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RESEARCH ARTICLE

Asphervon-related increase of bile secretion as a preventive measure and therapeutic agent for heliotrin induced hepatitis in rats

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ABSTRACT

Background: Considering the significant increase in the number of patients suffering from liver diseases of various etiologies, for example, viral, toxic, medicinal, alcoholic, and others, today, improving the quality and safety of pharmacotherapy of the hepatobiliary system diseases is an urgent problem of modern pharmacology and clinical hepatology. **Aim and Objectives:** The purpose of this study was to investigate the Asfervon related increase of bile secretion activity in rats with heliotrin-induced hepatitis. **Materials and Methods:** The experiments were carried out on outbred white rats, males, weigh 160–210 g. For studying the preventive effect of drugs, animals were injected orally in doses of 25, 50, and 100 mg/kg Asfervon, and Legalon – 100 mg/kg, before the administration of heliotrin for 2 days, and after the administration of heliotrin for the next 5 days. A model of acute toxic hepatitis was reproduced by a single injection of a freshly prepared aqueous solution of heliotrin at a dose of 250 mg/kg subcutaneously. **Results:** Animals who received Asfervon preventively at doses of 25, 50, and 100 mg/kg bile secretion decrease were less significant of 49.2, 17.2, and 20.3%, respectively. The preliminary administration of Asfervon increased the amount of excreted bile in comparison with the untreated group of animals by 38.3, 125.5, and 117.0%, respectively, at the indicated doses. **Conclusions:** Asfervon is a drug with a pronounced hepatoprotective activity, not inferior to the classic hepatoprotective medication Legalon. Asfervon promotes bile secretion in preventive and treatment experiments.

KEY WORDS: Heliotrin; Hepatitis; Bile secretion; Enzymes; Prophylaxis

INTRODUCTION

Despite some successes achieved in clinical hepatology, liver diseases remain one of the most common disorders in internal medicine.[1-4] In the treatment of these diseases, hepatoprotective medications occupy an important place.[4-7] Considering the significant increase in the number of patients suffering from liver diseases of various etiologies, for example, viral, toxic, medicinal, alcoholic, and others, today, improving the quality and safety of pharmacotherapy of the hepatobiliary system diseases is an urgent problem of modern pharmacology and clinical hepatology. It is known, that the simultaneous consumption of 8–12 medications with a single dose may cause the development of various forms of drug-induced hepatotoxic reactions, on average, in 28% of cases.[8]

At present, we can see the need for using hepatoprotective drugs in the complex therapy of liver diseases especially in comorbid conditions such as obesity, diabetes mellitus, and metabolic syndrome.[9] This circumstance determines one of the important tasks of pharmacology in terms of creating and

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developing effective medications to improve the hepatobiliary function. A promising direction in this regard is substances acquired from plants growing locally in the Republic of Uzbekistan. Usually, biologically active substances contained in medicinal plants are optimally balanced by nature itself, which are easily absorbed by the body and are less toxic than synthetic drugs.[10]

The group of pharmacological agents used in the complex treatment of liver diseases is not large.[11] We have previously shown that the gum resin *Ferula assafoetida* (conventionally named Asfervon) has a distinctly positive effect on the functional state of the liver in acute toxic hepatitis (ATH) induced by carbon tetrachloride.[12] Tetrachloromethane induced hepatitis is usually used to investigate the hepatoprotective activity of drugs as a classical model.[13] Under the influence of this toxic agent, fatty hepatosis usually develops with significant structural changes, which is not a characteristic of viral liver damage. In terms of testing treatment for liver pathologies, the alkaloid heliotrin is used, which contained in the seeds of the plant *Heliotropium lasiocarpum* heliotrope and has a selective damaging effect on hepatocytes, causing the development of pathologies very similar to the morphological changes encountered in humans.[14,15] However, the effect of Asfervon on the functional state of the liver in heliotrinic damage remained unclear.

F. assafoetida is a herbaceous, monoecious, perennial plant of the Umbelliferae family. It is a local plant of Central Asia, Eastern Iran, Afghanistan, and today it is grown mainly in Iran and Afghanistan, from where it is exported to the rest of the world. Resin (gum) is obtained from the rhizome of the *F. assafoetida* L plant, which is used as a seasoning in cooking while preparing various dishes in Afghanistan and Iraq, and India. Milky juice hardened in the air, that is, "Gum - resin" - assafoetida was included in the pharmacopeia of the former Soviet Union (I-VIII ed.), and the other 19 countries of the world, and according to the message of A. I. Utkin (1938) in the USSR State Pharmacopoeia (1925, VII ed.). It was recommended to obtain resin gum from root incisions of the plant Ferula foetida and galbanum (gum resin Galbanum) from the North Iranian ferule, especially *Ferula gummosa* Boiss, which is also found in Central Asia.[16]

Asafoetida is extracted from *Ferula* plants, which have large root crops or carrot-like roots, 12.5–15 cm in diameter at the crown when they are 4–5 years old, shortly before the flowers of the plants fall in March-April, and the upper part of the root of the living rhizome is exposed. Milky sap is released from the surface of the incision, after few days, the exudates are being cleared. The collection of the resin and the cutting of the root are repeated until the exudation stops (approximately 3 months after the first cut). The resin is sometimes harvested from successive cuts made at the junction of the stem or rhizome and root crops. Despite the huge potential for obtaining resin gum from this plant in Central Asia, including Uzbekistan, there are no medication substances available that are prepared on the basis of this plant.

The purpose of this study was to investigate the Asfervon related increase of bile secretion activity in rats with heliotrin-induced hepatitis.

MATERIALS AND METHODS

All experimental studies were carried out on sexually matured unbred white male rats, which were obtained from the vivarium of the Sanitary and Epidemiological Surveillance Department of the Main Medical Directorate under the Administration of the President of the Republic of Uzbekistan. Before the start of the experiment, all laboratory animals were carefully examined, weighed, their age, sex, and physical activity were taken into account. During the experiment, laboratory animals were kept in a vivarium in standard plastic cages by six animals in each with a standard diet and in a well-ventilated room with day/night light mode at a temperature of 20–25°C, humidity was at least 50%.

Plant Material and Preparation of Dry Extract

Dry extract of medicinal plants was obtained from plants: *Hypericum scabrum* L., *Mediasia macrophylla*, *Glycyrrhiza glabra* L., and *Ziziphora pedicellata* Pazij Vved. Aerial parts of *Hypericum perforatum* L., *Z. pedicellata* Pazij et Vved., and *M. macrophylla* as well as root and rhizome parts of *G. glabra* L. were obtained in summer of 2017 from foothills to medium zones of mountains of Tashkent region, Fergana, Samarkand, and Surkhandaryo regions of Uzbekistan. Plant material was dried under dark conditions at room temperature for 10 days. Taking into account that the soil is contained various bacterial spores, raw material of plants were treated with special methods. The dry material was milled, obtaining 4–6 mm particles and mixed in proportion 1.25:1.0:1.25:1.5 (productivity of dried extract was higher than other proportions) then extracted by water at 93–95°C temperature for 3 h. The extract was then separated from the sample residue by filtration through filter paper. The resulting extracts were concentrated in vacuum until remaining a crude solid extract, which was then dried in a thermostat at temperature of 60°C.

Experimental Models

All experimental studies were carried out on sexually mature laboratory animals obtained from the vivarium of the Sanitary and Epidemiological Surveillance Department of the Main Medical Directorate under the Administration of the President of the Republic of Uzbekistan. Before the start of the experiment, all laboratory animals were carefully

examined, weighed, their age, sex, and physical activity were taken into account. During the entire period of preparation for the experiment, laboratory animals were kept in a vivarium at a temperature of 20–25°C, the humidity of at least 50%, in a well-ventilated room and day/night light mode, in standard plastic cages, six animals per each cage, with a standard diet. The daily requirements were compiled in accordance with the protocols. All laboratory animals participating in the experiment before the start of the experiment had a healthy appearance and were active.

The experiments were carried out on outbred white rats, males, weigh 160–210 g. The experimental animals were divided into six groups, each group consisted of 8–10 animals. Two series of experiments were conducted. In the first series, the preventive effects of various doses of Asfervon and Legalon were studied, and in the second series, the therapeutic effects of the above-mentioned drugs were investigated. When studying the preventive effect of drugs, animals were injected orally in doses of 25, 50, and 100 mg/kg Asfervon, and Legalon – 100 mg/kg, before the administration of heliotrin for 2 days, and after the administration of heliotrin for the next 5 days. In the second series, after a single subcutaneous injection of a solution of heliotrin, 48 h later, experimental therapy with the above drugs was carried out for 7 days, once injected. The control group of rats in both series received a similar volume of water once a day. A model of ATH was reproduced by a single injection of a freshly prepared aqueous solution of heliotrin at a dose of 250 mg/kg subcutaneously.[17] 24 h after the final administration of the drugs, the biliary function of the liver was investigated by inserting a polyethylene catheter into the common bile duct of anesthetized animals (intraperitoneal administration of sodium ethaminal at a dose of 50 mg/kg).

The choleretic activity of the drug was judged by the total amount of excreted bile for 4 h of the experiment, as well as by the concentration and amount of its components, that is, bilirubin, cholesterol, and bile acids.[15,18]

In hourly portions, the concentration (mg%) and total amount (mg per 100 g of body weight) of bile acids, cholesterol and bilirubin were determined.[15,19]

One day after the last injection of drugs and hepatotoxin, the animals were decapitated under light anesthesia and blood was collected. The hepatoprotective effect of the above drugs was assessed by determining various biochemical markers characterizing liver function: The activity of alanine aminotransferase (ALT), gamma glutamine transferase (GGT), alkaline phosphatase (ALP), and the content of total bilirubin in the blood serum. Biochemical studies were carried out by photometric method on a semiautomatic biochemical analyzer Mindray (China, 2014) using kits from Human (Germany) and Cypress diagnostics (Belgium).

Permission from Ethic Committee of the Republic of Uzbekistan was taken for carrying out experiments on animals. All experiments were conducted in compliance with the requirements of the European Convention "On the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes" (Strasbourg 1986).

Statistics

The obtained results of the study were statistically processed using the Biostat 2009 software package. The data are presented as mean (M) and standard error of the M. The difference at a probability level of 95% and more ($P < 0.05$) was considered as a statically significant change.

RESULTS

The findings of the present study are described in Tables 1-3.

DISCUSSION

In addition to heliotrin and laziocarpine, the composition of heliotrin pubescent alcolloids was isolated from the aerial part of the plants contains saponins, N-heliotrin oxide, N-laziocarpine oxide, and other derivatives of gelatin and european bases, which caused significant changes in the hemodynamics of the organ and lead to severe pathology. After a single injection of the alkaloid, in 20–25% of cases, death occurred, mostly on the 2nd day.

Table 1: Influence of the preventive action of various doses of Asfervon and Legalon on the intensity of bile secretion and its chemical composition in rats with acute heliotrin hepatitis (for 4 h of the experiment; per 100 g of body weight)

Indicators groups	Dose, mg/kg	Bile, ml	Bile acids, mg	Cholesterol, mg	Bilirubin, ug
Intact	–	1.28±0.10	6.06±0.56	0.238±0.021	118.51±12.03
H_2O+ATH	–	0.47±0.03*	3.09±0.32*	0.096±0.008*	46.17±4.55*
Asfervon+ATH	25	0.65±0.07*	3.60±0.35*	0.128±0.006*,o	65.56±5.41*,o
Asfervon+ATH	50	1.06±0.08o	5.74±0.43o	0.207±0.009o	100.89±8.43o
Asfervon+ATH	100	1.02±0.06o	5.66±0.41o	0.193±0.011o	93.65±7.78o
Legalon+ATH	100	0.97±0.08o	5.49±0.33o	0.204±0.014o	99.44±8.51o

ATH: Acute toxic hepatitis, *Compared to intact ($P<0.05$), oCompared to untreated group ($P<0.05$)

Table 2: Influence of the preventive action of various doses of Asfervon and Legalon on some biochemical parameters of blood serum in rats with acute heliotrin hepatitis

Indicators groups	Dose, mg/kg	ALT, U/L	ALP U/L	GGT, U/L	Total bilirubin
Intact	–	69.14±5.58	306.18±23.61	2.66±0.32	11.43±0.84
H_2O+ATH	–	418.10±34.16*	639.48±42.59*	6.83±0.68*	28.12±1.89*
Asfervon+ATH	25	169.51±15.41*,o	503.43±52.74*,o	5.17±0.63*	24.51±2.49*
Asfervon+ATH	50	101.23±6.76*,o	314.98±21.06o	3.17±0.29o	13.83±0.75o
Asfervon+ATH	100	111.93±9.89*,o	339.61±34.47o	3.25±0.30*,o	16.65±1.25o
Legalon+ATH	100	93.41±7.76*	312.83±33.31°	3.65±0.19°	15.88±1.32°

ATH: Acute toxic hepatitis, ALT: Alanine aminotransferase, GGT: Gamma glutamine transferase, ALP: Alkaline phosphatase, *Compared to the intact (P<0.05), oCompared to the untreated group (P<0.05)

Table 3: Influence of the therapeutic effect of various doses of Asfervon and Legalon on the intensity of secretion of gel and its chemical composition in rats with acute heliotrin hepatitis (for 4 h of the experiment; per 100 g of body weight)

Indicators Groups	Dose, mg/kg	Bile, ml	Bile acids, mg	Cholesterol, mg	Bilirubin, ug
Intact	–	1.20±0.12	5.92±0.46	0.228±0.019	101.93±6.82
ATH+H_2O	–	0.31±0.07*	2.51±0.29*	0.106±0.011*	46.19±6.77*
ATH+Asfervon	25	0.57±0.06*	2.88±0.25*	0.144±0.015*,o	64.47±7.46*,o
ATH+Asfervon	50	0.92±0.10o	5.62±0.39o	0.206±0.016o	89.93±6.98o
ATH+Asfervon	100	0.88±0.08o	5.42±0.32o	0.182±0.017o	80.17±8.02o
ATH+Legalon	100	0.75±0 .07*,o	5.14±0.39o	0.185±0.011o	74.69±6.78*,o

ATH: Acute toxic hepatitis, *Compared to the intact (P<0.05), oCompared to the untreated group (P<0.05)

When the abdominal cavity of the animals was opened, a large amount of dark ascitic fluid appeared; a dense liver of a dark cinnamon light was noted. Morphological studies have shown that the liver, when exposed to heliotrin, was slightly decreased in mass, on a nutmeg-type section, hemorrhage was observed. Microscopically, the destruction of the walls of the central veins and capillaries was noted. In some places in the central parts of the lobules, the walls of the blood vessels were completely indistinguishable. Trabecula was gradually thinned out toward the center of the lobules. The Kupfer cells were disappeared. There were obstacles created for the blood flow of the portal vein in the center of the lobules, mostly blood clots. It is commonly considered that heliotrin poisoning is morphologically similar to toxic liver dystrophy in Botkin's disease. At the same time, the blood vessel damage is considered to be a factor playing a decisive role in this liver pathology.

The exocrine function of the liver is specific for hepatocytes/ therefore, the hepatocyte disorders are associated with the functional state of this organ. Therefore, exocrine organ activity is widely used as an indicator of the therapeutic and prophylactic action of new developed medication compounds.[14,15,18]

In the first series of experiments, the preventive effect on the liver exocrine function of Asfervon in comparison with the Legalon was studying in acute heliotrin hepatitis rat models. The results showed that both drugs showed beneficial effects for the management of heliotrin-induced hepatitis compared to the control animals. At the same time, in the group of rats previously receiving the investigated drugs, there was a decrease in lethal outcomes. In untreated animals, the volume of excreted bile decreased by 63.3% compared to intact animals; however, in those who received Asfervon preventively at doses of 25, 50, and 100 mg/kg, bile secretion decrease was less significant of 49.2, 17.2, and 20.3%, respectively. Legalon also showed beneficial effect and the bile secretion decrease was only 24.2%. It is noteworthy that the preliminary administration of Asfervon increased the amount of excreted bile in comparison with the untreated group of animals by 38.3, 125.5, and 117.0%, respectively, at the indicated doses. Since the secretion of bile is a process provided exclusively by liver cells, it can be assumed that the preventive administration of Asfervon decreases damage to the biological membranes of liver cells, allowing the preservation of their function and the organ as a whole.

Consequently, under the influence of previously administered Asfervon, the exocrine function of the liver is not only preserved but also somewhat stimulated in comparison with the untreated group of animals, which indicates the presence of hepatoprotective activity of the drug in the carbon tetrachloride model[12] and in the heliotrin hepatitis model.

It is known that bile has a complex composition and its components are the products of different types of metabolism.

Therefore, for a full assessment of the effect of drugs, the chemical composition was simultaneously determined.[18] The results of biochemical studies in this series of experiments showed that heliotrin induced hepatitis was accompanied by an almost two-fold decrease in bile acids secretion, and the preliminary administration of Asfervon clearly maintains its level. Hence, under the influence of the drug, the amount of excreted bile acids in the bile composition increases by 16.5, 85.7, and 83.2% compared to the untreated group of rats. It can be seen predominantly at the concentrations of 50 and 100 mg/kg. Cholesterol is excreted along with the bile acids. When this process is blocked, cholesterol accumulates in hepatocytes. In the case of heliotrin induced hepatitis, the concentration of cholesterol in bile was decreased by 59.7%, and in animals receiving drugs, was significant increases. From the data in Table 1, it can be seen that the differences in cholesterol excretion between Legalon and Asfervon were not insignificant.

Bilirubin, as a product of hemoglobin degradation, is excreted in bile exclusively in the conjugated form.[14,15,19] Our results showed that heliotrin-induced hepatitis was accompanied by suppression of bilirubin secretion by 61.0%, and in rats previously treated with Asfervon, in contrast, was increased by 118A%, especially at a dose of 50 mg/kg. We have found practically the same effect in animals that were preventively treated with Legalon. Based on the data, it can be stated that Asfervon and Legalon have a unidirectional effect, which was manifested in the preservation of the processes of glucuronidation of bilirubin, which prevents the development of jaundice, an integral indicator of liver damage.

Thus, based on the above data, it can be stated that Asfervon, like Legalon, has hepatoprotective activity, which ensures the safety of the functional state of hepatocytes when damaged by the alkaloid heliotrin.

As noted, the synthesis of bile acids from cholesterol and the formation of glucuronide bilirubin proceeds with the participation of microsomal enzymes and depends on the intensity of bioenergetic processes. Earlier it was shown that acute heliotrinic hepatitis is accompanied by a significant inhibition of the monooxygenase enzyme system, leading to a decrease in the processes of hydroxylation of endogenous compounds and xenobiotics.[20] This condition is usually accompanied by an inhibition of the detoxifying function of the liver. Therefore, the latter is an integral criterion for assessing the course and severity of the liver disease. In our opinion, these processes are based on inhibition of the functional activity of mitochondrial and microsomal electron transport systems leading to the development of circulatory histotoxic hypoxia. These data were reflected in the biochemical parameters of serum. Thus, the activity of liver enzymes was significantly changed. The ALT activity in rats poisoned with heliotrin increased more than 5 times, which was accompanied by a more than two-fold increase in the activity of ALP and GGT, the level of total bilirubin was also increased by 147.0%. If we take into account that these enzymes are the criteria for liver damage, then it can be stated that in heliotrin-induced hepatitis, membrane permeability was increased due to hypoxia. The free radical damage increased the activity of phospholipase A2, leading to the hydrolysis of phospholipids of the membranes of intracellular organelles of hepatocytes and inhibition of the intensity of biochemical processes involving membrane-bound enzymes. Preventive administration of the studied drugs showed a decrease in cell destruction. For instance, under the influence of Asfervon, the activity of ALT compared with the control was 63.3% lower, the ALP was almost 2 times lower, and GGT was decrease by 42.9–47.5%. Moreover, the level of total bilirubin in the serum was decreased. As can be seen from the data in Tables 2, in animals were preventively treated with Legalon, the direction of the change was similar to animals that received Asfervon, and in its pharmacological efficacy, Legalon did not surpass Asfervon.

The next series of experiments was devoted to establishing the therapeutic efficacy of Asfervon in heliotrin-induced hepatitis. As shown by the results of the experiments, heliotrinic hepatitis was accompanied by significant violations of the exocrine function of the liver, decreased in the content of bile acids, cholesterol, and bilirubin in bile [Table 3]. At the same time, the conducted experimental therapy significantly increased the level of the studied parameters. It is shown that Asfervon was to some extent superior to the hepatoprotective effect of Legalon. It should be noted that the therapeutic use of these drugs led not only to the stabilization of the general condition of the animal but also the decreased mortality. Consequently, the results of this work clearly show that the preventive administration of Asfervon decreased intrahepatic circulation lesions, decreased inhibition of the functional activity of the mitochondrial and microsomal electron transport systems due to the development of circulatory histotoxic hypoxia. In our opinion, the studied preparations of plant genesis directly affect the microvessels of the liver, especially on the endothelial cells, preventing a pronounced violation of transcapillary metabolism.

Taking into account the low toxicity of Asfervon, the results of previous[21] and current work, we can conclude that Asfervon may be recommended in practical medicine to treat infectious and toxic induced hepatitis.

CONCLUSIONS

Asfervon is a drug with a pronounced hepatoprotective activity, not inferior to the classic hepatoprotective medication Legalon. Asfervon promotes bile secretion in preventive and treatment experiments. Asfervon may decrease circulatory toxic hypoxia in heliotrin induced hepatitis. Asfervon showed a positive effect on exocrine

function, the chemical composition of bile, and biochemical parameters of serum.

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