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INFLUENS OF THE HERBAL REMEDY PANCREO-PLANT SN CONDITIONS OF ACUTE TOXIC HEPATITIS ON THE FUNCTIONAL ACTIVITY OF THE LIVER AND PEROXIDATION PROCESSES

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Abstract

The effect of the combined herbal remedy Pancreo-Plant at a dose of 72 mg / kg and the reference drug Silymarin at a dose of 25 mg / kg on the functional activity of the liver, lethality of animals, indicators of cytolysis and peroxidation processes under conditions of acute tetrachloromethane hepatitis were studied. It is proved that the herbal remedy Pancreo-Plant in conditions of acute hepatic intoxication normalizes the bile function, reduces the pathological processes of cytolysis, restores the parameters of carbohydrate metabolism and the immune system.

A pronounced antioxidant effect of the investigated agent was established, which manifests itself in a decrease in the content of lipid peroxidation products, namely, thiobarbituric acid products and diene conjugates, and in the normalization of the enzymatic and non-enzymatic link of endogenous antioxidant protection (reduced glutathione, catalase) and is statistically significantly higher than the effectiveness of the comparison preparation silymarin.

The combined herbal preparation Pancreo-Plant can be considered as a promising remedy for the treatment of toxic liver damage.

Keywords: acute toxic hepatitis, hepatoprotective effect, antioxidant effect, anticytolytic effect.

Introduction.

Toxic liver damage is one of the problematic issues of modern medicine in general and hepatology in particular, because for a combination of certain conditions (high concentration of xenobiotics, severe intoxication, the presence of concomitant diseases), they can lead to liver failure in some cases, with a fatal outcome. Toxic liver damage can have different phenotypes that mimic other liver diseases and complicate patient therapy [1]. According to various authors, the etiological factors of toxic hepatitis are usually organic solvents used in various industrial processes, such as spray painting, paint making, degreasing, metal processing, maintenance and manufacturing of aviation and auto manufacturing work, etc., as well as the use of drugs in the first is acetaminophen, albendazole, etc. [1,2,3,4].

Biomarkers for the identification of toxic liver damage are considered as specific biomarkers, for example, for diagnosis, these are acetaminophen-cysteine protein adducts; mobility, keratin-18, glutamate dehydrogenase, mitochondria DNA (microRNA-122, high mobility group box 1 protein, keratin-18, glutamate dehydrogenase, mitochondrial DNA) [5], and nonspecific biomarkers such as indicators of cytolysis, balance of lipid peroxidation antioxidant system (LPO-AOS) and functional activity of the liver [1].

Therapy of toxic liver damage should be aimed primarily at eliminating powerful oxidative stress, as well as reducing the cytolysis syndrome and restoring the functional activity of the liver [6] and as indicated in the publication by P. Fessas and al. (2020) [7] normalization of the immune system.

A promising drug for the treatment of toxic liver lesions with polymodal pharmacological effects, in our opinion, is the combined herbal preparation Pancreo-Plant, which is registered on the Ukrainian pharmaceutical market as a dietary supplement, improves digestion processes (capsules, PJSC KhFZ «Krasnaya Zvezda», Ukraine). One capsule of Pancreo-Plant contains : *Arctium Lappa (Radices)* - 100.0 mg, *Inula helenium (Rhizomata et radices)* - 30.0 mg, *Agrimonia eupatoria (herba)* - 90.0 mg, *Achillea millefolium (herba)* - 30.0 mg, *Matricaria chamomilla (flores)* - 15,0 mg, *Taraxacum officinale (Radices)* - 20.0 mg, *Galega officinalis (herba)* - 15.0 mg. Standardized vegetable raw materials of medicinal plants that are part of the dietary contain a range of biologically active substances from antioxidant, anhypoxic, anticytolytic action capable of normalizing metabolism, primarily the metabolism of carbohydrates, is a theoretical prerequisite for the presence of a hepatoprotective action in this agent, in conditions of acute toxic liver damage.

The aim of the work was to find out the possibilities of using polycomponent means Pancreo-Plant in conditions of acute carbon tetrachloride hepatitis.

Methods

Acute carbon tetrachloride hepatitis model. Acute tetrachloromethane hepatitis in male rats weighing 190-230 g was caused by a two-day intragastric administration of 50% oil solution of carbon tetrachloride at a dose of 0.8 ml / 100 g of body weight [8] once in addition.

The combined herbal preparation Pancreo-Plant at a dose of 72 mg / kg was administered to experimental animals intragastrically in a therapeutic and prophylactic regimen for 7 days, in 40 minutes. to modeling acute toxic hepatitis and 1 day after modeling hepatitis. The comparison drug Silymarin (trade name «Legalon») was administered according to a similar scheme at a dose of 25 mg / kg, which corresponds to the maximum therapeutic dose for humans 420 mg per day (2 capsules containing 70 mg of silymarin 3 times a day) [9]. Recalculation of doses for rats was made taking into account the coefficient of species sensitivity. Control animals received an equivalent amount of water.

When simulating liver pathology 24 hours after the last injection of hepatotoxins and the studied preparations of animals, narcotisuvali with 1% phenobarbital solution («Interchem» Ukraine), which does not affect the process of bile formation,

performed surgical preparation and collected the secreted bile in hourly portions for 3 hours. Then decapitation The rats were taken out of the experiment, blood was collected, the liver was removed to determine the CMF and to prepare a homogenate for biochemical analysis.

The effect of drugs on the functional state of the liver with its damage was assessed by biochemical parameters, studied in liver tissue, bile, and blood serum. The landslide in the LPO-AOS system was analyzed by the content of TBA-reactants, diene conjugates (DC), reduced glutathione (VG), and catalase activity in the liver homogenate and blood serum [10]. The exocrine function of the liver was assessed by the change in the intensity of bile secretion: the rate of bile secretion was taken into account for each hour of observation in mg / min / 100 for 3 hours and the content of cholesterol and bile acids was determined in it [10]. The activity of the marker enzyme cytolysis alanine aminotransferase (ALT) according to Reitman and Frenkel was determined in blood serum using a set of reagents from Lachema (Czech Republic). The state of lipid metabolism was characterized by the level of cholesterol in the blood serum according to the Lieberman-Burkhardt reaction.

We used 32 sexually mature white randombred rats weighing 180.0–240.0 g. The animals were kept under standard conditions in the vivarium of the Central Scientific Research Laboratory of the NUPh. The studies were carried out in accordance with the National «General Ethical Principles of Experiments on Animals» (Ukraine, 2001), corresponding to the provisions of the «European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes» (Strasbourg, 1986) [11]. The NUPh Bioethics Commission did not reveal any violations of moral and ethical standards during research work.

The obtained experimental data were processed statistically using the Student's t-test using the statistical analysis program Version 6. AnalystSoft Inc., StatPlus [12].

Results

The leading pathogenetic link in the toxic hepatitis, including tetrachloromethane, is the uncontrolled activation of LPO processes, which induces the destruction of hepatocytes with large-scale cytolytic syndrome and impaired liver functional activity, primarily bile secretory function.

The research results are shown in tables 1-4.

Acute carbon tetrachloride hepatitis with severe intoxication is characterized by the development of an inflammatory process and an increase in liver mass by 39% relative to the intact control group. the development of an inflammatory process in the organ with an increase in the mass of the liver. A marker of the destruction of hepatocytes is the development of a large-scale cytolytic syndrome, as evidenced by the decrease in ALT activity in the liver homogenate by 2.9 times, in the blood serum by 3.3 times (Table 1).

The introduction of Pancreo-Plant contributed to a significant normalization of the hepatocyte membranes, first of all, it was verified by the decrease in the activity of the cytolysis enzyme ALT by 1.8 – 1.9 times in the blood serum and in the liver homogenate relative to the indicators of the control pathology group (Table 1).

The pronounced anticytolytic action of the Pancreo-Plant drug contributed to a decrease in destructive-inflammatory processes in the liver and a probable decrease in CPM by 20% ($p < 0.001$) relative to the control pathology group.

The reference drug silymarin in its anticytolytic effect was statistically significant inferior to the means of Pancreo-Plant, and after the normalization of the CMF index it was at the level of the investigated drug (Table 1).

Acute toxic hepatitis is expected to be accompanied by a significant impairment of the liver secretory function in rats (Table 2).

The volume of bile in untreated animals of the group of control pathology was only 23% of the physiological level in intact animals, the rate of bile

secretion decreased by 3.5 times, which indicates the severity of the lesion and impairment of the functional activity of the liver (Table 2).

Under the conditions of the therapeutic and prophylactic administration of the Pancreo-Plant agent, the bile formation processes are restored, which is confirmed by the indicators of the rate of bile secretion and the volume of bile per 100 g of animals, which are slightly inferior to silymarin (Table 2).

It is known that cholesterol is a precursor of bile acids – the physiological regulators of the liver's secretory function. The reasons for the disturbance of the processes of bile formation and bile secretion are precisely pathological changes in cholesterol metabolism and the formation of bile acids, along with a decrease in the transport capacity of hepatocyte membranes. Changes in the content of cholesterol and bile acids are shown in table. 3.

In untreated rats of the control pathology group, acute carbon tetrachloride intoxication not only 2 times reduces the volume and rate of bile secretion, but also negatively affects the composition of bile, as evidenced by a significant decrease in cholesterol in bile, which was 44% of the level of intact control and a decrease in 1, 8 times the content of bile acids in bile (Table 3). At the same time, the content of cholesterol in blood serum during the same period of the study was 82% higher than the normal level. Installed hypercholesterolemia on a decrease in cholesterol and fatty acids in women to indicate the development of cholestasis syndrome in the liver.

A pronounced hypercholesterolemia was established against the background of a decrease in cholesterol and bile acids in bile, which indicates the development of cholestasis syndrome in the affected liver.

The introduction of Pancreo-Plant against the background of acute carbon tetrachloride intoxication significantly reduces hypercholesterolemia and cholestasis syndrome, as evidenced by a 1.3 – fold decrease in serum cholesterol and normalization of the content of bile acids and cholesterol in bile (Table 3).

An increase in the serum cholesterol content in the blood serum of animals of the control pathology group can also be regarded as a compensatory response to oxidative stress, because under conditions of hypercholesterolemia, cholesterol is more easily incorporated into the cell membranes and stabilizes them. Therefore, it was necessary to elucidate changes in the balance of LPO-AOS, for a more complete understanding of the pathogenesis pattern of toxic liver damage and the ability of the Pancreo-Plant agent to have an antioxidant effect (Table 4).

A pronounced hypercholesterolemia was established against the background of a decrease in cholesterol and bile acids in bile, which indicates the development of cholestasis syndrome in the affected liver.

Acute tetrachloromethane hepatitis was accompanied by the activation of LPO processes, as evidenced by a significant increase in intermediate (DC) and final (TBA-active substances) lipid oxidation products by 2.2 and 3.1 times in the liver homogenate in relation to intact control parameters.

In the group of control pathology, a significant decrease in the endogenous antioxidant system was also recorded, as evidenced by the depletion of the GV pool by 2 times compared with the intact control and a decrease in catalase activity by 41% (Table 4).

The expressed antioxidant activity of the combined herbal remedy Pancreo-Plant was verified by a significant decrease in the content of HA (2.2 times) and TBA-active substances (1.5 times) in the liver relative to the control pathology group.

The comparison drug silymarin reduced the corresponding peroxidation processes with a significantly lower efficiency, so the content of DC was reduced by 1.5 times, TBA-active substances by 1.9 times (Table 4).

The investigated agent Pancreo-Plant promoted the restoration of the function of the enzymatic and non-enzymatic link of endogenous AOS, as

evidenced by a significant increase in the level of GV in the liver homogenate to 78.7% relative to the intact control group in the blood serum to 94.4% of the physiological norm of intact animals.

The effect of silymarin on the recovery of the GV pool was lower, 67.1% and 74.6%, and the indicator in the blood serum was significantly inferior to the means of Pancreo-Plant.

Similar changes were observed when studying the activity of catalase, an enzymatic link in AOS. Pancreo-Plant normalized the catalase activity, which was only 16% lower than the intact control indicator and significantly exceeded the effectiveness of the comparison drug silymarin, with the introduction of which the catalase activity was 26% lower than the physiological level (Table 4).

So, the combined herbal preparation Pancreo-Plant at a dose of 72 mg / kg has a powerful antioxidant effect, the activity of the comparison drug silymarin at a dose of 25 mg / kg is higher in two directions: it suppresses the activity of LPO processes, as evidenced by a decrease in the level of TBA-reactants and DC on average 1.5-2.2 times; restores the functions of the enzymatic and non-enzymatic links of the antioxidant system, characterized by an increase in the level of GV and normalization of catalase activity (Table 4).

The results obtained on the establishment of the hepatoprotective effect of the Pancreo-Plant agent under conditions of acute hepatic intoxication with carbon tetrachloride can be explained by the combined composition of the investigated agent.

The Radices *Arctii lappa*, according to a number of authors [13,14,15], has a powerful antioxidant and anti-inflammatory effect. BAR of burdock root extract inhibiting induced nitric oxide synthase (iNOS) by modulating several cytokines.

It was also reported about the ability of bioactive compounds *Arctium lappa* to improve glucose homeostasis and reduce cell resistance to insulin [16].

Inula heleni indicated in modern scientific publications [17,18] has a pronounced antioxidant effect, anti-inflammatory effect and largely normalizes carbohydrate metabolism.

A significant contribution to the implementation of the antioxidant, anticytolytic and, as a consequence of the hepatoprotective effect of the Pancreo-Plant agent, is made by the compounds of *Agrimonia eupatori*, which, as proved by scientists, have an antitoxic effect, normalize lipid metabolism (triglycerides, cholesterol), have a pronounced antioxidant and anticytolytic activity.

Biologically active substances of the *Matricaria chamomilla* have a significant antioxidant, anti-cytolytic, anti-inflammatory effect. There is evidence of the hepato-protective effect of chamomile extract in conditions of liver damage to dimethylhydrazine, which is realized due to the antioxidant and anti-inflammatory action of flavonoids. [19,20,21].

As for the *Achillea millefolium* , along with the antioxidant, cytoprotective effect, modern publications have proven its ability to normalize carbohydrate and lipid metabolism, the activity of liver enzymes (ALT, ALP) under experimental streptozotocin diabetes, the authors note that the pharmacological effect of *Achillea millefolium* extract exceeded the effectiveness of the drug comparisons of metformin [22,23].

Gains positive inflow into the liver at the stage of growth of the growth genesis of the root *Taraxacum officinale*. Biologically active substances of Taraxacum officinale not only reduce oxidative stress and restore the activity of endogenous AOS, but also normalize the activity of hepatic enzymes, restore bile and protein synthesizing function. The positive effect on hepatocytes is confirmed by histological studies [24,25,26].

For the of Galega officinalis, a powerful antiradical effect has been proven, the ability to restore the body's endogenous antioxin system, and it is also known that this extract in conditions of diabetes helps to restore the pool of neutrophils in the bone marrow and reduce the number of

lymphoblasts and leads to inhibition of the process of apoptosis of lymphocytes. that is, it has a pronounced immune-regulating effect in conditions of diabetes mellitus [27,28].

The generalized characteristic of pharmacological effects of medicinal plants of means of Pancreo-Plant is given in table 5.

Analyzing the pharmacological effect of plant that are part of the combined herbal remedy Pancreo-Plant, it is shown in Table 5 and the results of our own research (Tables 1-4), one can make an assumption about the additive synergism of the Pancreo-Plant components, due to which a powerful hepatoprotective effect is realized in conditions of acute toxic liver damage.

Discussion

On the model of acute tetrachloromethane hepatitis, the combined herbal preparation Pancreo-Plant significantly reduces the activity of cytolysis processes and liver hypertrophy, normalizes the processes of bile formation and bile secretion, exhibits a pronounced antioxidant effect: inhibits the intensification of lipid peroxidation processes, normalizes the activity of AOS.

According to the experimental data obtained, a pronounced hepatoprotective effect of Pancreo-Plant was established in conditions of acute toxic carbon tetrachloride hepatitis. In the mechanism of the protective effect of the new agent on hepatocytes, a significant role is played by its ability to have a pronounced anticytolytic activity and a powerful antioxidant effect, significantly exceeding the effect of the comparison drug silymarin.

Pancreo-Plant is a promising remedy for the treatment of liver diseases and requires further in-depth studies in conditions of liver pathology of various origins.

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Table 1. Influence of Pancreo-Plant and silymarin on the liver mass coefficient and their anticytolytic effect in acute tetrachloromethane hepatitis in rats (n = 8)

	KMP, %	ALAT in the liver homogenate, mmol / h · l	ALAT blood circulation, mmol / h· l
Intact control	2,67±0,01	1,09±0,03	0,69±0,09
Control pathology	3,72±0,08**	3,17±0,11**	2,26±0,05**
Pancreo-Plant, 72 mg/kg	2,98±0,03**#	1,73±0,04*# $	1,16±0,03 *# $
Silymarin, 25 mg/kg	3,01±0,05**#	2,05±0,07**#	1,51±0,05**#

Notes: CMF - liver mass coefficient

1. Statistically significant differences with the indices of the intact control group * - p <0.01; ** - p <0.001;
2. Statistically significant differences with the indices of the control pathology group: # - p <0.001;
3. Statistically significant differences with the indices of the silymarin group: $ - p <0.001.

Table 2. Investigation of the effect of Pancreo-Plant and silymarin on the indices of biliary function on the model of acute carbon tetrachloride hepatitis (n = 8)

Experimental conditions	Bile volume, ml / 100g	Bile secretion rate, mg / min · 100 - 1
Intact control	2,07±0,10	4,76±0,12
Control pathology	0,48±0,03**	1,35±0,09 **
Pancreo-Plant, 72 mg / kg	1,15±0,04*#	3,11±0,13 **#
Silymarin, 25 mg / kg	1,29±0,14*#	3,39±0,20 **#

Notes: CMF - liver mass coefficient

1. Statistically significant differences with the indices of the intact control group * - p <0.001; ** - p <0.001;
2. Statistically significant differences with the indices of the control pathology group: # - p <0.001.

Table 3. The effect of Pancreo-Plant and silymarin on changes in cholesterol and bile acids in acute tetrachloromethane hepatitis in rats (n = 8)

Conditions experience	Blood serum cholesterol, mmol / l	Bile cholesterol, mg / min / 100g	Bile acids, mg / min / 100 g
Intact control	1,51±0,07	30,4±1,05	827±15,4
Control pathology	2,76±0,09**	13,4±0,53**	456±31,5 **
Pancreo-Plant, 72 mg / kg	2,14±0,08 *#	20,3±0,89**##	678±32,0 *#
Silymarin, 25 mg / kg	2,01±0,06*##	21,4±0,74**##	716±27,0 *##

Notes:

1. Statistically significant differences with the indices of the intact control group * - p <0.01; ** - p <0.001;
2. Statistically significant differences with the indices of the control pathology group: # - p <0.01; ## - p <0.001.

Table 4. Influence of Pancreo-Plant and silymarin on LPO-AOS parameters in conditions of acute carbon tetrachloride hepatitis in rats (n = 8)

Indicator	Experimental conditions			
	Intact control	Control pathologist	Pancreo-Plant, 72 mg / kg	Silymarin, 25 mg / kg
Liver homogenate				
TBK-reactant, μmol / g	80,6±0,88	246±4,65*	126±5,11*# $	183±4,68 *#
DC, μmol / g	4,94±0,23	10,9±0,35 *	6,05±0,45 # $	7,35±0,22 *#
VG, minds. od.	121±3,56	61,3± 1,96*	95,2 ±5,99*#	81,2±2,71*#
Catalase, μkat / l	0,39±0,02	0,23±0,01*# $	0,33±0,01*# $	0,29±5,11*#
Blood serum				
TBK-reactant, μmol / l	1,13±0,04	3,16±0,07*	1,82±0,07*# $	2,42±0,06 *#
VG, conventional units	67,8±1,31	29,4± 1,52*	64,4 ±2,35*# $	50,6±2,16 *#

Notes:
1. Statistically significant differences with the indices of the intact control group * - p <0.01;
2. Statistically significant differences with the indices of the control pathology group: # - p <0.01;
3. Statistically significant differences with the indices of the silymarin group: $ - p <0.05.

Table 5. Pharmacological effect of medicinal plants that are part of the combined drug Pancreo-Plant

Plant extract	Pharmachologic effect
Arctium Lappa (Radices)	antioxidant, anti-inflammatory, improves carbohydrate metabolism, reduces insulin resistance
Inula helenium (Rhizomata et radices)	antioxidant, anti-inflammatory normalization of carbohydrate metabolism
Agrimonia eupatoria (herba)	antioxidant, anticytolic, antitoxic, normalization of lipid metabolism
Achillea millefolium (herba)	antioxidant, anticytolic, hepatoprotective
Matricaria chamomilla (flores)	antioxidant, anticytolytic, protipal, hepatoprotective
Taraxacum officinale (Radices)	antioxidant, anticytolytic, normalization of gum and gum formation, hepatoprotective
Galega officinalis (herba)	antioxidant, immunocorrective