis* L. and *S. sclarea* L.) to the food of rats caused multidirectional changes in their metabolism. The addition of *S. officinalis* to the diet led to sharp increase in body weight (up to 130.8% of the initial weight for 30 days of the experiment). The body weight of the rats that had been treated with *S. sclarea* increased only by 103.8% of their initial weight and was lower than in the control group. Oil from *S. officinalis* increased daily weight gain up to 1771 µg/day (253.1% of the control group), and *S. sclarea* – decreased it to 194 µg/day (27.8% of the control group). In the group that had received *S. officinalis*, the relative weight of the brain (77.7% of control), spleen (80.4%), and thymus (59.1%) decreased. In the group treated with *S. sclarea*, the relative weight of the thymus decreased (43.4%) and the relative weight of the colon increased (159.7% to the control group).

Under the influence of *S. officinalis*, the concentrations of urea (78.3%), total bilirubin (59.5%) and triglycerides (67.1%) decreased, and the concentration of total protein (109.8%) and the activity of alkaline

phosphatase (435.1% of control) increased. Consumption of *S. sclarea* shoots increased the activity of alkaline phosphatase (276.5%), drastically decreases the atherogenic index (23.1% of the level of the control group) as a result of increasing the concentration of high density lipoprotein cholesterol (286.9%) and decreasing the concentration of low density lipoprotein cholesterol (67.7%). Also, in rats that had received *S. sclarea*, we observed increase in the concentration of cholesterol (128.5%) and decrease in the concentration of triglycerides (39.9%), decrease in the activity of gamma-glutamyl transferase (62.8%) and increase in the Ca/P ratio (up to 132.5% of the control group). No significant changes were observed in CBC and WBC differential of male rats that consumed *S. officinalis* and *S. sclarea* shoots.

According to the results of the open field test, the physical and orientational activity of male rats under the influence of *S. officinalis* significantly decreased by the end of the experiment. Emotional status of rats, on the contrary, decreased when they ate *S. sclarea* dry crushed shoots in the composition of their food.

Thus, excess body weight against the background of hypercaloric diet in rats led, in general, to more pronounced deviations from the norm when the animals ate *S. officinalis* dry crushed shoots. And vice versa, the addition of dry crushed shoots of *S. sclarea* to the diet of animals normalized body weight in comparison with the control group, and reduced the negative manifestations of obesity at the biochemical and organismal levels. According to these results, the substances contained in *S. sclarea* should be carefully studied for anti-atherosclerotic activity, and tea supplemented with *S. sclarea* shoots can be recommended as a corrective supplement in the diet of overweight people.

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