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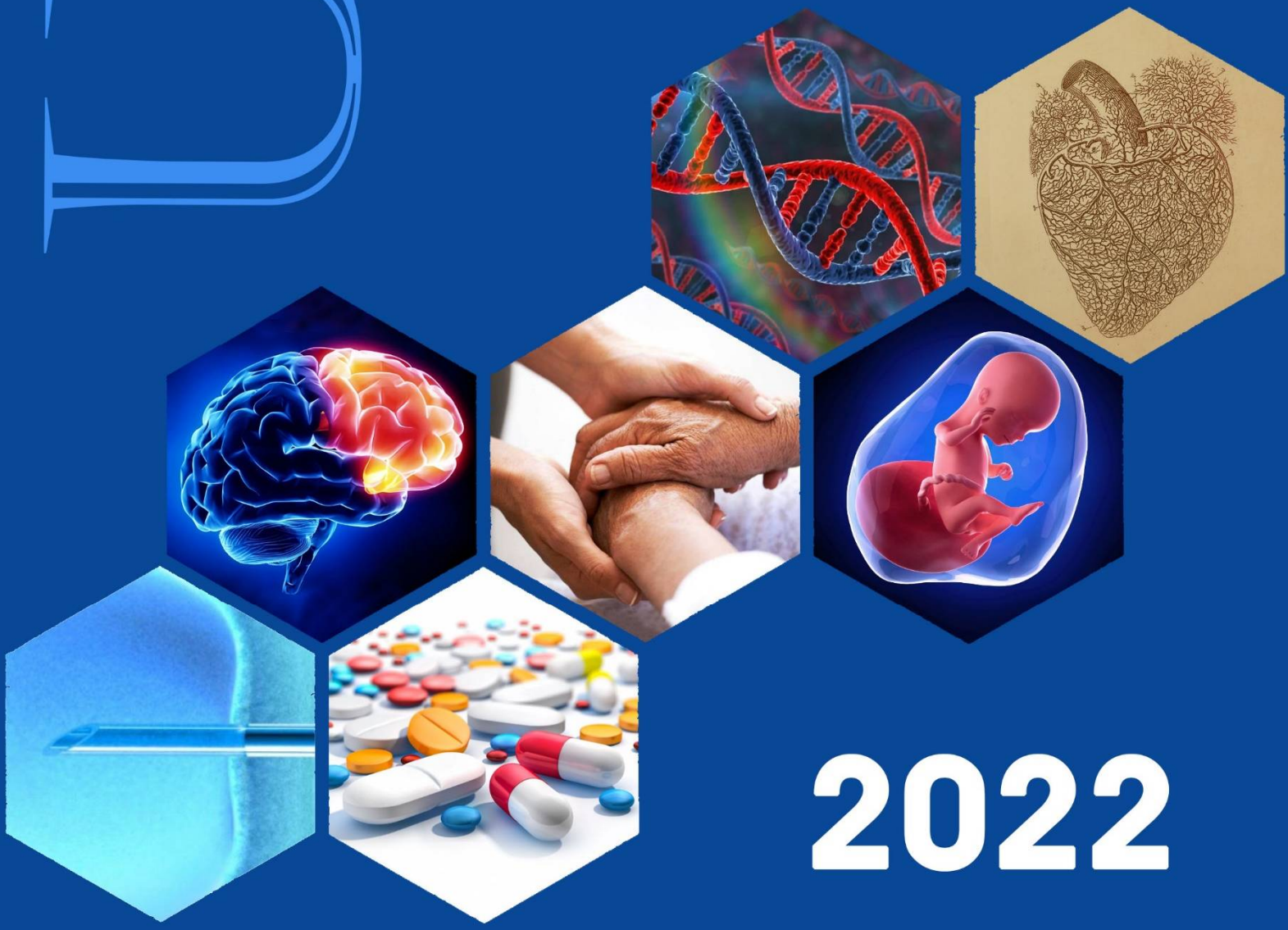

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STUDY OF THE HEPATOPROTECTOR PROPERTIES OF THE DRUG TAUCIN

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ABSTRACT

This article presents an analysis of recent research by scientists who have used the hepatoprotective properties of the drug tausin in rat liver. Taurine has a moderate positive inotropic effect and promotes natriuresis and diuresis. Although recent studies have shown improvement in exercise tolerance in patients with taurine [17], it remains unknown whether taurine reduces risk in the general population. In addition, the question of reducing the mortality rate of patients with taurine has not been studied. There is reason to believe that taurine can increase the life expectancy of patients
Keywords: hepatotoxic effect, hepatoprotective effect, rats, paracetamol, zinc diaspartate, combination of taucine.

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ИЗУЧЕНИЕ ГЕПАТОПРОТЕКТОРНОЙ ПРИРОДЫ ПРЕПАРАТА ТАУЦИН

АННОТАЦИЯ

В данной статье представлен анализ последних исследований ученых, которые использовали гепатопротекторные свойства препарата таусин в печени крыс. Таурин обладает умеренным положительным инотропным действием и способствует натриурезу и диурезу. Хотя недавние исследования показали улучшение переносимости физических нагрузок у пациентов, принимающих таурин [17], остается неизвестным, снижает ли таурин риск в общей популяции. Кроме того, вопрос о снижении смертности пациентов, принимающих таурин, не изучался. Есть основания полагать, что таурин может увеличить продолжительность жизни пациентов
Ключевые слова: гепатотоксический эффект, гепатопротекторной эффект, крысы, парацетамол, диаспартат цинка, комбинация таусина.

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TAUSIN PREPARATI GEPATOPROTEKTOR XUSUSIYATLARINI O'RGANISH

ANNOTATSIYA

Ushbu maqolada kalamush jigarida tausin preparatining gepatoprotektor xususiyatlarini o'rgangan olimlarning so'nggi tadqiqotlari tahlili keltirilgan. Таурин обладает умеренным положительным инотропным действием и способствует натриурезу и диурезу. Хотя недавние исследования показали улучшение переносимости физических нагрузок у пациентов, принимающих таурин [17], остается неизвестным, снижает ли таурин риск в общей популяции. Кроме того, вопрос о снижении смертности пациентов, принимающих таурин, не изучался. Есть основания полагать, что таурин может увеличить продолжительность жизни пациентов

Kalit so'zlar: gepatotoksik ta'sir, gepatoprotektiv ta'sir, kalamushlar, paratsetamol, sink diaspartat, tausin birikmasi.

Introduction. Taurine is approved for the treatment of congestive liver and heart failure (CHF) in Japan [16]. Like other drugs used for treatment, taurine not only reduces symptoms (shortness of breath and swelling), but also eliminates or reduces the need for other drugs such as digoxin [16]. Taurine has a moderate positive inotropic effect and promotes natriuresis and diuresis. Although recent studies have shown improvement in exercise tolerance in patients with taurine [17], it remains unknown whether taurine reduces risk in the general population. In addition, the question of reducing the mortality rate of patients with taurine has not been studied. There is reason to believe that taurine can increase the life expectancy of patients [15].

High doses of paracetamol, especially in combination with ethanol and other hepatotoxins, are risk factors for severe liver damage. In the mechanism of development of "paracetamol hepatopathy", its oxidation by liver cytochrome P450 with the formation of N-acetyl-p-benzoquinone plays a key role. The latter forms non-toxic conjugates with reduced glutathione in a reaction catalyzed by glutathione-S-transferase. When the pool of reduced glutathione in hepatocytes is depleted, the unconjugated metabolite of paracetamol covalently binds to nucleophilic macromolecules with the development of hepatotoxicity [1,2]. The key role of reduced glutathione in the detoxification of hepatotoxic N-acetyl-p-benzoquinone was the basis for the successful use of its precursor, acetylcysteine, in paracetamol poisoning [3]. In the present study, an attempt was made to study the ability of the combination of taurine with zinc diaspartate to improve the processes of impaired metabolism in the liver and organ function during paracetamol intoxication.

In the literature review process, we reviewed the analyzed literature in the following way:

Methods for assessing the activity of enzymes in the liver. One part of liver pieces was fixed in Carnoy's fluid and embedded in paraffin. Paraffin sections were stained with hematoxylin-eosin and used for histological studies. Other pieces of the liver were frozen in liquid nitrogen and, after mounting on an object holder according to the "control-experiment" principle, they were placed in a Leica CM 1850 cryostat at -15 0 C. μm served to determine the activity of succinate dehydrogenase (SDH) according to N. Nachlas et al. (1957), lactate dehydrogenase (LDH) according to R. Hess et al. (1958), NADH dehydrogenase (NADHDH) according to N. Nachlas et al. (1958) and acid phosphatase (AP) according to G. Gomori et al. (1950) [4].

Methods for assessing liver function. In plasma, the activity of alataminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), as well as the content of cholesterol, total bilirubin and its fractions was determined using routine laboratory methods. The results obtained were analyzed by nonparametric statistics using the Statistica 6.0 program for Windows (USA, license no. 6.1.478). In descriptive statistics, the median value (Me) and the interquartile range (Mann-Whitney U-test) were determined for each indicator. Differences between the control and experimental groups were considered statistically significant at $p<0.05$ [5].

Research results of scientists. Pashko A.Yu., Borisenok O.A., Bushma M.I. [4] scientists conducted experiments on 40 non-linear white male rats weighing 200 - 250 g in accordance.

Paracetamol (Sigma, Germany) was administered to the stomach as a suspension in starch mucus at a dose of 2.50 g/kg every 1 day for 10 days (5 doses). The following "taucine" formulations were tested, based on the principle of 1 g/mol zinc diaspartate (0.35 g) with various g/molar ratios of taurine: 20 (2.50 g) - "taucine-20" and 50 (6.25 g) - "taucine-50". They were administered to the stomach as a suspension in starch mucus at a dose of 0.50 g/kg/day for 10 days. Control rats were injected with starch mucus. 24 hours after the last administration of the substances, the rats were deprived of food for 24 hours. They were then sacrificed, blood collected and plasma obtained; liver samples were taken to assess the nature and degree of organ damage and metabolic disturbances in it [4].

Paracetamol (in the stomach in the form of a suspension in starch mucus at a dose of 2.50 g/kg, after 1 day - 5 doses) has a hepatotoxic effect, manifested by impaired metabolism and organ function [6].

Under the influence of "taucin-20" reduced activity of CP increases by 29% (table 1). Increased activity of alkaline phosphatase, the content of total bilirubin, and cholesterol is reduced, respectively, by 20, 14 and 17% (table 1).

"Taucine-50" led to an increase in reduced reaction products of SDH and LDH; NADH-DG and CF, respectively, by 17 and 29; 5 and 50% (Table 1). Increased activities of AlAT, AsAT and alkaline phosphatase, as well as the content of total bilirubin, its conjugated form and cholesterol are reduced by 43, 51 and 46, respectively; 18, 50 and 21%.

Table - 1

The effect of paracetamol (2.50 g/kg, once every 2 days - 5 doses), alone and in combination with "taucin-20", "taucin-50" (0.50 g/kg/day - 10 doses) , introduced into the stomach in the form of a suspension in starch mucus, on the activity of enzymes in rat hepatocytes

Measures under study (EDOP)	Experience conditions			
	The control	Paracetamol	Paracetamol + "taucine-20"	Paracetamol +
SDG	0,26 (0,25; 0,27)	0,23 (0,23; 0,24) 8,00 **(0,0015)** -	0,24 (0,23; 0,25) 24,00**(0,049)** 31,50(0,162)	0,27 (0,25; 0,28) 37,00(0,326) 5,00**(0,0007)**
LDH	0,55 (0,54; 0,61)	0,35 (0,32; 0,42) 0,00**(0,0002)** **-**	0,33 (0,25; 0,43) 0,00**(0,0002)** 43,50(0,623)	0,45 (0,43; 0,47) 7,00**(0,002)** 6,50**(0,001)**
NADH-DG	1,22 (1,20; 1,23)	0,95 (0,94; 0,96) 0,00**(0,0002)** -	0,99 (0,98; 1,01) 0,00**(0,0002)** 4,00**(0,0005)**	1,00 (0,98; 1,02) 0,00**(0,0002**) 4,00**(0,0005)**
KF	1,05 (1,01; 1,07)	0,80 (0,79; 0,81) 0,00**(0,0002)** -	1,03 (0,97; 1,07) 36,50(0,307) 0,00**(0,0002)**	1,20 (1,16; 1,21) 0,00**(0,0002)** 0,00**(0,0002)**

Note. Rows of numbers: the first - Me values, the second - quartiles, the third and fourth - U and p (in brackets) in comparison with control (above the line) and paracetamol-treated (under the line) rats. Statistically significant ($p < 0.05$) differences are highlighted in bold. EDOP - units of optical density.

A comparative analysis of the results of histochemical (liver) and biochemical (plasma) studies indicates that paracetamol at the selected dose, route and duration of administration has a hepatotoxic effect, manifested by inhibition of the activity of metabolic processes in hepatocytes and an increase in the activity of biochemical markers of hepatotoxicity in plasma.

The combination of taurine with zinc diaspartate has hepatoprotective properties that increase with increasing relative content of taurine ("taucine-50" > "taucine-20"). This is manifested by an improvement in metabolic processes, as evidenced by an increase in the reduced activity of SDH, LDH, NADH-DH and CF. Simultaneously, liver function improves, which is confirmed by a decrease

in plasma increased activity of ALT, AST, alkaline phosphatase, as well as an increased content of total bilirubin, its conjugated form and cholesterol.

In the mechanism of the hepatoprotective action of the combination of substances, apparently, the main role is played by the ability of taurine to neutralize hepatotoxic bile acids with the formation of non-toxic taurocholates. In addition, its regulatory role in cell differentiation and growth is known [7]. The hepatoprotective effect of zinc may be mediated by its role as a cofactor of antioxidant defense enzymes (superoxide dismutase and glutathione peroxidase) [8].

The more pronounced hepatoprotective effect of "taucine-50" in comparison with "taucine-20" seems to be due to the higher content of taurine in the combination. This indicates that taurine plays a dominant role in the hepatoprotective effect of the combination of substances.

Taurine is used as a drug in chronic heart failure, intoxication with cardiac glycosides and diabetes mellitus (dibicor); eye injuries, degenerative diseases of the cornea and cataracts (taufon); as a hepatoprotector (as part of the complex drug "tavamin") [2]. Inorganic and organic (zinc aspartate and orotate, oxalate and citrate, phytate and acetate) zinc salts are widely used not only externally, but also in the combined therapy of liver and connective tissue diseases, cerebral palsy, hypogonadism and hypozincemia [8,9].

Researches of scientists Pashko A.Yu., BushmaK.M., Borisenok O.A., Bushma M.I. [14]. Conducted 2 series of experiments.

First episode. Cholestasis, lasting 13 days, was modeled by ligation of the common bile duct above the confluence of the pancreatic ducts. The rats of the second experimental group were injected with a combination of taurine with zinc diaspartate, composed according to the principle of 1 g/mol zinc diaspartate (0.35 g) + 50 g/mol taurine (6.25 g) (“taucine-50”) [14].

It was started 24 hours after ligation of the duct (into the stomach as a suspension in starch mucus, 0.5 g/kg/day for 11 days). The comparison group was rats with cholestasis (the first experimental group), which were injected with starch mucus. The sham-operated animals (control) underwent the same manipulations, except for the ligation of the duct, and starch mucus was injected. 24 hours after the last administration of substances, rats were deprived of food for 1 day, decapitated, blood was collected and plasma was obtained [14].

Second series. The experiments were carried out on 24 non-linear white male rats weighing 250-300 g. The details of the experiment are presented in the first series. The duration of cholestasis was 21 days. Taucine-20 was tested (taurine, 20 g/mol + zinc diaspartate, 1 g/mol). It was administered at a dose of 0.5 g/kg/day for 19 days [14].

The degree of severity of hepatopathy was judged according to the indicators of hepatotoxicity in the blood plasma of rats. The spectrum of biochemical parameters was determined using a KONELAB 30i analyzer (Finland). In plasma, the activity of alanine amino- and aspartate aminotransferases (AlAT, AsAT) was determined by a modified, optimized kinetic method in accordance with the recommendations of the International Federation of Clinical Chemistry, y-glutamyl transpeptidase (GGTP) - by the kinetic method according to Perziyan and Slick [10], alkaline phosphatase (AP) - the method of Bessey, Lowry, and Brock [14]; the content of total bilirubin and its fractions was determined in the reaction of interaction with diazotized sulfanilic acid according to Yendrashik [11].

Cholestasis in rats lasting 13 days is accompanied by liver damage. This is evidenced by an increase in the plasma activity of ALT and AST, GGTP and alkaline phosphatase by 157 and 132, 76 and 99%, respectively. The content of total and unconjugated bilirubin increases by 46 and 39 times. Conjugated bilirubin absent in sham-operated rats is recorded.

The combination of taurine with zinc diaspartate ("taucine-50") has a hepatoprotective effect. Under its influence, the activity of AlAT and AsAT, GGTP and alkaline phosphatase decreases, as well as the content of total, unconjugated and conjugated bilirubin by 21-89%.

An increase in the duration of cholestasis up to 21 days is associated with more pronounced liver damage in rats. The activity of ALT and AST, GGTP and AP increases, respectively, by 211 and 178, 121 and 120%. The content of total bilirubin, as well as its unconjugated and conjugated fractions, increases by 49, 56 and 26 times, respectively.

Under these experimental conditions, a different ratio of taurine with zinc diaspartate (“taucine-20”) also has a hepatoprotective effect. This is evidenced by a decrease in the plasma activity of ALT and AST, GGTP and AP by 48 and 39, 44 and 36%, as well as the content of total, conjugated and unconjugated bilirubin by 67, 72 and 33%.

The results of the studies indicate that in rats with common bile duct ligation for 13 and 21 days, liver damage is recorded (judging by changes in biochemical markers of hepatotoxicity in plasma), more pronounced with an increase in the duration of cholestasis. In the mechanism of development of cholestatic hepatosohepatitis, a violation of bile evacuation plays a role. High concentrations of bile acids in it, which have a detergent effect, have a cytotoxic effect on hepatocytes. Their membranes, especially those rich in phospholipids, are damaged. The consequence of damage to the plasma membranes of hepatocytes is the release of cytosolic enzymes (AlAT, AsAT, GGTP, ALP) from them into the plasma. Hyperbilirubinemia develops as a result of blockade of pigment excretion with feces. The increased level of conjugated bilirubin is not associated with the activation of its glucuroconjugation processes, but is due to its release into the plasma through the damaged plasma membrane [14].

The combination of taurine with zinc diaspartate ("taucine-50", "taucine-20") has a hepatoprotective effect. This is manifested in the improvement of marker biochemical parameters of hepatotoxicity in plasma. The hepatoprotective effect of "taucine" is apparently due to the hepatoprotective properties of its constituent components. The ability of the amino acid taurine to neutralize hepatotoxic bile acids with the formation of non-toxic taurocholates is known. In addition, it has an antioxidant cytoprotective effect [2,12]. The hepatoprotective effect of zinc may be mediated by its role as a cofactor for more than 200 enzymes of intracellular metabolism, including antioxidant cell defense enzymes (superoxide dismutase, glutathione peroxidase) [8,13].

Conclusions. Since the discovery of taurine in 1827, many of its functions have been studied in scientific papers. The cytoprotective effect of taurine c (“taucin-50”, “taucin-20”) contributes to the improvement of the human clinical condition through various mechanisms, including antioxidant activity, energy production, Ca2+ ion homeostasis and osmoregulation. The combination of one or more of these cytoprotective effects leads to a reduction in the pathological changes and symptoms of a variety of diseases with the use of taurine, including liver pathology and metabolic disorders. Treatment of taurine with zinc diaspartate ("taucine-50", "taucine-20") also leads to a decrease in the severity of inflammatory diseases. Since taurine is a natural substance in the body, has few side effects, and plays a fundamental role in the functioning of most mammalian cells, the prospect of using it as an effective drug is encouraging. Although clinical evaluation of taurine has been limited to a small number of conditions, it has already been approved for use in Japan. Thus, taurine is a conditionally essential vital substance for humans with a variety of cytoprotective and therapeutic effects.

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