Experience and prospects of experimental study of the hepatoprotective effect of phytoadaptogens in chronic toxic liver damage

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SUMMARY

The article provides an overview of domestic and foreign scientific literature on the study of the hepatoprotective properties of phytoadaptogens. The most interesting experimental work carried out with various drugs based on adaptogens is considered in detail. The methodological approaches used to study various aspects of the protective action of drugs against the liver have been studied. The promising directions in experimental work in this area, which require further development, are outlined. The importance and relevance of the results of these studies for the creation of new hepatoprotective drugs based on biologically active substances with nonspecific (adaptogenic) action are reflected.

Key words: hepatoprotectors, adaptogens, toxic lesionsliver.

RESUME

The article presents an overview of the russian and foreign scientific literature on the study of hepatoprotective properties of phytoadaptogens. The most interesting experimental work carried out with various preparations based on adaptogens are discussed in detail. Studied methodological approaches were used to research various aspects of the protective effect of drugs on the liver. Promising areas designated in the experiments in this area that needs further development. The importance and relevance of these findings to create new hepatoprotective drugs based on biologically active substances with nonspecific (adaptogenic) effect is reflected.

Keywords: hepatoprotectors, adaptogens, toxic liver deseases.

In the process of life, a modern person is in contact with a large number of toxic xenobiotics (food preservatives, household chemicals, medicines, alcohol, etc.). One of the most frequently affected organs when exposed to toxins is the liver, since it is in it that the main metabolic processes are carried out aimed at their biotransformation, during which more

more dangerous substances [1]. In this regard, modern medicine faces an urgent task - the development of effective and safe methods for the prevention and treatment of toxic liver damage [2, 3, 4]. One of the ways to solve it is the use of drugs that protect the liver from the effects of damaging factors and accelerate its recovery after it - hepatoprotective drugs.

According to modern concepts, the action of hepatoprotective agents can be realized using the following mechanisms [5]:

- through antioxidant - vitamins (retinol, α-tocopherol, pantothenic acid, etc.), products based on plant polyphenols (legalon, silibor, flamin, etc.), thiols (cysteine, N-acetylcysteine);
- promoting the repair of hepatocyte membranes - drugs phospholipids (Essentiale, Lipostabil);
- stimulation of liver parenchyma regeneration (methionine, calcium pangamate, cytidine, orotic acid).

For the prevention and treatment of hepatic lesions, a variety of medicines, including those of herbal origin, are currently recommended for use. Due to their hepatoprotective action, they prevent and / or normalize liver dysfunctions and contribute to its structural preservation, while having high safety even with prolonged systematic use [6, 7, 8, 9, 10].

Among herbal remedies with a pronounced hepatoprotective effect, a special place is occupied by drugs that increase nonspecific resistance and adaptive capabilities of the body - phytoadaptogens [11].

The main pharmacological property of phytoadaptogens is the ability to act nonspecifically and universally, expanding the boundaries of human adaptation to external extreme factors of various nature (stress, various types of radiation, sharp climatic changes, physical exertion, intoxication with toxic substances with various toxic mechanisms, etc.). Moreover, their action is manifested, inter alia, in the protection of tissues from destruction, antioxidant and membrane stabilizing action, optimization of metabolic processes, and not due to their stimulation. The systematic use of these drugs leads to the formation of a structural trace of adaptation [12, 13, 14, 15, 16, 17, 18].

Also, the obligatory properties of phytoadaptogens are their high safety, low toxicity, lack of addiction and negative aftereffect even with prolonged systematic use [19]. These features make it possible to use the regular intake of phytoadaptogens as a preventive measure against the threat of an adverse factor [14].

In numerous experiments, phytoadaptogens have proven safety and highly efficiency against various poisons with multidirectional toxic effects on organs and tissues, including their pronounced hepatoprotective activity, which has been proven against such ecologically dangerous poisons as organochlorine, tetracycline, alcohol, etc. [1, 20, 21, 22, 23]. So, in the work of E.V.

Kryukovskaya [24] investigated the antitoxic activity of aralia tincture on frogs during acute intoxication with carbon tetrachloride (at a dose of 0.1 ml of 2.5% CCL oil solution4). Based on the experimental data obtained, it was concluded that aralia tinctures had a pronounced prophylactic effect in CCL intoxication4, intensified the detoxification processes, which was reliably evidenced by the delay in the extinction time and the acceleration of the restoration of the central nervous system reflexes and a decrease in the percentage of death of experimental animals.

In experiments on white mice L.N. Shantanova [25] proved that the complex phytoadaptogen Kardekaim, containing cardamom, elecampane, caragana, ginger, created according to the prescription of Tibetan medicine, after a single administration, reliably showed an antitoxic effect against carbon tetrachloride.

Let us dwell in more detail on the work of D.S. Molokovsky [21]. On the model of acute intoxication with carbon tetrachloride (2.5 ml / kg) in mice, a number of phytoadaptogens were studied: preparations of ginseng of both natural and biotechnological origin, tinctures of aralia, zamaniha, schisandra, extracts of rhodiola and eleutherococcus roots. As a result of the experiments, it was revealed that the prophylactic use of phytoadaptogen preparations contributes to the preservation of the detoxification function of the liver, inhibits the activation of lipid peroxidation caused by CCL4, reduces the severity of violations of the membrane permeability of hepatocytes. There was also a tendency to an increase in liver glycogen, the content of which decreased under the action of carbon tetrachloride. The criteria for assessing the protective effect of drugs against the liver were the indices of enzymes characterizing liver function (aspartate aminotransferase, alanine aminotransferase, aldolase), the duration of thiopental anesthesia and the content of malondialdehyde, and the histomorphological picture of the liver. The author associates the protective effect of phytoadaptogens with the antioxidant properties of these drugs, and the therapeutic efficacy - with the effect on the regenerative biosynthetic processes in the liver.

It should be noted that in this work, the extract of Rhodiola rosea, administered at a dose of 15 ml / kg of animal weight, did not show the high efficiency that was noted by other authors. Further studies of the preparations of Rhodiola rosea showed that such unexpectedly low results are associated with the use of D.S. Molokovsky of unreasonably high doses of rhodiola. So, in the works of L.V. Levina [26] and A.I. Yelkin [27], it was proved that the extract of rhodiola shows its maximum therapeutic effect in doses not exceeding 1 ml / kg, moreover, with an increase in the dose, the effectiveness decreases. In a series of experiments with CCL hepatotoxin intoxication4 a pronounced protective effect is manifested not only by the extract of Rhodiola rosea, but also substances isolated from it (rosin, salidroside, rosavin). At the same time, the hepatoprotective effect was enhanced with their long-term use [28, 29, 30].

It is also worth noting a study of the antitoxic properties of salidroside (at doses of 20, 50, and 100 mg / kg) conducted by Yan-Ling Wu et al. [31] on mice male sex at acute intoxication model hepatotoxin paracetamol (single injection at a dose of 300 mg / kg intraperitoneally). The results of histological and immunohistochemical analyzes showed that salidroside prevents a decrease in the level of intracellular glutathione and damage to hepatocytes by LPO products.

In experimental studies [13, 14], the prophylactic use of Eleutherococcus preparations reduced the consequences of acute poisoning with carbon tetrachloride. At the same time, it was revealed that the antitoxic effect of Eleutherococcus and other adaptogens increases with course use and is due to its nonspecific, resistogenic and adaptogenic effects. It is noteworthy that phytoadaptogens also demonstrated their hepatoprotective effect in experiments where substances were used as model poisons, in the mechanism of the toxic action of which liver damage was not the main one. So, in the studies of A.I. Yelkin [27] in case of animal intoxication with a number of toxic substances (aniline, sodium nitrous acid, chlorophos, asymmetric dimethylhydrazine) preparations of ginseng, Rhodiola rosea normalized the indicators, characterizing liver function. Moreover, the author associates their antitoxic effect, including with the protection of glycogen-synthesizing and detoxifying functions of the liver. It can also be noted that in experimental studies (with intoxication with asymmetric dimethylhydrazine), the protective properties of Rhodiola in relation to the liver were in many respects similar to those of the extract of Eleutherococcus, and in some cases exceeded it.

It is interesting to note that in the experimental work on the study of the antitoxic properties of the extract of Rhodiola and tincture from the biomass of the tissue culture of Rhodiola rosea under the conditions of chronic intoxication of rats with organophosphate insecticides (chlorophos and karbofos) S.V. Kozin discovered their protective properties in relation to the liver [1]. This was manifested in the normalization of a number of biochemical, enzymological parameters characterizing the safety of the liver, as well as the histomorphological picture of the liver. The author associates the protective effect of rhodiola preparations against the studied organophosphate insecticides, including their hepatoprotective effect. Thus, it can be concluded that a number of phytoadaptogen preparations have a protective effect, in particular an antitoxic one, which is realized, among other things, with the help of their hepatoprotective properties.

It should be noted that the study of the pharmacological action of phytoadaptogens has its own characteristics, such as: the need for long-term use of drugs to develop the maximum therapeutic effect; selection of an adequate dose of phytoadaptogen is necessary, since their “dose-effect” curve has a “dome-shaped” character and an inadvertent increase in the dose can lead to a decrease or even loss of the effect [14]; it is also necessary to pay attention to the fact that experimental models of adverse effects should not be very severe, otherwise the drugs will not show pharmacological action. Let us consider in more detail the experimental models of toxic liver damage described in the available literature, used to study the hepatoprotective properties of phytoadaptogens. So in the work of D.S. Molokovsky [21], when studying disorders in hepatocytes and mechanisms of hepatoprotective properties of phytoadaptogens (tinctures of ginseng leaves and roots, aralia roots, preparations from ginseng tissue culture, extracts of rhodiola and eleutherococcus roots), a model of acute toxic hepatitis caused by carbon tetrachloride was used. Hepatotoxin was injected subcutaneously to animals at a dose of 2.5 ml / kg of animal weight in the form of a 50% oil solution. To assess morphofunctional abnormalities in hepatocytes 18–20 hours after CCL injection4 took blood and liver from experimental animals. The barbiturate test (using hexenal and sodium thiopental) served as an indicator for assessing the detoxifying function of the liver, which indicates the preservation of hepatocytes in the experiments. The functional safety of the liver was judged by the duration of narcotic sleep, which was recorded by the indicator of the "lateral position" of the animals. The excretory function of the liver was assessed by the bromsulfalein test. In rats treated with CCL_4, the rate of elimination of bromsulfhalein from the blood was sharply reduced, which indicates functional disorders in the liver. When studying the prophylactic effect of phytoadaptogens, drugs were administered preventively for 6-7 days once a day intragastrically at a dose of 15 ml / kg, the last administration was carried out at least 16-18 hours before CCL administration4 at a dose of 2.5 ml / kg 50% oil solution. When studyingcurativehepatoprotective action of phytopreparations

carbon tetrachloride was introduced similarly at a dose of 5 ml / kg of animal body weight. After the injection of the toxin, the animals received phytoadaptogens for 6–7 days. 24 hours after the last injection of phytopreparations, a thiopental test was performed, as well as blood and liver sampling of animals.

Unfortunately, this work used a single dose for all phytoadaptogens. That is, the individual characteristics of the dependence of the effect on the dose of each drug were not taken into account. This was manifested, in particular, in the fact that the hepatoprotective effect of the Rhodiola rosea extract was not found.

It is also interesting to note the work of Ji-Xing Nan and co-authors [32], in which, when studying the hepatoprotective activity of an aqueous extract of Rhodiola Sakhalin roots on male rats (orally at doses of 50, 100, 200 mg / kg for 28 days), carbon tetrachloride. The hepatotoxin was mixed with an equal volume of corn oil and administered orally at a dose of 1 ml / kg of animal weight 2 times a week for 28 days. To assess morphofunctional disturbances in hepatocytes 3 days after the last dose of CCL_4 took blood and liver from experimental animals. Aspartate alanine aminotransferase activity levels, albumin levels, hydroxyproline and malondialdehyde levels, and liver histological changes were assessed.

Also US appears to promising consider some experimental models of intoxication that have been used to study other herbal medicines. It is possible that some of them could later be used in studies of phytoadaptogens. So, A.Yu. Terekhov [33] used indomethacin and tetrachlorocarbon models of hepatopathies to study the protective effect of biologically active substances from the flowers of open marigolds. The experiment was carried out on white outbred mice and rats of both sexes. CCL Model4 - hepatosis was reproduced by introducing intragastrically through a tube 3 times every other day with 50% CCL oil solution4 in vaseline oil at a dose of 0.15 ml / 100 g of animal weight, or 50% CCL oil solution4 was injected subcutaneously with 0.4 ml / 100 g of body weight once a day for four days. An experimental model of acute liver injury with indomethacin was reproduced as follows: indomethacin in the form of an aqueous suspension at a dose of 10 mg / kg of animal weight was orally administered to animals three times (once a day every day). Assessment of the functional state of the liver in acute CCL_4 -hepatosis and indomethacin lesion was carried out according to the following parameters: activity of alanine aminotransferase, alkaline phosphatase, cholinesterase in blood serum, thymol sample of blood serum, content of total and bound bilirubin in blood serum, content of cholesterol, triglycerides, phospholipids in serum and liver, glycogen in the liver, the histological picture of the liver of animals.

In the experimental work carried out by A.I. Vengerovsky [2], studied the ability of hepatoprotective agents - eplir and salsocollin - to eliminate structural, metabolic and functional disorders in the liver in various toxic hepatitis. Mice received daily for six days intragastrically studied hepatoprotectors and 1 ml / kg CCL_4 in a 10% solution of olive oil. The study drugs were injected into the rats through a probe and at the same time one of the listed hepatotoxins: CCL_4 - 1.25 ml / kg in 50% oil solution for four days; paracetamol - 2500 mg / kg in 25% suspension on starch mucus for 2 days; allyl alcohol - 100 mg / kg in 1% aqueous solution for 2 days; D-galactosamine - 500 mg / kg in 5% aqueous solution for 2 days; hydrazine hydrochloric acid - 200 mg / kg in 2% aqueous solution for 2 days. Further, the survival rate of animals, the dynamics of body weight, the relative weight of the liver, length of hexenal sleep, bromsulfalein test and a number of other indicators characterizing the functional state of the liver were determined: histological structure, the content of RNA, protein, glycogen, the activity of liver enzymes, ultrastructure of hepatocytes, excretory function of the liver, antitoxic liver function, content, rate of formation of LPO products and activity of the liver antioxidant system, content of liver lipid and phospholipid fractions, the content of lipids, protein, glucose, the activity of enzymes of hepatic origin in the blood. To study pharmacotherapy with phytopreparations (bearded gentian extract, cogfish extract, choleretic, antihepatotoxic tea, kaleflon) damage to the organs of the hepatobiliary system S.M. Nikolaev [34] used a model of acute liver intoxication with carbon tetrachloride. White rats were injected with 50% CCL oil solution4 at a dose of 4 ml / kg of animal weight daily for four days. The dynamics of the processes of free radical oxidation of liver lipids was recorded using the chemiluminescence method. In the experimental work of Surendra Kr. Sharma et al. [35] for study hepatoprotective properties of the alcoholic extract of the roots of the cultivated grape (Vitis vinifera L.), a tetrachlorocarbon model of toxic hepatitis was used. For 7 days, rats received 0.5 ml / kg of a 50% CCL oil solution once daily$_4$ intraperitoneally. On the eighth day, decapitation and sampling of blood and liver tissue samples were performed. The functional state of the liver after intoxication was assessed according to the following indicators: the activity of aspartate alanine aminotransferase, alkaline phosphatase, the content of bilirubin in the blood serum and the histological picture of the liver of animals. Another experimental hepatotoxin is tetracycline, used in the work of N.Yu. Bagan [20]. This antibiotic has a direct damaging effect on the liver and belongs to enzyme inhibitors. In the experiment, rats were intragastrically injected as a suspension on 1% starch paste using a syringe and a metal catheter at 0.5 g / kg, daily for five days. Carbon tetrachloride was used as the second damaging agent. Animals were injected under the skin with a 50% CCL oil solution$_4$ at a dose of 4 ml / kg of animal weight daily for four days. Studying the hepatoprotective properties of phytoadaptogens, in our opinion, more attention should be paid to chronic hepatic intoxication, since in most cases toxic substances enter the human body in small doses and for a long time (taking medications, alcohol consumption, contact with food preservatives, chemicals used in industry, agriculture, everyday life, etc.). However, an analysis of the available literature showed that experimental studies mainly simulated acute hepatic intoxication, and insufficient attention was paid to the directed study of the hepatoprotective properties of phytoadaptogens in models of chronic hepatic intoxication with hepatospecific toxins.

A number of authors associate the hepatoprotective effect of phytoadaptogens with their antioxidant, membrane stabilizing, and repair mechanisms [13, 14]. One of the main pathogenetic mechanisms of the development of various pathologies, including toxic liver damage, is the activation of peroxide processes, which leads to free radical damage to membrane cellular structures and, accordingly, to disruption of cellular functions [36]. Numerous experiments carried out both on modelsin vitro [26, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46], and on models in vivo [8, 9, 21, 26, 32, 41, 43, 47, 48, 49, 50], the high antioxidant activity of phytoadaptogens was proved. Their antioxidant effect can be carried out both through direct inhibition of free radical oxidation reactions and through the activation of the endogenous antioxidant system of the body.

So in the work of D.S. Molokovsky [21], it was found that preparations of ginseng and other phytoadaptogens significantly weakened and in some cases completely prevented LPO activation in the liver during CCL_4- induced hepatitis, which was confirmed by a decrease in the level of malondialdehyde in the blood of experimental animals. The concentration index of malondialdehyde is used to evaluate the effectiveness of antioxidants in experiments.in vivo, thanks to the fact that its concentration is directly proportional to the intensity of free radical oxidation processes. In experiments with model intoxication with alloxan and carbon tetrachloride - substances with a free radical damage mechanism, according to the author, Eleutherococcus displayed an antitoxic effect associated with a direct or indirect antioxidant effect.

According to I.V. Dardymova [12], one of the probable ways to implement the protective effect of ginseng and eleutherococcus can be both a direct effect on free radicals and indirectly through an increase in the amount of NADPH (hydrogen donor). The author also experimentally confirmed the antiradical effect of Eleutherococcus in the prophylactic use of the amount of eleutherozides in case of alloxan intoxication. The works of foreign authors also confirm the antioxidant effect of preparations based on ginseng and Eleutherococcus antioxidant effect of preparations based on ginseng and Eleutherococcus [50, 51, 52, 54, 55].

Thus, with a high degree of probability, it can be argued that the antioxidant mechanism plays a large, if not the leading role in the hepatoprotective properties under the antitoxic action of phytoadaptogens. Also, as one of the possible mechanisms of the hepatoprotective action of phytoadaptogens in toxic liver damage, one can assume their membrane-stabilizing effect.

In particular, in experiments by the method of A.N. Vanyushkin [55, 56] studied the membranotropic effect of phytoadaptogens. The technique is based on assessing the resistance of human erythrocyte membranes. Based on the fact that phytoadaptogens, as mentioned above, have antioxidant properties, it was assumed that they are capable of exhibiting membrane stabilizing properties. The method revealed a pronounced membrane-stabilizing effect of phytoadaptogens (Rhodiola rosea, ginseng, Eleutherococcus, Aralia, Leuzea), which depends on the content of specific BAS in them.

Experimental data suggested that one of the most important mechanisms of the hepatoprotective action of phytoadaptogens, namely, their therapeutic action after liver damage to a toxin, is the ability to increase reparative processes in the liver [14, 57].

Thus, a number of authors [12, 14, 57, 58] in animal experiments proved the ability of preparations of Eleutherococcus and Rhodiola rosea to significantly accelerate liver recovery after partial hepatectomy. According to scientific literature [6, 14, 59], one of the positive properties of phytoadaptogens is the possibility of their combined use with other biologically active substances of nonspecific action (vitamins, antioxidants, trace elements, etc.). At the same time, they show the ability to mutually potentiate each other, while maintaining high security.

Traditionally, most of the work on the study of phytoadaptogens was carried out in the USSR (in the former republics of the USSR) and in the countries of the Far East (China, Japan, Korea), i.e. in places where adaptogen plants grow. The difficult situation in domestic science that arose in the 90s led to a sharp reduction of research, including in the field of the study of phytoadaptogens. This explains the relatively small number of publications by Russian scientists on this topic in recent years. However, even from the materials presented in this article, it is clear that the interest in this problem in the world is quite great.

From our point of view, in the experimental study of the hepatoprotective action of phytoadaptogens, there are a number of promising areas that require further development:

- the use of models of chronic liver intoxication using toxic substances with hepatospecific action;
- study of the combined effects of several damaging factors along with hepatotoxic agents (intense physical activity, other xenobiotics, extreme temperatures, etc.), which will bring the experimental model closer to real conditions;
- conducting more detailed studies of hepatoprotective properties complex preparations based on phytoadaptogens and other biologically active substances of nonspecific action;
- experimental identification and study of the mechanisms of hepatoprotective action of phytoadaptogens.

The information obtained as a result of such experiments will make it possible to create new drugs, for example, complex agents, to develop new indications for their therapeutic and prophylactic use in chronic liver damage by various xenobiotics, which will expand the arsenal of effective and safe hepatoprotective agents.

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