ORIGINAL ARTICLE

Antioxidant and anticytolytic action as the basis of the Pancreo-Plant® hepatoprotective effect in acute liver ischemia

Antioxidační a anticytolytické účinky jako základ hepatoprotectivního účinku přípravku Pancreo-Plant® při akutní jaterní ischemii

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Received February 26, 2021 / Accepted May 11, 2021

Summary

In this experimental study, the effects of the combined herbal drug Pancreo-Plant® at a dose of 72 mg/kg and the comparison drug silymarin at a dose of 25 mg/kg on animal mortality, cytolysis activity, free radical oxidation, and functional activity of the liver in the conditions of acute experimental ischemia have been studied. A pronounced antioxidant effect of the studied agent has been found which was manifested in the reduction of the lipid peroxidation products content, namely thiobarbituric acid products and diene conjugates and normalization of the enzymatic and non-enzymatic chains of endogenous antioxidant protection (reduced glutathione, catalase). In the case of acute liver failure, Pancreo-Plant® exhibited a significant anti-cytolytic effect, restored carbohydrate metabolism and protein-synthetic function of the liver. It was found that the total hepatoprotective activity of the combined herbal drug Pancreo-Plant® exceeded the activity of the comparison drug silymarin.

Key words: acute hepatic ischemia • hepatoprotective action • antioxidant action • anti-cytolytic action • Pancreo-Plant®

Souhrn

V této experimentální studii byl zkoumán účinek kombinovaného rostlinného přípravku Pancreo-Plant® v dávce 72 mg/kg a srovnávacího léčiva silymarinu v dávce 25 mg/kg na úmrtnost zvířat, cytolytickou aktivitu, oxidaci volnými radikály a funkční aktivitu jater v podmínky akutní experimentální ischemie. Byl zjištěn výrazný antioxidační účinek studovaného přípravku, který se projevil snížením obsahu produktů lipidové peroxidace, konkrétně kyseliny thiobarbiturové a dienových konjugátů a normalizací enzymatických a neenzymatických řetězců endogenní antioxidační ochrany (snížený glutathion, kataláza). V případě akutního selhání jater vykazoval Pancreo-Plant® významný anticytolytický účinek, obnovil metabolismus sacharidů a schopnost jatek syntetizovat bílkoviny. Bylo zjištěno, že celková hepatoprotektivní aktivita kombinovaného rostlinného přípravku Pancreo-Plant® převýšila aktivitu srovnávaného léčiva silymarinu.

Klíčová slova: akutní jaterní ischemie • hepatoprotektivní účinek • antioxidační účinek • anticytolytický účinek • Pancreo-Plant®

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Introduction

According to the WHO, about 46% of global diseases and 59% of deaths are caused by chronic diseases, almost 35 million people worldwide die from chronic diseases, and the prominent place here belongs to liver diseases[1)]. The level of liver diseases is steadily increasing over the years. According to UK national statistics, liver diseases are the fifth most common cause of death. Liver diseases have been recognized as the second leading cause of death among all digestive diseases in the United States, and today experts say that more than 30% of the adult population of the Earth suffers from different liver diseases[2–4)].

Hypoxic hepatitis (HH) is one of the most serious liver pathologies, also known as ischemic hepatitis or liver shock. According to foreign authors[1)], HH considered

the most common cause of acute liver damage in intensive care patients, with the prevalence up to 10%. Hypoxic liver damage is defined as a massive but temporary increase in serum transaminases due to an imbalance between liver supply and oxygen in the absence of other acute causes of liver damage. It usually occurs in the elderly with right-sided congestive heart failure and low cardiac output. Provoking factors are arrhythmias or pulmonary oedema. Symptoms include weakness, shortness of breath and pain in the right upper quadrant. HH is less common in patients with severe hypoxemia or septic shock[4, 5]. Patients with signs of acute hepatic hypoxia / ischemia have a significantly higher risk of mortality. The level of hospital mortality from HH is 61.5%, at the same time the list of drugs for optimal pharmaco-correction of this pathology is insufficient[6].

Hepatic circulatory disorders, with ischemic manifestations and hepatocyte damage, as noted by some authors, have been reported for patients with COVID-19[7–9].

The complexity of the ischemic liver disease mechanisms precludes monotherapy due to insufficient exposure to only one part of the pathological cascade, and the lack of effective drugs with polytropic action necessitates the prescription of drug combinations that increase the risk of side effects[10–12].

Pancreo-Plant® (capsules, manufactured by PJSC HPP "Red Star", Ukraine) is registered at the pharmaceutical market of Ukraine as a dietary supplement that improves the digestive process. 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)* – 1–5,0 mg, *Taraxacum officinale (Radices)* – 20.0 mg, *Galega officinalis (heba)r* – 15.0 mg. Standardized medicinal plants of the dietary supplement containing a range of biologically active substances with antioxidant, antihypoxic, and anticytolytic action can normalize metabolism, especially a carbohydrate one. That is theoretically considered to be a prerequisite of the hepatoprotective action of this medicine at an acute ischemic liver disease.

The aim of the study was to investigate the possibility of using the multicomponent drug Pancreo-Plant® in conditions of total liver hypoxia followed by reperfusion.

Experimental part

Materials and methods

A model of ischemic acute liver failure (ALF) was reproduced in white nonlinear male rats. Total hepatic ischemia was reproduced under thiopental-sodium anesthesia (35 mg/kg intraperitoneally) by applying a special clamp to the vascular leg of the liver and bile duct for 25 min[13]. The clamp was then removed, liver reperfusion was restored, and muscles and skin were sutured in layers. Animal mortality was recorded during the first 24 h after pathology simulation. At the end of the first day, the animals were removed from the experiment (under ether anesthesia) and biomaterial was taken for biochemical studies.

The combined herbal drug Pancreo-Plant® at a dose of 72 mg/kg was administered to experimental animals intragastrically in a therapeutic-and-prophylactic regimen for 7 days for the last time in 40 minutes before the ALF modeling. The comparison drug silymarin (trade name Legalon®) was administered at 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) [Instructions for medical application]. Recalculation of doses for rats was done considering the coefficient of species sensitivity.

The anti-cytolytic effect of the test compound and comparison drugs was evaluated by the activity of cytolysis enzymes ALT and AST in the blood serum, changes in the liver mass index (LMI) specified the anti-inflammatory effect, and the cholestasis level was evaluated by changes in ALP activity. Changes in the LPO-AOS were analyzed for the content of TBARS, diene conjugates (DC), reduced glutathione (GSH) and catalase activity in the liver homogenate and blood serum. Biochemical parameters characterizing liver functions were also studied: carbohydrate metabolism by glycogen content (determination with arthron reagent in liver homogenate[14]), glucose (determination by glucose oxidase method in blood serum by the standard set "Phyllisit-Diagnostics", Ukraine); protein metabolism by total protein content (determination in blood serum by biuret reaction), ceruloplasmin (blood serum)[14].

A cohort of 34 adult white randomly bred rats weighing 180.0–240.0 g was used in the study. Animals were kept in a standard vivarium CSRL NUPh. The research was conducted in accordance with the National "General Ethical Principles of Animal Experiments" (Ukraine, 2001), which comply with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986)[15]. The Commission on Bioethics of NUPh did not reveal any violations of moral and ethical norms during the research work.

The obtained experimental data were processed statistically with the Student's t-criterion, using a program of statistical analysis, Version 6. AnalystSoft Inc., StatPlus[16].

Results and discussion

The hepatoprotective activity of Pancreo-Plant® and silymarin was assessed by an integrated indicator – reduced mortality (Table 1). Under conditions of ischemic ALF mortality of animals of the control pathology group is (50%), which indicates the severity

of the pathology and probably exceeds the rate of intact pseudo-operated rats (0%, $p < 0.001$) (Table 1).

According to the integrated mortality rate, the hepatoprotective activity of Pancreo-Plant®, with a mortality rate of 12.5%, probably exceeds 2 times the effect of the known hepatoprotector silymarin, where the mortality of experimental animals was 25% ($p < 0.05$).

Significant destructive changes in the liver in rats of the control pathology group were found to increase by 1.4 times ($p < 0.05$) to the liver mass coefficient (LMC) (Table 2). An increase in activity of cytolysis enzymes ALT and AST in blood serum by 2.1–2.3 times ($p < 0.05$) demonstrates considerable destruction of liver cells in the group of untreated animals, and increase by 1.9 times ($p < 0.05$) in ALP activity is an indicator of the development of severe cholestasis syndrome (Table 2).

The combined drug Pancreo-Plant® has a pronounced hepatoprotective effect, which is verified by the normalization of the LMC to the level of intact animals. Pancreo-Plant® has a significant anticytolytic effect, probably reduces the activity of cytolytic enzymes ALT and AST in blood serum by 1.8 times and 2.3 times ($p < 0.05$), respectively, relative to the control group rats with acute liver failure. The activity of ALP has no significant differences with the indicator of the group of intact pseudo-operated animals, which indicates the absence of cholestasis in animals under the conditions of administration of Pancreo-Plant® in the therapeutic-and-prophylactic regimen.

The known hepatoprotector silymarin was significantly less active in reducing LMC (3.83 ± 0.11 under the conditions of administration of Pancreo-Plant® against 4.27 ± 0.08 in animals treated with silymarin, $p < 0.05$). Although the comparison drug had a probable anticytolytic effect, but statistically significantly less than Pancreo-Plant®. Less pronounced effectiveness of silymarin was found in the indicator of cholestasis prevention, which was assessed by changes in ALP activity.

Acute liver damage with its large-scale ischemia was accompanied by the development of strong oxidative stress of the organ, which was verified by a significant intensification of LPO processes and a decrease in antioxidative activity (Table 3).

In the control pathology group, there was an increase in the content of TBA reactants in the liver homogenate and blood serum by 2.6 and 2.2 times, respectively ($p < 0.05$), the level of DC increased by 1.4 times ($p < 0.05$) relative to the group of pseudo-operated animals. The severity of oxidative stress was confirmed by a probable decrease in the enzymatic and non-enzymatic chains of AOS, which was determined by a decrease in GSH content by 1.5–1.8 times ($p < 0.05$) in blood serum and liver homogenate and a decrease in catalase activity by 1.8 times (Table 3). The obtained data attests that the endogenous antioxidant defense of the body fails and oxidative stress gains strength and induces cell destruction.

Administration of the combined herbal drug Pancreo-Plant® to animals in the therapeutic-and-prophylactic regimen normalized the LPO-AOS balance and reduced the oxidative stress manifestations. The decrease in the intensity of LPO processes was verified by a probable decrease in TBA reactants by 34% ($p < 0.05$) in blood serum and by 47% ($p < 0.05$) in liver homogenate; DC

Table 1. Effect of Pancreo-Plant® and the comparison drug silymarin on the mortality of rats with acute hepatic ischemia

Group	Control pseudo-operated rats (n = 8)	Control pathology – ALF (n = 10)	Pancreo-Plant®, 72 mg/kg + ALF (n = 8)	Silymarin, 25 mg/kg + ALF (n = 8)
Mortality died/animals in the group (%)	0/8 (0)	5/10 (50)	1/8 (12.5)	2/8 (25)
p	–	$p_{2-1} < 0.05$	$p_{3-2} < 0.05$ $p_{3-4} < 0.05$	$p_{4-1} < 0.05$ $p_{4-2} < 0.05$

ALF – acute liver failure

Table 2. Effect of Pancreo-Plant® and the comparison drug silymarin on liver mass coefficient and activity of cytolysis enzymes and inflammation in blood serum of rats with acute liver ischemia

Experimental conditions		Control – pseudo-ope-rated rats	Control pathology – ALF	Pancreo-Plant®, 72 mg/kg + ALF	Silymarin, 25 mg/kg + ALF
Liver mass coefficient, %		3.58 ± 0.10	4.98 ± 0.15*	3.83 ± 0.11#$	4.27 ± 0.08*#
Blood serum enzymes	ALT, mmol/h•l	0.60 ± 0.01	1.26 ± 0.06*	0.68 ± 0.02#$	0.84 ± 0.05*#
	AST mmol/h•l	0.57 ± 0.02	1.34 ± 0.08*	0.67 ± 0.01*#$	0.87 ± 0.05*#
	Alkaline phosphatas, mmol/l	1.12 ± 0.09	2.15 ± 0.09*	1.23 ± 0.04 #$	1.58 ± 0.08*#

ALF – acute liver failure

*statistically significant differences with the indicators of the pseudo-operated control group ($p < 0.05$)

#statistically significant differences with the indicators of the group of control pathology (ALF) ($p < 0.05$)

$statistically significant differences with the indicators of the silymarin group ($p < 0.05$)

in liver homogenate reduced by 1.3 times ($p < 0.05$) relative to the control pathology group.

The mechanism of antioxidant action of the combined herbal drug Pancreo-Plant® involves the restoration of activity of both non-enzymatic AOS (increase in GSH content by 37% ($p < 0.05$) relative to the control pathology group) and enzymatic (increase of catalase activity by 25% relative to the control pathology group) chains (Table 3).

The administration of the comparison drug silymarin at acute hepatic ischemia helped to reduce LPO activation and restore AOS, but this antioxidant activity was significantly less than that of Pancreo-Plant®. Thus, the decrease of TBARS in liver homogenate and blood serum on the background of the administration of silymarin decreased relative to the control group by 21% and 18% ($p < 0.05$), respectively, that is 2 times less effective than the new drug Pancreo-Plant® (Table 3).

Similar changes were observed for the DC concentration in the blood serum, which was reduced by 13% under the influence of silymarin. Although these changes were likely relative to the control group, but significantly less to the level of DC influenced by Pancreo-Plant®. Normalization of the endogenous antioxidant system indicators, both enzymatic and non-enzymatic chains under conditions of silymarin administration, was also inferior to the combined herbal drug Pancreo-Plant®. Restoration of GSH content and catalase activity on the background of the administration of the reference drug is significantly inferior to the action of the studied one.

Table 3. Effect of Pancreo-Plant® and the comparison drug silymarin on pro-oxidant-antioxidant balance in rats with acute liver ischemia (n = 25)

Indicator	Experimental conditions			
	Control – pseudo-operated rats (n = 8)	ALF		
		Control pathology (n = 5)	Pancreo-Plant®, 72 mg/kg (n = 7)	Silymarin, 25 mg/kg (n = 6)
Liver homogenate				
TBARS, μmol/g	78.5 ± 0.76	207 ± 4.95*	111 ± 5.08*#$	165 ± 5.68*#
DC, μmol/g	6.08 ± 0.31	8.73 ± 0.18*	6.49 ± 0.21#$	7.43 ± 0.21*#
GSH, c.u.	122 ± 3.46	67.9 ± 2.41*	103 ± 1.39*#$	84.7 ± 2.83*#
Blood serum				
TBARS, μmol/g	1.12 ± 0.06	2.42 ± 0.06*	1.61 ± 0.08*#$	1.96 ± 0.11*#
GSH, c.u.	62.2 ± 1.78	41.2 ± 2.09*	56.3 ± 1.22*#$	49.9 ± 0.92*#
Catalase, mkat/l	0.37 ± 0.02	0.21 ± 0.02*	0.32 ± 0.01*#	0.27 ± 0.01*#

ALF – acute liver failure
*statistically significant differences with the indicators of the pseudo-operated control group ($p < 0.05$)
#statistically significant differences with the indicators of the group of control pathology (ALF) ($p < 0.05$)
$statistically significant differences with the indicators of the silymarin group ($p < 0.05$)

Table 4. Effect of Pancreo-Plant® and the comparison drug silymarin on the indicators characterizing the functional activity of the liver in rats with acute hepatic ischemia (n = 25)

Indicator	Experimental conditions			
	Control – pseudo-operated rats (n = 8)	ALF		
		Control pathology (n = 5)	Pancreo-Plant, 72 mg/kg (n = 7)	Silymarin, 25 mg/kg (n = 6)
Liver homogenate				
Glycogen, μg/ml	1270 ± 39.8	724 ± 25.7*	1127 ± 42.8*# $	990 ± 4 6.7*#
Blood serum				
Glucosum, μmol / g	8.84 ± 0.06	5.86 ± 0.17*	7.69 ± 0.15*# $	6.77 ± 0.12*#
Total protein, g/l	73.6 ± 1,27	54.9 ± 1.99*	69.0 ± 1.94#	60.4 ± 1.26*#
Ceruloplasmin, g/l	0.53 ± 0.01	0.47 ± 0.03	0.52 ± 0.01	0.49 ± 0.01

ALF – acute liver failure
*statistically significant differences with the indicators of the pseudo-operated control group ($p < 0.05$)
#statistically significant differences with the indicators of the group of control pathology (ALF) ($p < 0.05$)
$statistically significant differences with the indicators of the silymarin group ($p < 0.05$)

Therefore, the antioxidant effect of the combined herbal drug Pancreo-Plant® probably exceeds the activity of silymarin.

Under the conditions of ischemic ALF, a probable decrease in the functional activity of the liver was found (Table 4).

A marker of decreasing the protein-synthetic function is a decrease in total protein concentrations in blood serum in animals of the control pathology group by 1.3 times relative to the control pathology group of pseudo-operated rats. Decrease in the protein-synthetic function was confirmed by a 12% decrease in ceruloplasmin.

Acute hepatic ischemia was characterized by a significant violation of carbohydrate metabolism, which was determined by a 43% decrease ($p < 0.05$) of glycogen in liver homogenate and glucose concentration decrease in blood serum by 34% ($p < 0.05$) (Table 4).

The combined herbal drug Pancreo-Plant® reliably restores the functional activity of the liver.

The administration of the combined herbal remedy to the level of the intact group of pseudo-operated animals normalizes the protein-synthetic function, which was verified by increasing the total protein content in blood serum by 1.2 times ($p < 0.05$) relative to the control pathology group, complete recovery of ceruloplasmin level has also been registered.

The positive effect of the administration of the combined herbal drug Pancreo-Plant® in the therapeutic and prevention regimen on the indicators of carbohydrate metabolism should be noted. There was fixed the normalization of the glycogen amount to the physiological level, which exceeds the indicator of the control pathology group by 1.6 times ($p < 0.05$) and glucose in the blood serum, the concentration of which is 1.3 times ($p < 0.05$) higher than in untreated animals (Table 4).

The comparison drug silymarin restored the protein-synthetic function equal to Pancreo-Plant® in total protein and ceruloplasmin indicators, but its effect on carbohydrate metabolism is statistically significantly inferior to Pancreo-Plant®. Silymarin increases the glycogen level by 1.3 times, glucose level by 1.1 times (Table 4).

The obtained results of the experimental study to establish the hepatoprotective effect of the Pancreo-Plant® in the conditions of acute ischemia-reperfusion of the liver can be explained by the combined composition of the studied drug.

Radices Arctii lappae extract, according to a number of authors[17, 18] contains non-volatile compounds, including lignans, fatty acids, acetylene compounds, phytosterols, polysaccharides, caffeic acid derivatives, flavonoids, terpenes/terpenoids, volatile compounds, carboxylic and fatty acids (lignans, fatty acids, acetylenic compounds, phytosterols, polysaccharides, caffeoylquinic acid derivatives, flavonoids, terpenes/terpenoids and volatile compounds such as hydrocarbons, aldehydes, methoxypyrazines, carboxylic and fatty acids, monoterpenes and sesquiterpenes). Arctigenin and its glycoside, arctiine, are the two main active ingredients of *Arctium lappa*, which according to Gao Q. et al. (2018)[19] have a powerful antioxidant and anti-inflammatory effect by inhibiting induced nitric oxide synthase (iNOS) by modulating several cytokines.

The ability of bioactive compounds *Arctium lappa* to improve glucose homeostasis and reduce cell resistance to insulin has also been reported[20].

Rhizomata et radices Inulae extract contains inulin and other polysaccharides, bitter substances, essential oil, saponins, resins, gums, mucus, a small amount of alkaloids, gelenin, and as noted in the publications of Gierlikowska B. et al. (2020), Tavares WR et al. (2019)[21, 22] it has a pronounced antioxidant effect, anti-inflammatory effect and it significantly normalizes carbohydrate metabolism.

Bioactive compounds of *Agrimonia eupatoria (herba)* extract make a significant contribution to the realization of antioxidant, anticytolytic and, as a consequence, the hepatoprotective effect of Pancreo-Plant. As shown in the study by Cho YM et al (2018)[23], *Agrimonia eupatoria (herba)* extract protects against liver damage by lowering lipids (triglycerides, cholesterol) and antioxidant activity. This clinical study also proved a significant anticytolytic effect found by reducing the activity of ALT and AST.

Biologically active substances of *Flores Chamomillae* extract (chamomile) are also known to have anti-oxidant, anticytolytic, anti-inflammatory effects[24, 25]. In a modern study by Shebbo S. et al. (2020)[26] for the first time established hepatoprotective effects of *Flores Chamomile* aqueous extract in the intermediate stage of colorectal cancer in mice, which induced by the administration of Dimethylhydrazine – a potent carcinogen for the colon and liver. The results showed the potential hepatoprotective effects of chamomile extract against liver damage, proliferation and inflammation caused by dimethylhydrazine. Flavonoids of the extract due to antioxidant, antiproliferative and anti-inflammatory properties had a significant hepatoprotective effect.

Antioxidative properties are also characteristic of tannins and flavonoids of *Galega officinalis (herba)* and *Achillea millefolium (herba)*.

Conclusions

The combined herbal drug Pancreo-Plant® has a significant hepatoprotective effect, positively affecting various chains of the pathogenetic cascade in the ischemic liver. Biologically active plant compounds of *Arctium lappa (Radices)*, *Inula helenium (Rhizomata et radices)*, *Agrimonia eupatoria (herba)*, *Achillea millefolium (herba)*, *Matricaria chamomilla (flores)*, *Taraxacum officinale (Radices)*, *Galega officinalis (herba)*, due to the sum of their antioxidant and anticytolytic action have a significant hepatoprotective effect under conditions of total liver ischemia, followed

by reperfusion. In terms of hepatoprotective activity, the combined herbal drug Pancreo-Plant® probably exceeds the effectiveness of the known hepatoprotective silymarin. The positive difference between the studied drug and the comparison drug is its ability to normalize carbohydrate metabolism on the background of acute liver failure.

Pancreo-Plant® is a promising drug for the treatment of liver diseases and requires further in-depth research in the context of liver pathologies of various origins.

Conflict of interest: none.

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