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EFFICACY OF HERBAL ESSENTIAL OILS AT TETRAHLORMETHANE INDUCED HEPATITIS IN LABORATORY RATS

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In this paper, the efficacy of essential oils in the composition of Fitohol herbal medicinal product against the background of tetrachloromethane induced toxic hepatitis in laboratory rats has been studied. It was established that the injection of Fitohol in rats at the dose of 0.03 g per 100 g of body weight positively influenced the clinical condition of animals, facilitated the manifestation of hepatocellular failure and the development of destructive changes in hepatocytes (reducing the activity of alkaline phosphatase, alanine and aspartate aminotransferases in blood plasma and oxyproline, hexosamines and malonic dialdehyde in liver homogenates) in acute toxic hepatitis. In the long-term intoxication of rats with CCl4, the effect of Fitohol was manifested in improving the functional state of the hepatobiliary system and some restoration of the protein- synthesizing liver function.

Key words: herbal medicinal product, tetrachloromethane induced toxic hepatitis, blood plasma, liver homogenate, white rats.

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The liver is one of the most important organs playing a decisive role in the physiological processes of the body. Along with its important functions in the metabolism (accumulation of glycogen, decomposition of erythrocytes, production of hormones and blood plasma proteins), it plays a central role in the detoxification and transformation of chemicals, and therefore to some extent it is exposed to their harmful effects, which increases its susceptibility to diseases [10].

Treatment and prevention of liver diseases at the early stages, when pathological changes in its structures have not become irreversible, is important. However, synthetic pharmacological drugs used to treat liver diseases are often toxic and have many side effects [9]. Therefore, considerable attention is paid to the possibility of using alternative medicinal preparations, which are natural products or their derivatives. Among them, plant-based preparations, the main advantage of which is safety and long-term therapeutic potential, rank high.

Due to the presence of biologically active substances (essential oils, flavonoids, glycosides, tannins, organic acids, etc.), they have hepatoprotective, choleretic and detoxification properties [14], antibacterial and antioxidant activity [8, 15], reduce the level of glucose and cholesterol [5], prevent the development of malignant tumors [6]. Thus, the use of phytopreparations for the purpose of treating pathological conditions of the body is a promising trend. However, the ratio and content of the active plant components in them should be the subject of careful study, since some of them in large quantities may have strong toxic properties [3, 6].

Modeling of pathological conditions in laboratory animals has become widespread in experimental humane and veterinary medicine, including the use of tetrachloromethane (CCl4) for this purpose, administration of which to rats permits to cause various forms of liver pathology in animals - from acute and chronic hepatitis to its cirrhosis of varying manifestation degrees [2, 14]. Toxic hepatitis in animals is accompanied by changes in the intensity and direction of biochemical processes, metabolic disorders and organ structures at the cellular level, and therefore the study of biochemical blood parameters of rats is an informative method for determining the disorders of the synthetic and excretory function of the liver against the background of using medicinal products.

The purpose of the work was to study the hepatoprotective effect of essential oils in the composition Fitohol herbal medicinal product in nonlinear males of white rats against the background of toxic hepatitis induced by administration of tetrachloromethane (CCl4).

Materials and methods. The model of the toxic liver damage caused by an organic hepatotropic poison - carbon tetrachloride (tetrachloromethane, CCl4) was taken as a basis [2]. A solution of

tetrachloromethane was prepared of the pure (99.99% purity) preparation by adding olive oil. The final concentration of the solution was 50%. Experiments were carried out on sexually mature nonlinear males of white rats aged 6 months with a weight of 0.17-0.18 kg, which were selected on the basis of analogues [1]. They were kept on a standard vivarium diet of the Dnipro State Agrarian and Economic University. All animals had free access to food and drinking water.

The registered Fitohol herbal medicinal product (TU U 10.9-32490422-004: 2012) is a mixture of herbal raw material and medicinal products extracts (tinctures), which, as a medicinal product, contains: Capsella bursa-pastoris herb extract (Capsella bursa-pastoris (L.) Medik.), Helichrysum arenanum flowers extract (Helichrysum arenarium L.), Tanacetum vulgare flowers extract (Tanacetum vulgare L.), peppermint tincture (Mentha piperita L.), common valerian root tincture (Valeriana officinalis L.), common belladonna leaves tincture (Atropa belladonna L.), as well as magnesium sulfate, sodium salicylate, hexamethylenetetramine, glycerol, ethanol.

The experiments were carried out in two stages. At the first stage the efficacy of Fitohol herbal preparation was studied for treating acute tetrachloromethane-induced toxic hepatitis. Laboratory animals were divided into groups: the control group rats (n = 36) were injected subcutaneously into the shoulder with 50% CCI4 oil solution in the dose of 0.5 ml per 100 g of body weight once a day three times a week, and the experimental group animals (n = 36) were given Fitohol from the first day on the background of CCI4 in the dose of 0.03 g per 100 g of body weight daily for 30 days. Euthanasia of the experimental animals was performed on the 7th, 14th and 30th day of the experiment.

At the second stage, biochemical changes in blood plasma against the background of long-term intoxication of rats with CCI4 were determined. Animals of the control group (n = 15) were subcutaneously injected 50% CCI4 oily solution in the dose of 0.05 ml per 100 g of body weight 2 times a week; rats of experimental group II (n = 15), against a background of toxic hepatitis, Fitohol was given in the dose of 0.03 g per 100 g of body weight daily from the 4th week for the period of 16 weeks. Biochemical parameters of laboratory animals' blood plasma were studied after their euthanasia the day after the last administration of the herbal preparation. Separately, at each stage of the study, groups of intact animals were formed (n = 12 and n = 15).

Clinical signs of toxic hepatitis in experimental rats were estimated by a set of indices: appearance, behavior, appetite, body weight, skin elasticity, the coat state [1]. During the experiment, the requirements of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes" (Strasbourg, 1986), the Law of Ukraine "On the Protection of Animals from Cruel Treatment" No. 3447 dated February 21, 2006, were observed. The material for the study was plasma and liver homogenate.

Euthanasia of animals was performed with sodium thiopental. To obtain plasma, blood was taken from the heart of rats into heparin containing test tubes, which were then centrifuged at 3000 rpm for 15 minutes. Homogenate for biochemical studies was obtained from the animal samples of the normal and pathologically altered left side lobe of the liver (25 g) after pre-perfusion with physiological solution by means of differential homogenization.

Laboratory study was carried out at the clinical biochemistry laboratory of the Research Centre of Biosafety and Environmental Control of Agro-Industrial Complex (Dnipro). The plasma levels of cholesterol, bile acids, ß-lipoproteins, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) activity; in the liver homogenates, the total proteins content, oxyproline (OP), hexosamines (HA) and malonic dialdehyde (MDA) were determined with "Miura" automated biochemical analyzer (Italy) in compliance with the recommendations of the Panel of Experts of the International Federation of Clinical Chemistry (IFCC) using the High Technology reagent kits (USA), PZ Cormay S.A. (Poland) and Spinreact S.A. (Spain).

The results were processed using the Statistica 10 software package (StatSoft Inc., USA). Reliability of the difference between the samples was assessed according to the Student's t-criterion, having first checked the normality of their distribution. Differences were considered reliable for $P < 0.05$.

Results of the study and their discussion. Observations have established that in animals' intoxication with tetrachloromethane, Fitohol mitigated the course of the pathological process. On the second day after CCI4 administration to rats (control group), lethargy, adynamia, and loss of appetite were observed. Signs of intoxication grew and were manifested to the fullest extent on the 5th day, and then gradually faded. In the rats, which were administered Fitohol simultaneously with CCI4 (experimental group I), the phenomena of intoxication came later (on the 4th-5th days) and were less pronounced. The external signs of poisoning within two weeks have completely disappeared, while in control animals they were still manifested.

Mechanisms of haloalkanes hepatotoxic action, including CCI4, are associated with the development of centrilobular necrosis, infiltration of the liver by inflammatory cells, fatty dystrophy and apoptosis of hepatocytes. The AP activity increase in the control group rats compared to the experimental ones by 1.7-3.9 times (p = 0.031-0.0004) may indicate a worsening of bile outflow, which, as a rule, tends to complicate hepatitis (table 1).

Table 1

Activity of rats' blood serum enzymes in acute toxic hepatitis (M ± m, n = 12)

Group	Toxic hepatitis, days	Enzymes activity		
		ALT, U/l	AST, U/l	AP, U/l
control (CCl_4)	7	138.3±7.19	78.3±7.20	947.8±5.40
Experimental I (CCl_4+Fitohol)		128.4±3.96	72.2±6.99	342.7±3.59*
control (CCl_4)	14	50.4±3.23	66.1±5.04	708.8±11.27
Experimental I (CCl_4+ Fitohol)		48.0±3.51	57.6±3.59	180.3±6.11*
control (CCl_4)	30	90.1±5.32	102.7±6.11	702.7±6.69
Experimental I (CCl_4+ Fitohol)		60.2±3.60*	90.5±5.14	420.0±4.82*
Intact	-	54.0±4.10	81.6±4.89	416.4±4.99

Note: * – difference compared to the control group rats at p<0.05.

Significant increase of ALT activity in experimental animals compared to the intact ones (by 2.4-2.6 times) against the background of tetrachloromethane may indicate a development of hepatocellular failure, cytolytic syndrome and biliary obstruction during the first week of toxic hepatitis modeling. At the same time, there was no significant difference between the activity of transaminases (ALT and AST) in the experimental animals, with the exception of ALT in the rats of experimental group I it was lower by 33% at the 30th day of the experiment (p = 0.0012) than in the control, which may indicate some cumulative effect of herbal preparations as hepatoprotections.

Development of hypocholesterolemia suggests the presence of destructive changes in the liver parenchyma. In toxic hepatitis (table 2), in the control group animals, during 7 days, serum cholesterol level reduced by 38% (p = 0.047) and by 14% by 37% (p = 0.008), compared to the first experimental group of rats , which was apparently a result of deep damage to hepatocytes and their synthetic activity disorder. At the same time, the difference between the animals of the first experimental group and the intact rats was unreliable. There were also no significant differences in the content of bile acids.

Table 2

Dynamics of lipid metabolism indices in blood plasma of rats in acute toxic hepatitis (M ± m, n = 12)

Group	Toxic hepatitis, days	Cholesterol, mmol/l	Bile acids, mmol/l	ß-lipoproteins, units
control (CCl_4)	7	0.92±0.07	0.209±0.017	25.9±3.19
Experimental I (CCl_4+Fitohol)		1.47±0.11*	0.229±0.019	27.1±1.34
control (CCl_4)	14	0.82±0.03	0.186±0.007	191.7±11.23
Experimental I (CCl_4+ Fitohol)		1.29±0.08*	0.207±0.026	124.2±15.73*
control (CCl_4)	30	1.52±0.14	0.379±0.029	108.9±9.74
Experimental I (CCl_4+ Fitohol)		1.46±0.29	0.331±0.034	80.6±6.86*
Intact	-	1.80±0.12	0.188±0.035	11.1±1.38

Note: * – difference compared to the control group rats at p<0.05.

The normal level of lipoproteins provides the most important stage in the elimination of lipids from the blood. Cholesterol, which is transported in their composition serves as a source for the synthesis of bile acids and, thus, leaves the body. It was found that the blood serum β-lipoprotein concentration in experimental group I reduced by 35% on the 14th day (p = 0.0073) and it was lower than control by 26% on the 30th day (p = 0.049). This may indicate an improvement in the course of animals' lipid metabolism in response to Fitohol.

Increase of the HA content indicates an increase in the decomposition of carbohydrate-protein components of the connective tissue and the inflammatory process activity, the duration of which leads to the destruction of liver tissues. In our case (table 3), their growth in rat homogenate of the liver tissues 7 days after the initiation of CCl4, may indicate the development of the necrobiotic process in hepatocytes and the presence of inflammatory process. It was more pronounced in the control rats, since the level of HA in them was higher on the 7th day - by 22% (p = 0.046) and on the 30th day - by 9% (p = 0.0009) than in the experimental group.

Oxyproline (OP) is one of the main amino acids of collagen, which permits to consider it as a marker, which reflects catabolism of this protein during the liver fibrosis development. It was found that on the 7th day after artificially induced liver inflammation there was an increase in the content of OP,

indicating the development of destructive changes in the liver tissues. In the control group, it was higher by 54% (p = 0.0004) than in the experimental group rats, the content of oxyproline in which, due to the action of Fitohol, remained within the limits of intact animals. On the 14th day, its concentration increased in rats of all groups, but was lower by 18% (p = 0.021) than in the control. The tendency to reduce the content of oxyproline in liver tissue homogenates up to the 30th day of observation occurred in both groups, and only in the experimental group it was at the level of intact animals.

Table 3

Dynamics of rat liver homogenates biochemical indices in acute toxic hepatitis (M ± m, n = 12)

Group	days	Proteins, mg/1g tissue	Oxyproline, μmol/mg protein	Hexosamines, μmol/mg protein	MDA, μmol/mg protein
control (CCl_4)	7	63.8±7.48	33.9±2.19	210.4±16.18	0.414±0.021
Experimental I (CCl_4+Fitohol)		99.3±5.97*	15.7±1.17*	163.5±12.69*	0.154±0.018*
control (CCl_4)	14	54.0±4.6	26.5±1.39	168.1±13.08	0.218±0.058
Experimental I (CCl_4+ Fitohol)		63.4±1.87	21.8±1.52*	163.9±15.69	0.259±0.006
control (CCl_4)	30	68.6±4.01	19.8±2.63	469.1±5.37	0.139±0.013
Experimental I (CCl_4+ Fitohol)		75.0±9.1	11.8±2.46	425.4±2.95*	0.151±0.024
Intact	-	73.9±3.73	15.4±4.09	88.8±6.03	0.208±0.042

Note: see table 1.

Assumption about the protective properties of Fitohol in the initial period (7th day) of acute toxic hepatitis is confirmed by the level of malondialdehyde (MDA) in the rat liver tissue homogenates. Due to its significant prevalence in the control group animals (by 2.7 times; p = 0.0031), the MDA content in the experimental rats was even lower than the level of the intact animals. On the 14th and 30th day there was a tendency towards normalization of this index in the control group, and therefore the content of MDA in rats of all groups did not differ significantly. Prevention of the malondialdehyde accumulation - the final product of lipid peroxidation in liver tissue homogenates – due to the effect of Fitohol suggests that this herbal medicinal product also has a protective and antioxidant effect on cellular membranes of hepatocytes.

In the long-term administration of CCl4 (for 16 weeks) to white rats (control) in their blood serum (table 4), compared to the intact animals, there was a decrease in the total protein content – by 1.2 times, cholesterol – by 1.7 times, a significant increase in the content of bilirubin - by 2.7 times, in cholesterol - by 1.5 times, in the activity of ALT - by 3.5 times, and in alkaline phosphatase - by 4.9 times, which may indicate a significant damage to hepatocytes and disorders of metabolic processes against the background of cholestasis development.

Table 4

Biochemical indices of rat blood plasma in CCl4-induced toxic hepatitis within 16 weeks (M ± m, n = 15)

Index	Measuring units	Group		
		Control	Experimental II	Intact
Total protein	g/l	59.6±3.33	66.5±4.41	72.8±3.12
Bilirubin	μmol/l	32.4±6.92	10.4±2.51*	12.0±3.43
Cholesterol	mmol/l	1.02±0.14	1.56±0.11*	1.74±0.15
ALT	U/l	265.2±2.75	118.2±4.23*	75.6±4.53
AP	U/l	1843.7±6.43	940.3±8.19*	375.5±5.85

Note: * – difference compared to the control group rats at p<0.05.

Administration of Fitohol from the 4th week after CCl4 administration (experimental group II) had a positive effect on the liver cells function, reducing the content of bilirubin and ALT activity in rats, respectively, by 3.1 (p = 0.047) and by 2.2 (p = 0. 0002) times compared to the control group. The AP activity was reduced almost twice (p = 0.0004), but signs of cholestasis were observed in the future. The trend towards a higher total protein content by 11.6% and cholesterol by 53% (p = 0.0331) in rats under Fitohol effects may indicate some recovery of the liver protein-synthesizing function and lipid metabolism improvement in the long-term intoxication with tetrachloromethane.

Metabolic processes are primarily controlled by the liver and its disruption contributes to liver injury. Since the changes associated with CCl4 induced liver damage are similar to that of acute viral hepatitis [4], the ability of a hepatoprotective drug to lessen the harmful effects or to preserve the normal hepatic physiological mechanisms, which have been distressed by a hepatotoxin, is the index of its protective effects. It is known that with toxic hepatitis [12], the increase in membrane permeability causes leakage of liver enzymes (ALT, AST and ALP) into blood circulation as shown by abnormally high levels of serum hepatic markers. The results of present study is in agreement with studies the authors' [7, 14] in which extracts of medicinal plants causes concomitant reduction in the serum enzyme activities of ALT, AST and ALP as

compared to the toxicant ethanol and carbon tetrachloride treated group, whereas in present study such a reduction in serum enzyme levels is due to herbal medicinal product (Fitohol) is also observed. As well as other researchers [13], we tend to believe that the protective effects of essential oils in the composition medicinal plants in when artificially induced toxic hepatitis in laboratory rats can be explainable attributed to the cell membrane stabilizing ability of the extracts, preventing the liver dysfunction and the transfer of enzymes into the serum. The hepatoprotective effect of plant extracts was also associated [4, 14] with the presence of antioxidant compounds in them, which increased the level of antioxidant enzymes and prevented the accumulation of lipid peroxidation products. A similar effect was confirmed in our study, when the level of MDA in acute toxic hepatitis was several times lower with the use of Fitohol. In summary, we assume that the high hepatoprotective efficacy of Fitohol may be due to the synergistic and supra-additive action of essential oils in medicinal plants included in its composition, also as mentioned by other researchers [11].

Conclusions

1. It was established that under the conditions of simulated CCl4-induced toxic hepatitis in white rats there was a deterioration of the general clinical condition, development of hepatocellular failure, cholestasis and degenerative changes in the liver, which is confirmed by the biochemical parameters of blood plasma and its homogenates.

2. It was found that application of Fitohol to animals with toxic hepatitis contributed to normalization of a number of biochemical indices reflecting the functional state of the hepatobiliary system, opening the possibility of using this herbal medicinal product as a hepatoprotective agent.

Prospects for further research lie in determining the dose and developing schemes for the use of Fitohol in the treatment of small domestic and productive animals in the gastrointestinal tract pathology and other concomitant diseases.

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Реферати

ЕФЕКТИВНІСТЬ РОСЛИННИХ ЕФІРНИХ ОЛІЙ ЗА ТЕТРАХЛОРМЕТАНОВОГО ГЕПАТИТУ В ЛАБОРАТОРНИХ ЩУРІВ

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У роботі вивчена ефективність застосування ефірних олій у складі рослинного препарату фітохол на тлі тетрахлорметанового токсичного гепатиту в

ЭФФЕКТИВНОСТЬ РАСТИТЕЛЬНЫХ ЭФИРНЫХ МАСЕЛ ПРИ ТЕТРАХЛОРМЕТАНОВОМ ГЕПАТИТЕ У ЛАБОРАТОРНЫХ КРЫС

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В работе изучена эффективность применения эфирных масел в составе растительного препарата фитохол на фоне тетрахлорметанового токсического гепатита у лабораторных

лабораторних щурів. Встановлено, що випоювання фітохолу щурам в дозі 0,03 г на 100 г маси тіла позитивно впливало на клінічний стан тварин, полегшувало прояв гепатоцелюлярної недостатності та розвиток деструктивних змін в гепатоцитах (знижуючи активність лужної фосфатази, аланін- і аспартатамінотрансферази в плазмі крові та оксипроліну, гексозамінів та малонового діальдегіду – в гомогенатах печінки) за гострого токсичного гепатиту. За тривалої інтоксикації організму щурів CCl_4 дія фітохолу проявлялася в покращенні функціонального стану гепатобіліарної системи та деяким відновленням білоксинтезуючої функції печінки.

Ключові слова: рослинний препарат, тетрахлорметановий токсичний гепатит, плазма крові, гомогенат печінки, білі щури

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крыс. Установлено, что выпойка фитохола крысам в дозе 0,03 г на 100 г массы тела положительно влияла на клиническое состояние животных, облегчала проявление гепатоцеллюлярной недостаточности и развития деструктивных изменений в гепатоцитах (снижая активность щелочной фосфатазы, аланин- и аспартатаминотрансферазы в плазме крови и оксипролина, гексозаминов и малонового диальдегида – в гомогенатах печени) при остром токсическом гепатите. При длительной интоксикации организма крыс CCl_4 действие фитохола проявлялось в улучшении функционального состояния гепатобилиарной системы и некоторым восстановлением белоксинтезирующей функции печени.

Ключевые слова: растительный препарат, тетрахлорметановый токсический гепатит, плазма крови, гомогенат печени, белые крысы.

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PROTECTIVE EFFECT OF QUERCETIN ON THE ORAL CAVITY TISSUES IN RATS IN THE PRESENCE OF GENOTOXICANT AND ALIMENTARY DEFICIENCY OF POLYPHENOLS

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The purpose of the study was to establish the effect of the flavonoid quercetin on the oral cavity tissues in rats in the presence of genotoxicant fluorouracil with insufficient intake of plant polyphenols. The experiment was carried out on 21 white rats of the Wistar line. Intact animals were kept on a standard vivarium diet. The control group received a 5% fluorouracil solution *per os* □g□nst th□b□kgr□und □f □fl□v□n□d d□t; fr□shl□ r□□r□d 7.5% □t□t□st□r□h g□l w□s □□□l□d t□th□□r□l mu□s□ f th□ rats. Group 3 rats were additionally treated daily with a gel containing quercetin at a dose of 0.25 mg/kg. The experiment lasted 70 days. The gums turned out to be more sensitive than the buccal mucosa to long-term exposure to the genotoxicant fluorouracil in the case of nutritional deficiency of plant polyphenols. Quercetin in the accepted experimental conditions showed a significant anti-inflammatory effect in the buccal mucosa.

Key words: fluorouracil, nutritional deficiency of plant polyphenols, quercetin, gums, buccal mucosa, protective effect, rats.

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The occurrence of dental morbidity has recently increased due to the increased content of toxicants in the external environment. The consumption of medicinal xenobiotics has also increased significantly.

Fluorouracil is an antitumor agent used in mono- or polychemotherapy, is a structural analogue of pyrimidine, in terms of chemical structure – 2,4-dioxy-5-fluoropyrimidine. It is known that pyrimidine bases: cytosine, uracil, thymine are a part of nucleic acids. In the organism, fluorouracil can enter into a competitive relationship with uracil, being its antimetabolite, and thus turns out to be a biochemical substrate for enzymes responsible for the metabolism of uracil. Along with inhibition of DNA bases synthesis, the drug can be included in both DNA and RNA, and thus lead to inhibition of DNA synthesis and all RNA fractions, because the functioning of DNA as a DNA matrix is disrupted [12]. Considering all of the above, fluorouracil is a genotoxicant. It is classified as a highly toxic substance. When using fluorouracil, there may be pronounced changes in peripheral blood, inhibition of bone marrow hematopoiesis, hemorrhagic phenomena of various localization, stomatitis, ulceration of the mucous membrane of the oral cavity and digestive tract.

Recent studies have shown the diverse effects of plant polyphenols (including flavonoids) on a living organism: antioxidant, anti-inflammatory, cytoprotective, antimicrobial, antiviral, etc.

Currently, the antioxidant activity of flavonoids is paid great attention as a possible mechanism through which the biological effects of this group of compounds are realized [10]. For a long time, flavonoids have been considered as the most important antioxidants [15]. Their defining chemical property