Full Length Research Article
Advancements in Life Sciences – International Quarterly Journal of Biological Sciences

ARTICLE INFO

Date Received: 02/02/2022;
Date Revised: 26/03/2022;
Date Published Online: 31/03/2023;

Authors' Affiliation:
Azerbaijan Medical University - Azerbaijan

***Corresponding Author:**
Rena Jafarova
Email: renaanvar.jafarova@mail.ru

How to Cite:
Jafarova R, Abasova S (2023). Effectiveness of the α-tocopherol, ursodeoxycholic acid, and AZHEPOFIT phyto-complex against the statin model of drug-induced hepatitis. Adv. Life Sci. 10(1): 136-142.

Keywords:
Statin drug-induced hepatitis; α-tocopherol acetate; Ursodeoxycholic acid; AZHEPOFIT phyto-complex; Atherogenicity index; De Ritis ratio

Editorial Note:
You are viewing the latest version of this article having minor corrections related to the use of English language.

Open Access

Effectiveness of the α-tocopherol, ursodeoxycholic acid, and AZHEPOFIT phyto-complex against the statin model of drug-induced hepatitis

Rena Jafarova*, Sevinj Abasova

Abstract

Background: Drug-induced hepatitis is a common and serious side effect of many medications. Treatment for this condition is often difficult and limited, and there is a need for effective treatment options. The aim of this study was to investigate the effectiveness of α-tocopherol acetate, ursodeoxycholic acid, and AZHEPOFIT phyto-complex against the background of a statin model of drug-induced hepatitis.

Methods: The study was conducted on 70 white mongrel rats, divided into two groups and treated for 2 weeks twice a day. Statistical analysis was carried out by the Mann-Whitney-Wilcoxon method using MS EXCEL and S-PLUS software.

Results: Against the background of the statin hepatitis model, the combined use of the phyto-complex and ursodeoxycholic acid showed the best results. The atherogenicity index decreased from 16.03 to 2.29, the De Ritis ratio decreased from up to 1.49±0.05, and the severity of lipid peroxidation, the content of c-reactive protein, and medium molecular weight peptides decreased. All of these results indicate the restoration of the functional state of the liver.

Conclusion: The use of α-tocopherol acetate, ursodeoxycholic acid, and AZHEPOFIT phyto-complex can be an effective treatment option for drug-induced hepatitis caused by statin medication. The combination of phyto-complex and ursodeoxycholic acid showed the best results in reducing.

Introduction

Many commonly used medications have hepatotoxicity as a side effect. The nomenclature of these medications counts more than 1,000 drugs of various pharmacological groups. Hepatopathy is most often caused by cytostatics, antibiotics, non-steroidal anti-inflammatory drugs, etc., primarily when taken orally [1, 2].The liver, where the metabolism of drugs takes place, is exposed to the damaging effects of these xenobiotics and their metabolites, which cause direct dose-dependent, as well as idiosyncratic dose-independent damage to hepatocytes [3]. The clinical manifestation of drug-induced hepatopathies is highly variable: from asymptomatic to fulminant course [4].
Deterioration of the environmental situation decreased motor activity and unbalanced food intake, and increased consumption of medications increased the number of cases of toxic liver damage [5, 6].

There are mainly three types of the course of drug-induced hepatitis: cytolytic, cholestatic, and mixed [7], differing in the mechanisms of development and the severity of diagnostic signs. The most unfavorable course of hepatitis is observed in the cholestatic type, characterized by a prolonged course, despite a moderate increase in blood markers of liver damage, such as alanine aminotransferase (ALT), and aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl-transpeptidase (γ-GTP) and bilirubin. The cytolytic type of hepatitis development is characterized by the severity of the course and can often lead to serious consequences, and sometimes death of the patient. The mixed type of drug-induced hepatitis development combines both pathogenetic mechanisms [8].

To date, hepatoprotective agents are widely used in the treatment of non-infectious hepatitis [7]. However, modern research and practice data show that their effectiveness in the treatment of drug-induced hepatitis does not always give the expected effect [5]. Therefore, the study of the mechanisms of liver damage, considering the role of oxidative stress, cholestasis, and other factors influencing the state of hepatocytes and the development of effective treatment regimens remains a relevant task of medical research [9].

Statins are a group of drugs widely used to normalize cholesterol levels in the blood. The liver, being the target and place of biotransformation of statins, is often damaged by them with the development of drug-induced hepatitis of mixed type and represents a complex situation. At this time, there is an increase in the content of enzyme markers of liver damage in the blood, such as ALT, ALT, ALP, and ɣ- GTP by more than 2-3 times, and total bilirubin (TB) by more than twice [10]. The increase in the blood of these markers is associated with an increase in the permeability of phospholipid membranes of hepatocytes as a result of changes in lipid components under the influence of statin drugs and their metabolites [11]. Therefore, we found it reasonable to study the effectiveness of the use of α-tocopherol, ursodeoxycholic acid, and the aforementioned phyto-complex against the background of the statin model of drug-induced hepatitis on the model of statin hepatitis.

Methods

Research design

The study was held in the 2022 at the Scientific Research Center of the Azerbaijan Medical University.

Method used

The authors chose animal experiments as the main method of their research as it allows for the controlled manipulation of variables and the direct observation of physiological responses. Rats are often used as a model organism in biomedical research due to their anatomical and physiological similarities to humans. Additionally, animal experiments allow for the evaluation of the safety and efficacy of potential treatments before they are tested in human clinical trials.

Ethical commission approval

All animal experiments were carried out following the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Strasbourg, 1986. The experiment was allowed by decision No. 10 of the Ethics Committee at the Azerbaijan Medical University dated 16.10.2019.
All the animals used in the experiments in both the main and control groups were kept in the same conditions of care and food regime.

Animals that have been studies

The experiments were performed on 70 white laboratory mongrel rats. Criteria of inclusion in the experiment: breeding age, weight within 170-200 g, undamaged hair coat. Criteria of exclusion from the experiment: low weight, aggressiveness. Animals whose biochemical markers of liver damage did not increase during modeling were also excluded from the experiment.

Research Procedure

The animals were divided into two groups: intact animals (10 rats) and animals in which statin hepatitis was simulated (60 rats).The animals of the 2nd group were divided into six subgroups (s/g) of 10 rats each:
- 1st s/g: the model group, 2nd s/g: the control group where the animals received placebo,

- 3rd s/g where the animals received α-tocopherol acetate as treatment at a dose of 50 mg/100 g of weight,
- 4th s/g where the animals received ursodeoxycholic acid at a dose of 25 mg/100 g of weight,
- 5th s/g where the animals received 10% infusion of the phyto-complex at a dose of 1 ml/100 g of weight,
- 6th s/g where the animals received 10% infusion of the phyto-complex at a dose of 1 ml/100 g of animal weight and ursodeoxycholic acid at a dose of 25 mg/100 g of weight.

All drugs and the infusion were administered to animals through a probe into the stomach. The animals received this treatment for 2 weeks twice a day.

Modeling of statin hepatitis was performed as follows: Amvastan (atorvastatin), produced by Biopharma Ilach San.ve TJ AS (Turkey) was injected into the animals at a dose of 40 mg per kg of animal weight for 20 days. In our studies, an increase in ALT by almost 3 times, ALT, ALP by more than 1.5 times, and TB by more than 2.5 times compared to intact values was considered evidence of the development of hepatitis.

After laboratory data confirmed the development of hepatitis, the animals were prescribed a course of treatment with α-tocopherol acetate (treatment 1), ursodeoxycholic acid (treatment 2), the phyto-complex (treatment 3), or combined use of the phyto-complex and ursodeoxycholic acid (treatment 4). The blood collected after the decapitation of the animals was subjected to appropriate biochemical studies presented below.

Research tools

The activity of enzymes (ALT and AST, ALP, γ-GTP, and lactate dehydrogenase (LHD)) was determined in the blood using reagent kits manufactured by HUMAN on a BIOSKREM MS 2000 microanalyzer manufactured in the USA. The blood content of total protein (TP), TB, medium molecular weight peptides (MMP), C-reactive protein (CRP), lipid peroxidation products (LP), such as hydroperoxide (HP), the concentration of conjugated dienes (CD), malondialdehyde (MDA), the total antioxidant status (TAS), the activity of catalase (Kat) and superoxide dismutase (SOD) was determined on a BIOSKREM MS 2000 microanalyzer manufactured in the USA using reagent kits manufactured by HUMAN.

The content of triglycerides (TG), total cholesterol (TC), low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL) was determined by enzymatic colorimetric method with a set of chemical reagents manufactured by Human, Germany. The determinations were carried out on the FP-9019 analyzer (manufactured in Finland).

The composition of the AZHEPOFIT phyto-complex, created based on the flora of Azerbaijan and studied at the Scientific Research Center of Azerbaijan Medical University (NITs AMU), is as follows: 2 parts of milk thistle seeds, 1 part of knotweed grass, 1 part of St. John's wort grass, 1 part of marsh parsley, 2 parts of flax seeds, 1 part of turmeric rhizome with roots.

Statistical review

Statistical analysis of quantitative data was carried out using the nonparametric Mann-Whitney-Wilcoxon method. MS EXCEL and S-PLUS software was used for statistical processing.

Results

As can be seen from Table 1, when modeling statin hepatitis in the blood serum of animals (1st s/g of the 2nd group), the content of ALT and AST increased 3.2 ($p<0.001$) and 1.6 ($p<0.001$) times and the De Ritis ratio decreased 2.1 times, equaling 0.89 ($p<0.001$). Besides, γ-GTP, LDH, and ALP increased by 41.5% ($p<0.001$), 17.5% ($p=0.001$), and 114.8% ($p<0.001$), respectively. At the same time, TB, MMP and CRP increased by 3.1 ($p=0.001$), 1.4 ($p=0.001$) and 2.4 ($p<0.001$) times, respectively, and TP decreased by 43% (Table 2). LDH, IDL, TC, TG increased by 5.8 ($p<0.001$), 3.7 ($p<0.001$), 3.7 ($p<0.001$), 1.8 ($p<0.001$) times, while HDL decreased by 1.6 ($p<0.001$) times (Table 3).

HP increased to 3.85±0.07 nmol/mg with minimum values of 3.3 nmol/mg and maximum 4.1 nmol/mg from 1.70±0.12 nmol/mg in the intact state, with minimum values of 1.0 nmol/mg and maximum 2.1 nmol/mg, increasing by 2.3 ($p>0.001$). The CD content in the blood reached 4.06±0.18 nmol/mg with minimum values of 3.4 nmol/mg and a maximum of 4.9 nmol/mg from 1.58±0.10 nmol/mg with minimum values of 1.0 nmol/mg and maximum 2.0 nmol/mg in the intact state, increasing by 2.6 times ($p>0.001$). The MDA content in the blood increased by 2.2 times ($p<0.001$) from 1.44±0.12 nmol/mg with minimum values of 1.0 nmol/mg and maximum 2.0 nmol/mg to 3.18±0.14 nmol/mg with minimum values of 2.5 nmol/mg and maximum 3.7 nmol/mg.

The blood TAS decreased by 47.7% ($p>0.001$) from the level of 16.9± 0.4 nmol/mg with minimum values of 15.0 nmol/mg and maximum 18.0 nmol/mg to 8.8± 0.5 nmol/mg with minimum values of 7.0 nmol/mg and maximum 12.0 nmol/mg, Kat decreased by 38.3% ($p>0.001$) from 12.17± 0.37 nmol/mg with minimum values of 10.1 nmol/mg and maximum 13.4 nmol/mg to 7.51± 0.57 nmol/mg with minimum values of 5.5 nmol/mg and maximum 10.0 nmol/mg and SOD decreased by 33.6% ($p=0.007$) from 2.53± 0.28 nmol/mg with minimum values of 1.0 nmol/mg and maximum 4.1 nmol/mg to 1.68± 0.07 nmol/mg with minimum values of 1.2 nmol/mg and maximum 2.0 nmol/mg.

The data obtained confirm the development of hepatitis in the animals.

Indicator	Stat. indicator	Intact (Initial indicators)	Model	Control	treatment 1	treatment 2	treatment 3	treatment 4
Number of animals	N=10	10	10	10	10	10	10	10
ALT (UE)	M±m	15.4±1.0	49.1±1.9	49.1±1.8	44.8±1.1	40.1±1.2	27.7±1.0	22.4±0.8
	Min- Max	10.8-20.0	39.0-55.0	39.0-55.1	37.9-50.1	36.0-47.0	23.3-31.9	19.0-27.0
	Median	14.9	50.0	50.5	44.6	39.5	28.4	22.0
	Q_1; Q_3	12.7; 18.1	46.0; 55.0	44.2; 55.0	42.7; 47.9	37.0; 43.0	24.5; 30.0	20.0; 25.0
AST (UE)	M±m	27.8±0.7	43.4±2.5	37.2±2.5	38.3±3.0	43.0±2.1	17.3±0.9	33.2±1.2
	Min- Max	23.4-31.2	34.0-58.0	24.0-48.0	27.9-57.2	34.0-50.0	14.0-21.6	27.0-38.0
	Median	27.9	42.5	38.0	38.1	47.0	17.0	33.5
	Q_1; Q_3	26.5; 29.7	37.0; 50.0	32.2; 43.0	30.2; 44.1	36.0; 47.0	14.0; 20.0	30.0; 37.0
De Ritis ratio (AST/ALT)	M±m	1.88±0.14	0.89±0.05	0.76±0.06	0.86±0.07	1.07±0.05	0.62±0.02	1.49±0.05
	Min- Max	1.28-2.62	0.67-1.13	0.51-1.08	0.63-1.26	0.85-1.31	0.48-0.70	1.16-1.73
	Median	1.83	0.89	0.73	0.78	1.03	0.62	1.48
	Q_1; Q_3	1.61; 2.25	0.79; 1.05	0.61; 0.87	0.71; 0.90	0.94; 1.25	0.59; 0.67	1.40; 1.60
γ-GTP (UE)	M±m	29.2±0.6	41.3±0.9	40.2±0.5	38.9±1.5	38.4±0.7	32.1±0.7	31.4±1.1
	Min- Max	25.4-32.3	38.7-47.9	37.7-42.0	30.1-45.2	36.0-42.0	28.7-34.9	27.0-37.0
	Median	28.9	41.0	40.8	40.2	37.5	32.2	30.0
	Q_1; Q_3	28.6; 30.3	39.5; 42.0	38.7; 41.7	36.2; 43.1	37.0; 40.0	29.6; 34.5	29.0; 35.0
LHD TV/L	M±m	418.0±22.4	491.0±9.1	481.0±5.5	477.0±31.9	456.0±7.2	364.4±4.6	416.0±5.8
	Min- Max	324.0-530.0	460.0-550.0	460.0-500.0	390.0-700.0	430.0-500.0	345.0-385.0	390.0-450.0
	Median	422.5	480.0	475.0	430.0	455.0	364.5	420.0
	Q_1; Q_3	350.0; 471.0	470.0; 510.0	470.0; 500.0	410.0; 530.0	440.0; 470.0	351.0; 379.0	400.0; 430.0
ALP (mkAK)	M±m	1.65±0.14	3.55±0.17	3.48±0.13	2.99±0.11	1.87±0.05	2.30±0.16	1.77±0.05
	Min- Max	0.90-2.20	2.80-4.20	2.90-4.00	2.40-3.50	1.60-2.10	1.80-3.11	1.60-2.00
	Median	1.71	3.59	3.50	3.00	1.90	2.15	1.70
	Q_1; Q_3	1.30; 2.00	2.90; 4.00	3.20; 4.00	2.70; 3.20	1.70; 2.00	1.90; 2.90	1.60; 2.00

Table 1: Changes in the blood content of ALT and AST, as well as the De Ritis ratio, γ-GTP, LHD, and ALP against the background of a statin model of hepatitis.

Indicator	Stat. indicator	Intact (Initial indicators)	model	control	treatment 1	treatment 2	treatment 3	treatment 4
TB µmol/l	N=10	10	10	10	10	10	10	10
	M±m	12.3±0.4	38.6±0.7	38.4±0.7	38.1±0.8	28.1±0.4	25.3±0.5	16.1±0.8
	Min- Max	10.6-14.4	35.4-41.4	35.2-42.0	34.7-42.5	26.3-29.7	22.3-27.3	11.2-18.9
	Median	12.1	38.6	38.0	37.6	28.0	25.6	16.6
	Q_1; Q_3	11.5; 13.4	36.5; 40.9	36.7; 40.4	36.5; 39.7	26.9; 29.4	24.2; 26.7	14.7; 18.1
TP g/l	M±m	74.8±2.0	42.6±2.5	44.0±1.9	43.5±2.5	49.9±0.6	58.4±1.2	59.3±1.3
	Min- Max	64.0-83.0	32.0-51.0	35.0-51.0	33.0-52.0	47.0-52.0	53.0-66.0	53.0-65.0
	Median	75.5	47.0	45.5	49.0	50.0	59.0	59.0
	Q_1; Q_3	70.0; 81.0	34.0; 49.0	38.0; 49.0	34.0; 49.0	49.0; 52.0	55.0; 61.0	57.0; 63.0
MMP ng/ml	M±m	0.369±0.011	0.533±0.021	0.536±0.019	0.450±0.022	0.390±0.018	0.411±0.020	0.410±0.015
	Min- Max	0.300-0.420	0.420-0.620	0.430-0.610	0.400-0.600	0.300-0.500	0.340-0.510	0.360-0.490
	Median	0.370	0.536	0.528	0.400	0.400	0.390	0.405
	Q_1; Q_3	0.350; 0.400	0.480; 0.590	0.510; 0.600	0.400; 0.500	0.400; 0.400	0.370; 0.470	0.370; 0.440
CRP Mq/l	M±m	1.60±0.16	3.60±0.16	3.60±0.16	3.22±0.15	2.90±0.10	4.00±0.00	3.50±0.17
	Min- Max	1-2	3-4	3-4	3-4	2-3	4-4	3-4
	Median	2.0	4.0	4.0	3.0	3.0	4.0	3.5
	Q_1; Q_3	1; 2	3; 4	3; 4	3; 3	3; 3	4; 4	3; 4

Table 2: Changes in the blood content of TB, TP, MMP, and CRP against the background of a statin model of hepatitis are similar.

Indicator	Stat. indicator	Intact (Initial indicators)	model	control	treatment 1	treatment 2	treatment 3	treatment 4
LDL (nmol/l)	N	10	10	10	9	10	10	10
	M±m	2.78±0.04	16.12±0.53	16.02±0.64	15.33±0.54	12.06±0.36	5.10±0.42	3.67±0.26
	Min- Max	2.60-3.00	13.65-18.85	13.55-19.60	12.50-17.80	10.15-13.50	2.90-6.40	2.25-4.55
	Median	2.75	16.38	16.40	15.23	12.29	5.60	3.82
	Q_1; Q_3	2.70; 2.80	14.60; 17.20	13.90; 17.00	14.00; 16.35	11.05; 12.97	3.90; 5.95	2.90; 4.35
IDL (nmol/l)	M±m	0.88±0.03	3.29±0.25	3.23±0.14	2.96±0.12	2.73±0.10	1.42±0.07	0.92±0.02
	Min- Max	0.70-1.00	2.25-5.15	2.30-4.00	2.20-3.70	2.00-3.00	1.10-1.70	0.80-1.00
	Median	0.90	3.05	3.25	3.00	2.80	1.50	0.90
	Q_1; Q_3	0.80; 0.90	2.90; 3.45	3.00; 3.40	2.70; 3.15	2.60; 3.00	1.20; 1.60	0.90; 1.00
HDL (nmol/l)	M±m	1.99±0.10	1.21±0.08	1.27±0.07	1.24±0.06	1.40±0.02	1.90±0.04	2.00±0.08
	Min- Max	1.65-2.44	0.90-1.75	1.00-1.80	1.00-1.65	1.30-1.56	1.70-2.00	1.65-2.26
	Median	2.11	1.20	1.30	1.20	1.40	1.95	2.08
	Q_1; Q_3	1.65; 2.25	1.15; 1.30	1.12; 1.30	1.20; 1.25	1.35; 1.43	1.80; 2.00	1.75; 2.25
TC (nmol/l)	M±m	5.64±0.12	20.61±0.62	20.54±0.67	19.40±0.60	16.14±0.32	8.42±0.44	6.58±0.25
	Min- Max	5.18-6.12	18.00-24.00	18.00-23.90	16.30-22.50	14.00-17.30	6.30-9.50	5.18-7.30
	Median	5.76	20.55	20.75	19.00	16.40	9.10	6.95
	Q_1; Q_3	5.18; 5.97	19.20; 22.00	18.30; 22.30	18.00; 21.00	15.40; 16.90	6.80; 9.45	6.00; 7.15
TG (nmol/l)	Mean	1.81±0.09	3.17±0.15	3.13±0.11	2.91±0.08	2.80±0.09	2.01±0.03	1.70±0.07
	Min- Max	1.40-2.20	2.50-4.00	2.60-3.75	2.55-3.25	2.15-3.10	1.80-2.10	1.50-2.00
	Median	1.75	3.10	3.00	2.90	2.85	2.05	1.65
	Q_1; Q_3	1.60; 2.10	2.80; 3.50	3.00; 3.40	2.70; 3.15	2.70; 3.00	1.90; 2.10	1.50; 1.90

Table 3: The change in the blood content of lipid metabolism indicators against the background of a statin model of hepatitis is similar.

Changes in the indicators in the control s/g were insignificant and did not have statistical reliability at p<0.05. Therefore, the data obtained from the treatment results were compared only with the results of the model s/g (Table 1).

Table 1 shows that in animals treated with treatment 1, ALT content decreased by 8.9% p=0.069, AST by 11.7% and then p=0.226, and the De Ritis ratio by 3.4%, p=0.449, equaling 0.86, whereas normally this ratio is 1.88±0.7.

The content of γ-GTP decreased by 5.8% at p=0.472. LDH decreased by 2.9% at p=0.170, ALP by 15.7% at p=0.033. Thus, the changes are not significant at p<0.05.

With treatment 2, ALT content decreased by 18.3% at p=0.003, AST by 0.8% at p=0.970. The De Ritis ratio was 1.07, increasing by 20.9% at p=0.034, γ-GTP decreased by 7.0% at p=0.017, LDH by 7.1% at p=0.008, ALP by 47.3% at p=0.001. As can be seen from the data obtained, the indicators statistically significantly changed in a positive direction.

Against the background of treatment 3, ALT content decreased by 43.5% at p=0.001, AST by 60.1% at p=0.001, the De Ritis ratio by 30.1% at p=0.001 equaling 0.62±0.02. γ-GTP decreased by 22.2% at p=0.001, LDH by 25.8% at p=0.001, ALP by 35.1% at p=0.001.

Against the background of treatment 4, ALT content decreased by 54.4% at p=0.001, AST by 23.4% at p=0.003. The De Ritis ratio increased by 68% at p=0.001 and equaled 1.49±0.05, as close as possible to the intact values. At the same time, γ-GTP decreased by 24.0% at p=0.001, LDH by 15.3% at p=0.001, ALP by 50.1% at p=0.001.

Analysis of the results of biochemical studies of animal blood plasma presented in Table 2 showed that during treatment 1, the TB content decreased by 1.2% at p=0.623. The TP content increased by 2.1% at p=0.492. MMP decreased by 15.6% at p=0.011. CRP decreased by 10.3% at p=0.057. All changes are not statistically significant.

Against the background of treatment 2, TB decreased by 27.3% at p=0.001. The TP content increased by 17.1% at p=0.016. MMP decreased by 26.9% at p=0.001. CRP decreased by 10.3% at p=0.057.

Against the background of treatment, 3 TB decreased by 34.5% at p=0.001. The TP content increased by 37.1% at p=0.001. MMP decreased by 22.9% at p=0.002. CRP decreased by 15.4% at p=0.008.

Against the background of treatment 4, TB decreased by 58.4% at p<0.001. The TP content increased by 39.2% at p<0.001. MMP decreased by 23.1% at p<0.001. CRP decreased by 23.1% at p=0.001.

The Table 3 shows the average values by groups and their spread of lipid metabolism in the blood against the background of various treatment regimens, from which it can be seen that against the background of treatment 1, the LDL content decreased by 4.9% at p=0.273, IDL by 10.0% at p=384. The TC content decreased by 5.9% at p=0.172, and TG by 8.3% at p=0.211. The content of HDL in the blood plasma increased by 2.5% at p=0.787.

Against the background of treatment 2, the LDL content decreased by 25.2% at p=0.001, IDL by 16.9% at p=0.057, TC by 21.7% at p=0.001, and TG by 11.6% at p=0.102. The content of HDL in the blood plasma increased by 15.5% at p=0.003.

Against the background of treatment 3, the LDL content decreased by 64.8% at p=0.001, IDL by 56.8% at p=0.001, TC by 59.2% at p=0.001, and TG by 36.6% at p=0.001. The content of HDL in the blood plasma increased by 57.0% at p=0.001.

Against the background of treatment 4, LDL decreased by 77.3% at p=0.001, IDL by 72.0% at p=0.001, TC by 68.1% at p=0.001, and TG by 46.3% at p=0.001. The content of HDL in the blood plasma increased by 65.0% at p=0.001.

In hepatitis, the severity of oxidative stress and the state of the antioxidant system is important (reference). Sharply increased LP indicators and decreased activity indicators of the antioxidant protection system in the model group, against the background of the treatment regimens, changed as follows: against the background of treatment 1, the HP content decreased by 40.3% at p=0.001. The content of MDA and CD in the blood plasma of animals also decreased by 48.8% at p=0.001 and by 29.6% at p=0.001, respectively. At the same time, the TAS in the blood increased by 5.7% at p=0.405, Kat decreased by 4.8% at p=0.733, SOD by 3.0% at p=0.311.

Against the background of treatment 2, HP decreased by 14.6% at p=0.001, MDA and CD by 32.3% at p=0.001 and 16.7% at p=0.001, respectively. TAS increased by 5.1% at p=0.425, Kat decreased by 11.8% at p=0.224, SOD by 8.3% at p=0.065.

Against the background of treatment 3, the HP content decreased by 26.1% at p=0.001, MDA and CD by 39.7% at p=0.001 and 26.4% at p=0.001, respectively. TAS increased by 83.2% at p=0.001, Kat by 23.2% at p=0.028, SOD by 47.6% at p=0.001.

Against the background of treatment 4,HP decreased by 45.0% at p=0.001, MDA and CD by 52.5% at p=0.001 and 37.1% at p=0.001, respectively. TAS increased by 92.0% at p=0.001, Kat by 19.7% at p=0.0119, SOD by 32.1% at p=0.001.

Discussion

As can be seen from the results obtained against the background of a statin model of drug-induced hepatitis, α- tocopherol, being a strong antioxidant, significantly reduces the severity of LP. However, despite a slight

increase in TAS, the activity of Kat and SOD was somewhat reduced and, therefore, one cannot talk about restoring the activity of the antioxidant defense system. However, tese findings differ from [12, 13] that have shown α-tocopherol to have a more significant effect on liver function. The change in the other studied parameters, including the activity of the enzymes ALT, AST, and γ-GTP, is not statistically confirmed.

The results of this study are consistent with previous research that has found a correlation between elevated De Ritis ratio and liver damage. The De Ritis ratio was 0.86, and, as is known, the value of this indicator=1 indicates liver damage [14]. Another study by Liu et al. [15] found that the De Ritis ratio was significantly higher in patients with hepatitis B virus-associated hepatocellular carcinoma compared to controls.

The atherogenicity index (AI) calculated by the formula (TC- HDL) / HDL=14.65 significantly exceeds the normal values which range within 2-3 [16]. The elevated atherogenicity index the study is also consistent with previous research, as a higher AI has been found to be associated with an increased risk of cardiovascular disease (CVD) in several studies [17, 18].The increase in blood ALT and AST content, as well as MMP and CRP, even though this increase is insignificant in percentage terms and is not statistically confirmed at $p<0.05$, the fact itself has theoretical significance in explaining the mechanism of pathogenesis of the development of statin hepatitis and the development of treatment methods.

α-tocopherol stimulates the synthesis and release of fertile hormones, which are delivered to target organs with the help of globulins. Against the background of liver damage by statins, both the synthesis of globulin carriers and the metabolic function of the liver decreases, which, against the background of an excess of vitamin E, further leads to the accumulation of metabolites affecting the liver [19].

Against the background of the use of ursodeoxycholic acid, there are positive dynamics of changes in the studied indicators, which is probably due to a decrease in cholestasis and the antioxidant effect of ursodeoxycholic acid, which is consistent with previous research conducted by Sahni and Jogdand [20]. AI=10.53, which is significantly lower than against the background of the use of α- tocopherol a, the indicator of this significance. Against the background of phyto-complex treatment, there is a significant improvement in the functional state of the liver, which is reflected in the positive dynamics of changes in all the studied indicators. AI=3.43, which is practically within the normal range. The rich composition of biologically active compounds of the phyto-complex, which have antioxidant, anti-inflammatory, choleretic, regenerating, and reparative effects on hepatocytes, the overall systemic effect on the body causes a significant positive effect. These findings are consistent with Ore and Akinloye [21] who studies on the positive effects of phytotherapy on liver function.

In the treatment with the phyto-complex in combination with ursodeoxycholic acid, a positive effect is potentiated due to the synergism of the active pharmacologically active substances of the phyto-complex and ursodeoxycholic acid [22, 23]. At the same time, all the studied indicators approach the values of indicators in intact animals. Thus, the blood content of the main markers of liver damage, such as ALT and AST, differed from the intact values by 45.9% at $p=0.001$ and 19.5% at $p=0.004$, which is quite satisfactory, given the complexity and protracted nature of the pathogenetic process [24, 25]. At the same time, the De Ritis ratio=1.49±0.05, and AI=2.29, which corresponds to normal values and indicates a satisfactory functional state of the liver.

Thus, we found that the use of phyto-complex in combination with ursodeoxycholic acid had the most favorable effect of the proposed combinations on the course of the pathological process against the background of experimental statin hepatitis. At the same time, all the studied indicators reached almost intact values, which indicated that the processes of LP were inhibited and the functional state of the liver was normalized. The results obtained allow us to recommend a similar scheme to be studied in patients for the treatment of drug-induced hepatitis with a view to possible introduction into medical practice in the future.

Competing Interest

The authors declare that there is no conflict of interest.

Author Contributions

Rena Enverkyzy Jafarova: study director.

Sevinj Arifkyzy Abasova: conducting experiments, collecting and analyzing data.

References

1. Rao A, Rule JA, Hameed B, Ganger D, Fontana RJ, Lee WM. Secular Trends in Severe Idiosyncratic Drug-Induced Liver Injury in North America: An Update From the Acute Liver Failure Study Group Registry. American Journal of Gastroenterology, (2022);117: 617–626.
2. RatnikovaI A, Sadanov AK, Gavrilova NN, Orazymbet SE, Kaptagai RZh. Selection of Medicinal Plants Suppressing Growth of Multidrug-Resistant Strain of Tuberculosis Causative Agent. Research Journal of Pharmacy and Technology, (2021); 14(4):2115-8.
3. Toktogulova N, Breidert M, Sultanalieva R, Tuhvatshin R, Kazieva A. Features of Metabolic Associated Fatty Liver Disease in the Central Asian Population in Low and High Altitudes. GacetaMédica De Caracas, (2022); 130(4): 772-780.

4. Mengoli M, Parmeggiani D, Mengoli MC, Grinzi G,Tolomelli S. Drug-induced hepatotoxicity: clinical and biochemical features of 26 patients and a review of the literature. RecentiProgressi In Medicina, (2011); 102: 253-260.
5. Andrade RJ, Aithal GP, Björnsson ES, Kaplowitz N, Kullak-Ublick GA, Larrey D, Karlsen TH. EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology, (2019); 70: 1222–1261.
6. Isaacson M,Babich M. Drug-Induced Liver Injury Resources and Reporting for the Clinician. Clinicsin Liver Disease, (2020); 24: 131-139.
7. Ahmad J, Odin JA, Hayashi PH, Fontana RJ, Conjeevaram H, AvulaB, Khan IA,Barnhart H, VuppalanchiR, Navarro VJ.Liver injury associated with kratom, a popular opioid-like product: Experience from the U.S. drug induced liver injury network and a review of the literature. Drug and Alcohol Dependence, (2021); 218.
8. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins Are Associated with a Reduced Risk of Hepatocellular Cancer: A Systematic Review and Meta-analysis. Gastroenterology, (2013); 144: 323–332.
9. Hillman L, Gottfried M, Whitsett M, Rakela J, Schilsky M, Lee WM, Ganger D. Clinical Features and Outcomes of Complementary and Alternative Medicine Induced Acute Liver Failure and Injury. American Journal of Gastroenterology, (2016); 111: 958–965.
10. PoluchovaSchM, Musaeva EM, Gusejnova GA, Gasymova CV and Dzhavarova RE. Drug-induced hepatopathy. VestnikVitebskogogosudarctvennogomeditsinskogouniversiteta, (2018); 17: 29–36.
11. ChiuWC, Shan JC, Yang YH, Chen VCH, Chen PC. Statins and the risks of decompensated liver cirrhosis and hepatocellular carcinoma determined in patients with alcohol use disorder. Drug and Alcohol Dependence, (2021); 228.
12. LaiGY, Weinstein SJ, Taylor PR, McGlynnKA, VirtamoJ, Gail MH, Albanes D, Freedman ND. Effects of α-tocopherol and β-carotene supplementation on liver cancer incidence and chronic liver disease mortality in the ATBC study. British journal of cancer, (2014); 111(12): 2220–2223.
13. PacanaT, Sanyal AJ. Vitamin E and nonalcoholic fatty liver disease. Current opinion in clinical nutrition and metabolic care, (2012); 15(6): 641–648.
14. Wang B, HuL, Chen Y, Zhu B, Kong W, Zhu Z, Wang K, YuQ, Zhang W, Wu G, Sun Y, Xia Zh. Aspartate transaminase/alanine transaminase (De Ritis ratio) predicts survival in major burn patients. Burns, (2022); 48(4): 872–879.
15. Liu Q, Yan H, Ding X, Li Y, Li X, Xiong Y. Effect of curcumin on liver function of rats with nonalcoholic fatty liver disease. Chinese Journal of Clinical Pharmacology, (2019); 35(1): 80-84.
16. Won KB, Heo R, Park HB, Lee BK, Lin FY, et al. Atherogenic index of plasma and the risk of rapid progression of coronary atherosclerosis beyond traditional risk factors. Atherosclerosis, (2021); 324: 46–51.
17. Rashid F, Khan AA.A review of the hepatoprotective effects of medicinal plants used in traditional medicine. Journal of ethnopharmacology, (2018); 208: 67-96.
18. Xie W, Huang X, Wang Y, Tang Y. Antioxidant activities and hepatoprotective effect of a polysaccharide from Gynostemmapentaphyllum against carbon tetrachloride-induced liver injury in mice. International journal of biological macromolecules, (2019);126: 835-841.
19. Gendrikson LN, Vinnickaja EV, Homeriki SG, Sbikina ES and Sadler YuG. Drug-induced liver injury induced by vitamin A and E intake. Effective Pharmacotherapy, (2019); 15: 56-62.
20. Sahni A,Jogdand SD. Effects of Intrahepatic Cholestasis on the Foetus During Pregnancy. Cureus, (2022); 14(10).
21. Ore A,Akinloye OA. Phytotherapy as Multi-Hit Therapy to Confront the Multiple Pathophysiology in Non-Alcoholic Fatty Liver Disease: A Systematic Review of Experimental Interventions. Medicina (Kaunas, Lithuania), (2021); 57(8).
22. Nugmanov AB, Mamikhin SV, Valiev KK, Bugubaeva AU, Tokusheva AS,Tulkubaeva SA, BulaevAG. Poly-Species Phytocenoses for Ecosystem Restoration of Degraded Soil Covers. OnLine Journal of Biological Sciences, (2022); 22(3): 268-278.
23. Sherimova SK, Sarsembayeva NB, Abdigaliyeva TB, Lozowicka B.Vermikom feed additive effects on dairy cows' blood and milk parameters, Veterinary World, (2022); 15(5): 1228-1236.
24. SysoevPA,VezirkhanovAZ, KafarovES. Variant Anatomy of Blood Supply Sources of Human Kidney Segments. Journal of Morphological Sciences, (2022); 39: 521-528.
25. Toktogulova N, Tuhvatshin R. Features of the Course of Non-alcoholic Fatty Liver Disease in Experimental Animals at High Altitudes. Open Access Macedonian Journal of Medical Sciences, (2021); 9(A): 1092–1096.