PHARMACOLOGY AND PHARMACY

THE EFFECT OF COMPLEX PHARMACOTHERAPY REGIMENS USING A HERBAL REMEDY FROM *HIPPOPHAE RHAMNOIDES* ON BIOCHEMICAL BLOOD PARAMETERS OF RATS WITH PARACETAMOL HEPATITIS

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ABSTRACT

Background. *The use of complexes of synthetic and herbal remedies as hepatoprotectors in the treatment of liver pathologies of various etiologies is an urgent task of pharmacology. A promising type of medicinal plant raw material is an extract of Hippophaes rhamnoides leaves. The hepatoprotective effect of extract of Hippophaes rhamnoides leaves in combination with ademethionine has not been studied to date.*

The aim of the work. *To study changes in biochemical markers of hepatic function in the application of complex schemes of pharmacotherapy of experimental liver damage with paracetamol using Extractum foliorum Hippophaes rhamnoides.*

Materials and methods. *The experimental study was performed on Wistar rats. The animals were divided into six groups. Group 1 (intact) – animals without a model of liver damage and without treatment; in Group 2 (control) paracetamol was used to create experimental hepatitis without treatment (positive control group); in Group 3 (comparison) a combination of "silibinin + ademethionine" was used on a model of paracetamol hepatitis; in Group 4 (experimental) extract of Hippophaes rhamnoides leaves was used on the model of paracetamol hepatitis; in Group 5 (experimental) ademethionine was used on a model of paracetamol hepatitis; in Group 6 (experimental) a combination of extract of Hippophaes rhamnoides leaves and ademethionine was used on a model of paracetamol hepatitis. The functional state of the liver of experimental animals was determined by biochemical parameters.*

Results. *When using a combination of extract of Hippophaes rhamnoides leaves with ademethionine, the studied biochemical parameters significantly ($p < 0.05$) differed from the numerical values in the negative control group and were closest to those in the intact group than in other experimental groups.*

Conclusion. *A comparison of the effectiveness of the use of extract of Hippophaes rhamnoides leaves in combination with ademethionine by the total effect on blood biochemical parameters determines this complex as a promising drug for further research.*

Key words: *Extractum foliorum Hippophaes rhamnoides, paracetamol experimental hepatitis, complex pharmacotherapy regimens, paracetamol, ademethionine, blood biochemical parameters*

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ВЛИЯНИЕ КОМПЛЕКСНЫХ СХЕМ ФАРМАКОТЕРАПИИ С ИСПОЛЬЗОВАНИЕМ ФИТОСРЕДСТВА ИЗ *HIPPOPHAE RHAMNOIDES* НА БИОХИМИЧЕСКИЕ ПОКАЗАТЕЛИ КРОВИ КРЫС С ПАРАЦЕТАМОЛОВЫМ ГЕПАТИТОМ

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РЕЗЮМЕ

Обоснование. *Использование комплексов синтетических и растительных средств в качестве гепатопротекторов при лечении патологий печени различной этиологии является актуальной задачей фармакологии. Перспективным видом лекарственного растительного сырья является фитопрепарат – экстракт листьев облепихи крушиновидной (Extractum foliorum Hippophaes rhamnoides). Гепатопротекторное действие экстракта листьев облепихи крушиновидной в сочетании с адеметионином к настоящему времени не изучено.*

Цель работы*. Исследование изменений биохимических маркеров печёночной функции при применении комплексных схем фармакотерапии экспериментального повреждения печени парацетамолом с использованием Extractum foliorum Hippophaes rhamnoides.*

Методы*. Экспериментальное исследование выполнено на крысах линии Wistar. Животные были разделены на шесть групп: 1-я интактная группа – животные без модели повреждения печени и без лечения; 2-я контрольная группа – с применением парацетамола для создания экспериментального гепатита без лечения (группа негативного контроля); 3-я сравнительная группа – использование комбинации «силибинин + адеметионин» на модели парацетамолового гепатита; 4-я опытная группа – использование «экстракта листьев облепихи крушиновидной» на модели парацетамолового гепатита; 5-я опытная группа – использование «адеметионина» на модели парацетамолового гепатита; 6-я опытная группа – использование комбинации «экстракт листьев облепихи крушиновидной + адеметионин» на модели парацетамолового гепатита. Функциональное состояние печени экспериментальных животных определено по биохимическим показателям.*

Результаты. *При определении в сыворотке крови крыс уровня таких показателей, как аспарагиновая аминотрансфераза, аланиновая амионтрансфераза, щелочная фосфатаза, гамма-глютамилтранспептидаза, а также общего билирубина было установлено, что при применении сочетания экстракта листьев облепихи крушиновидной с адеметионином биохимические показатели статистически значимо ($p < 0,05$) отличались от численных значений в группе негативного контроля и были наиболее приближены к таковым в интактной группе, чем в других опытных группах.*

Заключение*. Сравнение эффективности применения экстракта листьев облепихи крушиновидной в сочетании с адеметионином по суммарному влиянию на биохимические показатели крови определяет данный комплекс как перспективную схему терапии парацетамолового гепатита.*

Ключевые слова: *Extractum foliorum Hippophaes rhamnoides, парацетамоловый экспериментальный гепатит, комплексные схемы фармакотерапии, парацетамол, адеметионин, биохимические показатели крови*

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BACKGROUND

Drug-induced liver injury is one of the important problems of modern hepatology. Many drugs are toxic to the body, even in therapeutic doses, which often leads to acute liver failure [1, 2]. A rather diverse arsenal of drugs that act differently against the liver cells is used for the therapy of various liver diseases [3]. Plant-derived drugs have a number of advantages over their synthetic counterparts in their effects on the homeostasis system. The bioactive metabolites produced by plants appear to be of interest as platforms for the synthesis of combinatorial combinations of synthetic and herbal drugs [4]. The use of various combinations of hepatoprotectors in the treatment of liver pathologies is quite in demand in modern conditions [5]. Pharmacological activity of *Hippophae rhamnoides foliae extract* is caused by the presence of quercetin, kaempferol, isoramnetin, catechins, flavone glycosides, etc. in the composition of the phytoextract [6, 7]. The evidence from various literature sources indicates that the presence of biologically active substances belonging to the group of phenols or polyphenols in pharmacological agents of natural origin defines their antioxidant properties [8–10]. Meanwhile, it should be emphasised that in general the spectrum of pharmacological activity of *Hippophae rhamnoides foliae extract*, peculiarities of action in conditions of combined use with other pharmacological agents have not been sufficiently studied to date.

THE AIM OF THE STUDY

To study changes in biochemical markers of hepatic function when applying complex schemes of pharmacotherapy of experimental liver injury with paracetamol using *Hippophae rhamnoides foliae* extract.

MATERIALS AND METHODS

The experimental study was performed using 60 white Wistar rats of both sexes weighing 180–200 g. The animals were kept in the certified vivarium of General and Experimental Biology Institute (GEBI) of the SB RAS (the Siberian Branch of Russian Academy of Sciences). All experiments were performed in accordance with the international rules for working with experimental animals, GOST 33044-2014, Principles of Good Laboratory Practice (OECD Guide 1:1998, IDT), according to the Order of the Government of the Russian Federation dated November 8, 2013 No. 2067-r. Animals were kept with free access to food and water on a diet that complied with GOST standards. The protocol of the experiment was approved by the Ethical Committee of the GEBI SB RAS (Minutes No. 2 dated November 5, 2017).

Before commencing the experiments, rats fulfilling the inclusion criteria for the study were allocated into six groups:

I. Intact rats.

II. Control group – animals with acute paracetamol-induced hepatitis.

III. Experimental group – combination "silibinin + ademethionine".

IV. Experimental group – phytopreparation "*Hippophae rhamnoides foliae* extract".

V. Experimental group – pharmacopoeial preparation "ademethionine" [10, 11].

VI. Experimental group – combination "*Hippophae rhamnoides foliae* extract + ademethionine".

Exclusion criteria for laboratory animals:

1) Presence or development of other somatic pathologies;

2) Immature, early age (up to 6 months);

3) With insufficient mass.

The experimental model of hepatitis in rats was reproduced by intragastric administration of paracetamol (acetaminophen) to animals once a day at a dose of 500 mg/kg for 2 days [12].

To treat experimental hepatitis, animals of experimental groups were orally administered daily in the morning hours (before feeding) for 14 days with aqueous solutions of the tested agents: *Hippophae rhamnoides foliae* phytoextract was dissolved in purified water at a dose of 100 mg/kg of animal body weight ("the most optimal pharmacotherapeutic" mode of administration [13]). *Hippophae rhamnoides foliae* extract was obtained by triple extraction with 40 % ethanol in GEBI SB RA; "silibinin" ("Vifitech") was administered at a dose of 200 mg/kg according to the scheme; "ademethionine" ("Veropharm") was administered at a dose of 200 mg/kg.

Distilled water in the first and second groups (intact animals with normofunction of the liver and with experimental hepatitis) was provided in equi-volume quantities according to the scheme.

Animals were removed from the experiment by immediate decapitation under light ether anesthesia.

At the moment of animal discharge from the experiment, blood was collected from the tail vein and the serum content was determined of:

1) asparagine aminotransferase (AST) (BioSystems, Spain; cat. no. 11830);

2) alanine aminotransferase (ALT) (BioSystems, Spain; cat. no. 11832);

3) alkaline phosphatase (ALP) (BioSystems, Spain; cat. no. 11832);

4) total bilirubin (BioSystems, Spain; cat. no. 11832);

5) gamma-glutamyl transpeptidase (GGTP) (BioSystems, Spain; cat. no. 11832).

Enzyme studies were performed by the kinetic method recommended by the German Society for Clinical Chemistry and the Clinical Manual for Laboratory Tests at 25 °C.

An automatic biochemical analyzer "Sapphire-400" (TokyoBoeki, Japan) and Human test systems (Germany) were used as a measuring instrument. Statistical data processing was performed using Statistica 6.0 for Windows program (StatSoft Inc., USA). Statistical significance of the differences between the compared values was calculated using the parametric Student's criterion and the non-

parametric Mann – Whitney U-criterion. Data differences were considered statistically significant at $p \leq 0.05$ [14].

RESULTS

According to the results of this study, it was found that AST level was statistically significantly increased in the group of animals with acute paracetamol hepatitis by 49.4 % ($p < 0.05$) compared to that in the intact group (Table 1).

The AST index in rats of the experimental groups did not statistically significantly differ from the observed values in the control group. However, the use of *Hippophae rhamnoides foliae* extract in combination with ademetionine contributed to a more significant decrease in AST value in comparison with other studied groups.

Under conditions of simulated experimental hepatitis, ALT level in the negative control group was statistically significantly increased by 22 % as compared to that in the intact group during the development of paracetamol-induced lesions than in the intact group, evidenced by the development of liver pathology. When comparing the studied index in group III with the same value in the control group in paracetamol hepatitis, it was found that ALT level decreased by 11.2 %, in Group IV – by 15.4 %, in Group V – by 11.1 %, in Group VI – by 12.4 %. However, statistically significant differences were registered only in Groups III and VI. In comparing the index of this aminotransferase in Group VI rats with paracetamol-induces hepatitis that received *Hippophae rhamnoides foliae* extract in combination with ademetionine and Group III rats that received silibinin with ademetionine, it can be seen that the ALT level was found to be identical. At the same time in animals of VI experimental group the smallest differences in ALT value were registered in comparison with that in intact animals.

The studies revealed that in animals with experimental paracetamol hepatitis the activity of alkaline phosphate and GGTP in serum was statistically significantly increased compared to the value in intact rats by 37.7 % and 75.7 %, respectively, as is evident from Table 1. The mean levels of alkaline phosphate and GGTP, which are marker enzymes of cholestasis, in the experimental groups were statistically significantly lower than in the control group of animals. In these conditions, the administration of *Hippophae rhamnoides foliae* extract in combination with ademetionine caused a statistically significant decrease in the level of alkaline phosphate activity by 13.2 % compared to the control. Similar changes were observed in the action of silibinin with ademetionine, *Hippophae rhamnoides foliae* extract and ademetionine separately: alkaline phosphate activity decreased by 12.9 %, 10.8 % and 12.1 %, respectively, relative to the control. GGTP enzyme level data in different experimental groups did not differ significantly from each other, and all of them were statistically significantly different from this index in rats of the control group.

After paracetamol administration, the bilirubin level in the control group increased by 114.3 % (Fig. 1).

In comparing the index of bilirubin in rats of the experimental group, administered silibinin with ademetionine, with that in animals of the control group, it was found that the level of bilirubin decreased by 31.1 %. With the values in Group IV this difference amounted to 24.4 %, in Group V – 33.3 %, in Group VI – 37.7 %. Using a combination of *Hippophae rhamnoides foliae* extract with ademetionine in rats with paracetamol-induced hepatitis resulted in a 10.7 % decrease in bilirubin level compared to the same indicator in the blood of rats of the III experimental group receiving the combination "silibinin + ademetionine". At the same time, the level of bilirubin in the blood of animals of all experimental groups had statistically significant

TABLE 1

BLOOD BIOCHEMICAL PARAMETERS OF RATS IN A MODEL OF ACUTE PARACETAMOL HEPATITIS

Biochemical indicators	Group I: intact ($n = 10$)	Group II: paracetamol hepatitis ($n = 10$)	Group III: silibinin + ademethionine ($n = 10$)	Group IV: *Hippophae rhamnoides foliae* extract ($n = 10$)	Group V: ademethionine ($n = 10$)	Group VI: *Hippophae rhamnoides foliae* extract + ademethionine ($n = 10$)
AST, U/L	44.30 ± 1.62	66.20 ± 5.94*	59.20 ± 4.24	61.20 ± 2.76	64.00 ± 5.45	57.80 ± 2.12
ALT, U/L	172.16 ± 4.35	209.90 ± 1.07*	186.30 ± 17.37**	197.10 ± 14.78	194.40 ± 3.75	183.80 ± 13.08**
ALP, U/L	657.80 ± 35.07	906.10 ± 26.87*	788.50 ± 7.28**	808.20 ± 42.00**	796.30 ± 29.06**	786.30 ± 20.79**
GGTP, U/L	7.14 ± 0.31	29.5 ± 1.7*	23.7 ± 1.3**	25.1 ± 1.7**	24.2 ± 1.4**	22.3 ± 1.5**

Note. Differences are statistically significant compared to: * – intact group ($p < 0.05$); ** – control group ($p < 0.05$); n – number of animals in each group.

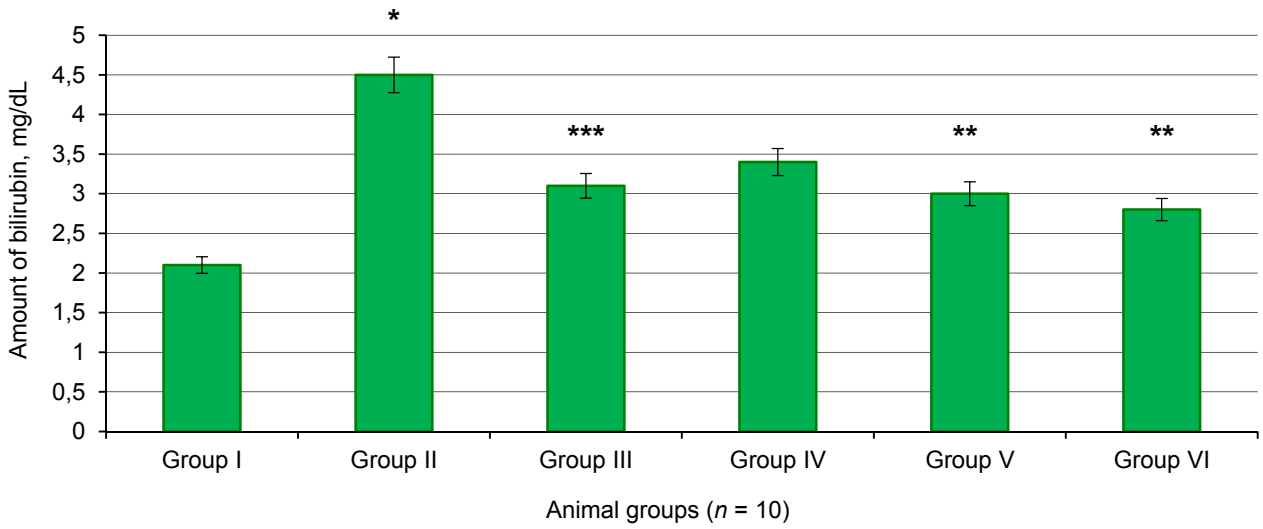

FIG. 1.

*Bilirubin concentration in rat serum in a model of acute paracetamol hepatitis. Differences are statistically significant compared to the values in: * – intact group ($p < 0.001$); ** – control group ($p < 0.05$); n – the number of animals in each group*

differences with the indicators in the control. However, it should be emphasised that the bilirubin level in Group VI rats was restored to the values in intact rats.

DISCUSSION

One of the urgent problems of pharmacology is the search for effective and safe hepatoprotectors for the treatment of drug-induced liver damage. In particular, using a model of acute liver injury paracetamol is similar in pathogenesis to drug-induced hepatitis [15]. According to the literature, hepatotoxic doses of paracetamol lead to centrilobular necrosis and liver failure [16–18].

It follows from the review article devoted to the combined use of drugs by S.V. Okovitiy (2020) that there is currently little information about experimental and clinical studies devoted to the study of the feasibility and possibility of combined use of hepatoprotectors [5, 19].

In a study by I. Giangrandi et al. (2016) it was shown that taking a combination of silymarin (140 mg/day) and ademetionine (200 mg/day) for 12 months (patients with non-alcoholic fatty liver disease) without additional dietary correction led to a decrease in the level of biochemical indicators against the background of regression of liver steatosis [20]. According to A.Y. Au et. al. (2013), "silibinin + ademethionine" combination inhibits both inflammation and oxidative stress by affecting different signalling pathways mediated by nuclear factor NF-B and transcription factor Nrf2 [21].

According to the results of the experiment, it was revealed that the administration of paracetamol produced changes in AST, ALT, ALP, alkaline phosphate, GGTP and total bilirubin activities. Paracetamol and its breakdown products in control animals with toxic hepatitis lead to damage of lipid bilayer of hepatocyte membranes, activation of cytolysis and cholestasis syndromes, disruption of protein, carbohydrate, bioenergetics metabolism and inhibition of enzyme systems of xenobiotics detoxification. When administering the combination of "silibinin + ademethionine", a statistically significant decrease in the level of all studied parameters compared to the control was observed. After administering *Hippophae rhamnoides foliae* extract in the therapeutic regime, hepatoprotective activity was revealed. Thus, the course administration of phytoextract in monotherapy mode causes a decrease in total bilirubin and alkaline phosphatase. It was also revealed that when the liver of rats was damaged by paracetamol and "ademetionine" therapy, the indices of the studied parameters were close to those of the intact group. Correction of the disorders revealed by paracetamol exposure with the combination of "*Hippophae rhamnoides foliae* extract + ademethionine" led to the improvement of rat liver functional status indices, as assessed by the studied markers of liver damage: AST, ALT, GGTP, total bilirubin and alkaline phosphatase. But in comparing all experimental groups of animals treated with different regimens, it is worth noting that the groups of rats that received combinations of drugs had better results compared to rats treated with mono-medications alone. High doses of paracetamol are commonly known to cause necrosis of some liver hepatocytes, and it takes quite a long time for hepatocytes to recover. Nevertheless, administration of the combination "*Hippophae rhamnoides foliae* extract + ademethionine" during the experiment contributed to significant improvement of liver condition in acute paracetamol poisoning.

CONCLUSION

Thus, in toxic hepatitis caused by paracetamol administration, the combined use of "*Hippophae rhamnoides foliae* extract + ademetionine" as well as "silibinin com-

bined with ademetionine", in contrast to "*Hippophae rhamnoides foliae* extract" and "ademethionine" as mono-medications, leads to better recovery of activity level of some biochemical indices of blood serum in experimental animals and thus, as a result, has a more pronounced hepatoprotective effect. The obtained data provide a prerequisite for further research and application of the complex "*Hippophae rhamnoides foliae* extract + ademethionine" for correction of liver diseases caused by various toxic agents.

Conflict of interest

The authors of this article declare no conflicts of interest.

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