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Hypolipidemic and Antiatherosclerotic Activity of Polysaccharides of *Ferula Kuhistanica*

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Abstract This scientific work is devoted to the study of the hypolipidemic and antiatherosclerotic activity of *Ferula Kuhistanica* polysaccharides. Experiments were carried out on rats and rabbits. It was revealed that in experiments on rats with reproducible hyperlipidemic conditions, when administered prophylactically, and in experiments on atherosclerotic rabbits, when administered prophylactically, it slows down the development of negative changes in lipid metabolism.

Keywords Polysaccharide, *Ferula kuhistanica*, Lipid metabolism, Antiatherosclerosis, Blood, Rats and rabbits

1. Introduction

Plant polysaccharides are attracting increasing attention in recent years due to the identification of their numerous biological effects indicating the promising use of these substances in therapeutic and prophylactic purposes [1]. The discovery of hypolipidemic and antiatherosclerotic effects in some polysaccharides could be one of the promising directions in this respect [2,3]. Continuing research in this aspect, we studied a total polysaccharide preparation isolated from Ferula kuhistanica plant widespread in the Central Asian region. Its effect on lipid metabolism state was studied in rats with hyperlipidemia and in rabbits directly with experimental atherosclerosis.

2. Materials and Methods

Total preparation of polysaccharides, extracted from above-ground parts of *Ferula kuhistanica* [4], used in experiments contains galacturonic acid and neutral monosaccharides: galactose, glucose, arabinose, xylose and rhamnose in the ratio 8.2:2.1:1.0:4.3:1.0. Hypolipidemic and anti-atherosclerotic properties of the preparation were studied in 42 outbred white rats (males, 200-250 g) - normal and with experimental hyperlipidemia, as well as in 18 rabbits (3-3.5 kg males) of grey chinchilla breed with experimental atherosclerosis (the experiments were performed in duplicate). The drug in all cases was administered per os at a dose of 250 mg/kg (in preliminary studies established as the most effective).

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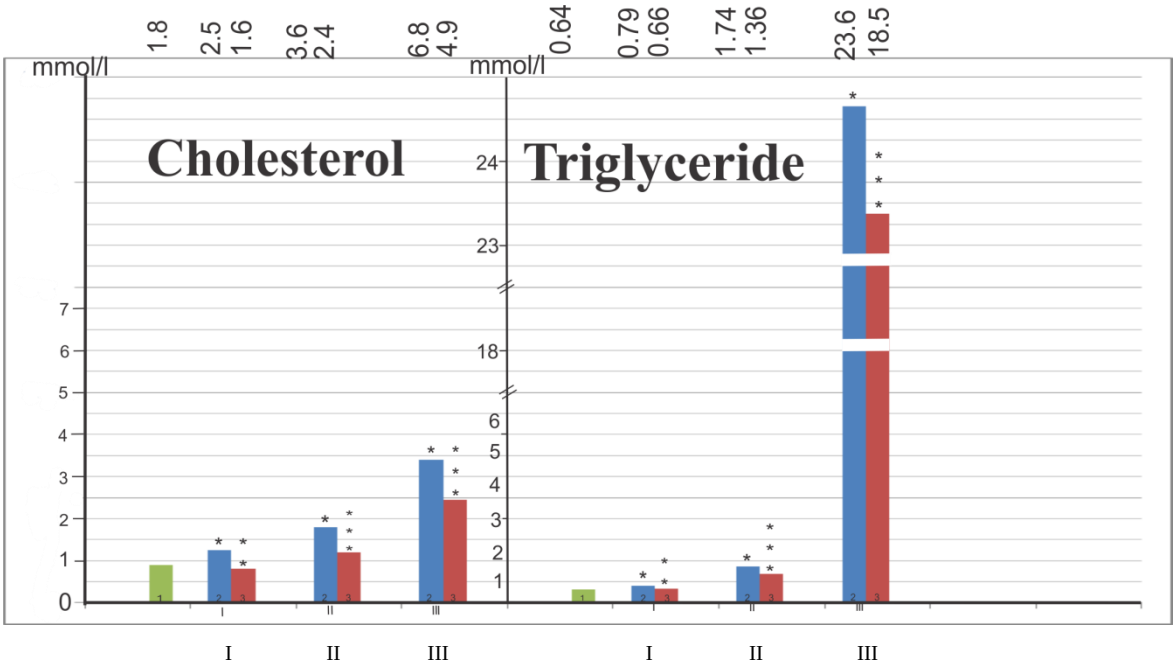
Experiments were performed in compliance with international regulations (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 22 September 2010 on the protection of animals used for scientific purposes). The animals were slaughtered by immediate decapitation under mild ether anaesthesia. Normal rats were administered the test drug either once or for 7 days. In case of reproducing hyperlipidemia the drug was administered for the preceding seven days. Endogenous hyperlipidemia was induced according to the method [5] - animals were deprived of food for 24 hours with unlimited access to water.

Ethanol hyperlipidemia was induced by injecting rats with 50% ethanol solution for three days in increasing doses, the animals being taken into the experiment after 10 hours (before ethanol injection the rats had been fasted for 8 hours with an unrestricted access to water) [6]. Triton hyperlipidemia was induced by intraperitoneal injection of triton WR-1339 at a dose of 225 mg/kg into rats, they were used in the experiment after 17 hours [7].

Atherosclerosis in rabbits was reproduced by per os injection of cholesterol solution in cotton oil at a dose of 0.3 g/kg for 3 months. One month later the animals were also orally administered the test total polysaccharide preparation and administered until the end of the experiment. Cholesterol, triglycerides, pre-β- and β-lipoprotein fractions and α-cholesterol content in animal serum were determined using Cypress diagnostics (Belgium) biochemical kits on Secomam-UV-Vis Basic VI.18 biochemical analyzer from Secomam (France). In the aorta cholesterol was determined according to the method [8], triglycerides according to the method [9]. Numerical data were statistically processed using Student's t-criterion.



(I-endogenous, II-ethanolic, III-tritonic)
1-intact animals, 2-control (hyperlipidemia), 3-hyperlipidemia + polysaccharides
*significantly to the indicators of intact animals, **-to control ($p<0.05$)

Figure 1. Effect of the amount of polysaccharides from *Ferula kuhistanica* on the content of cholesterol and triglycerides in the blood serum of rats with experimental hyperlipidemias

Table 1. Effects of total polysaccharide preparation from *Ferula kuhistanica* on parameters of lipid metabolism in blood serum of rabbits with experimental atherosclerosis (M±m, n=6)

Indicators investigated	Intact animals	Atherosclerosis (control)	Atherosclerosis + polysaccharide preparation
Cholesterol, mmol/l	2,12±0,05	27,6±2,7*	14,7±0,41*1
Triglycerides, mmol/l	0,66±0,03	6,7±0,29*	5,5±0,41*1
α- cholesterol, mmol/l	0,62±0,02	1,14±0,07*	0,74±0,02*1
Pre-β- and β-lipoproteins, mmol/l	4,13±0,13	38,4±2,6*	7,58±0,34*1
Atherogenicity coefficient	2,43±0,14	23,9±2,1*	18,9±0,42*1
α- cholesterol/total cholesterol	0,29±0,01	0,041±0,003*	0,050±0,001*1
Pre-β- and β-lipoproteins α- cholesterol	6,73±0,3	34,9±1,6*	10,2±0,25*1

Note. * - Significantly relative to intact animals; 1 - significant to control ($p<0.05$)

3. The Results of Research

The experiments showed that a single injection of total preparation of polysaccharides from *Ferula kuhistanica* into rats caused no significant changes in cholesterol and triglycerides content in serum of intact animals (reduction by 7.8 and 4.2% with $p>0.05$). Reliable reductions in cholesterol by 22.2% and triglycerides by 14.1% were observed after 7 days of administration. More pronounced hypolipidemic effect of the polysaccharide preparation was observed in models of reproduced hyperlipidemia. Thus, its pretreatment for 7 days largely prevented the development of mobilizing hyperlipidemia in fasting rats: the serum levels of total cholesterol and triglycerides were 36.0 and 16.5% lower in comparison with the control animals and practically corresponded to the norm (Fig. 1). In rats with ethanol hyperlipidemia pretreated with polysaccharide preparation, serum cholesterol and triglycerides contents were 33.3 and 21.2% lower than in the corresponding control animals, while in rats with triton hyperlipidemia treated with polysaccharide preparation, they were 27.9 and 21.6% lower than the control animals (Fig. 1). Data on the ability of the polysaccharide preparation from *F. kuhistanica* to improve lipid metabolism in case of its pathological shifts were also confirmed in experiments on rabbits with experimental atherosclerosis.

It is shown in the table above that cholesterol injection in rabbits during 3 months promoted the increase of endogenous cholesterol in blood serum in comparison with intact animals by 13.0 times and triglycerides by 10 times. An increase in atherogenic forms of low density lipoproteins was also revealed. The observed increase of α-cholesterol

was not positive in this case as indicated by the sharp decrease of α-cholesterol to total cholesterol ratio by 85.9%. A 9-fold increase in calculated atherogenicity ratios (total cholesterol - α-cholesterol/ α-cholesterol) and a 5-fold increase in the ratio of pre-β- and β-lipoproteins to α-cholesterol were also observed in control rabbits. Administration of a total polysaccharide preparation from *F. kuhistanica* has largely prevented the occurrence of negative shifts in lipid metabolism. First of all, lower serum levels of cholesterol and triglycerides (46.7 and 17.9% less than in controls, respectively) attracted attention. Pre-β- and β-lipoprotein fractions were also markedly lower than in controls (by 80.3%). The atherogenicity coefficient when administered to rabbits with developing atherosclerosis by the end of the experiment was 18.7% lower than in control, the ratio of α-cholesterol to total cholesterol increased by 21.9, and the ratio of the total fraction of pre-β- and β-lipoproteids to α-cholesterol decreased by 69.6% (table 1). In experiments performed on rabbits given cholesterol, a certain protective effect of the total polysaccharide preparation under these conditions was also found in relation to atherosclerotic lesions of the aorta.

Thus, the intima of aortas of all individuals of the control group was covered with atherosclerotic plaques of different size and convexity, which was most noticeable in the area of the aortic arch and the mouths of the intercostal arteries. The degree of aortic lesions in the animals ranged from 60 to 75%. When the studied polysaccharide preparation was administered in two rabbits the aortic intima was without visible atheromatous lesions. The area of lesions with atherosclerotic plaques in the remaining animals was 42-50%. At the same time the determination of cholesterol and triglycerides content in aorta showed that in contrast to the control, where these indices were 7.2 and 4.3 times higher than in intact animals, the total polysaccharide preparation contributed to their reduction by 27.9 and 25.3% respectively ($p< 0.05$).

4. Conclusions

Thus, the total polysaccharide preparation from F. kuhistanica both in experiments on rats with reproducible hyperlipidemic conditions with prophylactic administration, and in experiments on atherosclerotic rabbits with prophylactic-treatment administration, restrained the development of negative changes in lipid metabolism. The revealed hypolipidemic and antiatherosclerotic properties of the polysaccharide preparation from *F. kuhistanica*, as well as the majority of other compounds of plant origin previously studied by us [10,11,12] (although expressed to a lesser extent), are nevertheless of considerable interest and open the prospect of its use in practical health care for the treatment of pathological conditions of lipid metabolism.

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