Lipid-lowering activity of plant polysaccharidesK.I. Rovkina, E.E. Buyko, V.V. Ivanov, O. A. Kaydash, A.M. Guryev, M.S. Yusubov, M.V. Belousov

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SUMMARY

A comparative study of the hypolipidemic effect of polysaccharide complexes of blood-red hawthorn leaves Crataegus sanguinea Pall was carried out on the model of hyperlipidemia caused by long-term feeding of Wistar rats with a high-fat diet rich in cholesterol. silver birch leaves and downy birch Betula pendula Roth., Betula pubescens Ehrh. and the aerial part of alfalfa sowing Medicago sativa L. The addition of birch polysaccharides (1.5%) to the atherogenic feed led to a decrease in the level of total cholesterol, mainly in the proatherogenic fraction of low density lipoproteins. The concentration of cholesterol in the antiatherogenic fraction of high density lipoproteins decreased to a lesser extent, while the atherogenic index decreased significantly. Hawthorn polysaccharides had a less pronounced lipid-lowering effect, and alfalfa polysaccharides did not improve the lipid spectrum of blood against the background of an atherogenic diet. Possible mechanisms of the hypolipidemic action of polysaccharides are discussed.

Key words: plant polysaccharides, hypolipidemic activity, high-fatdiet, cholesterol, simvastatin.

RESUME

The current study on the hypolipidemic action of the Crataegus sanguinea Pall., Betula pendula Roth., Betula pubescens Ehrh. and Medicago sativa L. polysaccharide complexes was conducted on the model of long-term high-fat cholesterol-rich diet-caused hyperlipidemia in Wistar rats. The birch polysaccharides (1.5%) addition to the atherogenic diet led to decrease the level of total cholesterol mainly in the proatherogenic fraction of low-density lipoproteins. The cholesterol concentration in the anti-atherogenic fraction of high-density lipoproteins decreased to a lesser extent, while the atherogenic index decreased significantly. Crataegus polysaccharides had a less pronounced lipid-lowering effect, and Medicago sativa polysaccharides did not improve the blood lipid spectrum on the background of a highfat cholesterol-rich diet.

Keywords: plant polysaccharides, lipid-lowering activity, high-fat diet, cholesterol, simvastatin.

INTRODUCTION

According to the World Health Organization, 17.5 million people die from cardiovascular diseases worldwide every year. The main damage to the health of the Russian population is caused by ischemic heart disease and cerebrovascular disease. Along with such risk factors as smoking, sedentary lifestyle, obesity, diabetes mellitus, metabolic syndrome, atherosclerosis is one of the main causes of cardiovascular diseases [1, 2]. Dyslipidemias causing atherosclerosis are diagnosed in 17% of the world's population, which suggests a dangerous non-infectious epidemic [3]. Currently, lipid-correcting drugs include HMG-CoA reductase inhibitors (statins), fibrates, nicotinic acid and its derivatives, ezetimibe (reducing cholesterol absorption), as well as agents with other mechanisms of action (sequestrants of bile acids, ω-3 polyunsaturated fatty acids, antioxidants) [3]. At the present stage of development of medicine, the main class of drugs for the correction of dyslipidemia are statins, which have a significant evidence base [4, 5]. Statins are highly effective, but not devoid of side effects (myotoxicity, hepatotoxicity, neurotoxicity, nephrotoxicity, hyperglycemia) [6–8]. Fibrates also have side effects - they cause gastrointestinal problems, disrupt the exchange of fat-soluble vitamins. They are contraindicated in case of insufficient kidney and liver function, cholelithiasis, pregnancy and lactation [9, 10]. The most significant side effect of niacin is the development of liver failure, and contraindications to its appointment are arterial hypotension, gout, type 2 diabetes mellitus [11, 12].

Thus, despite the wide arsenal of drugs used for the treatment of atherosclerosis and its complications, the problem of anti-atherosclerotic therapy has not yet been fully resolved, and the search for substances that can reduce the level of atherogenic lipids, as well as new possible molecular targets for their action, remains urgent. ...

Research into the development of drugs for the treatment of dyslipidemia is being pursued in a variety of ways. Promising sources of lipid-lowering agents are substances of plant origin, which are characterized by low toxicity and complex effect on the body [13]. The hypolipidemic and antiatherosclerotic effect of medicinal plants is determined by the content of biologically active substances in them: polysaccharides, flavonoids, phospholipids, steroid saponins, hormone-like substances and enzymes [14]. In the last decade, special attention has been paid to polysaccharides of plant origin, which have a wide spectrum of pharmacological activity and, in particular, have hypolipidemic, hypoglycemic, and antioxidant effects [15–18].

Thus, based on the literature data presented above, the aim of the study was to study the hypolipidemic activity of polysaccharides isolated from plants of the Siberian region.

MATERIALS AND METHODS

Object of study

The material for obtaining polysaccharides was blood-red hawthorn leaves Crataegus sanguinea Pall., Silver birch and downy birch leaves Betula pendula Roth., Betula pubescens Ehrh., Harvested in the Tomsk region, and the aerial part of sowing alfalfa Medicago sativa L., harvested in Krasnoyarsk ... Raw materials were procured in June 2016.

The isolation of polysaccharides was carried out by extraction with water acidified with hydrochloric acid to pH = 2–3 at a water bath temperature of 90 ° C for 2 hours. The resulting extract was separated from the meal and evaporated. The thickened aqueous residue was poured into ethyl alcohol 96% in a ratio of 1: 3 and left for 12 hours at 4 ° C. The polysaccharide precipitate was centrifuged and dissolved in purified water, followed by dialysis through a Thermo Scientific SnakeSkin semi-permeable membrane with a pore size of 3.5 kDa, frozen and dried using an IlShin BioBase MCFD8508 freeze dryer.

The content of uronic acids was determined spectrophotometrically using 3,5- method with dimethylphenol in the presence of concentrated sulfuric acid [19]. The analysis of the monosaccharide composition was carried out by gas chromatography of acylated polyols [20]. The weight average molecular weight (Mw) was determined by size exclusion chromatography on an Ultimate 3000 liquid chromatograph (Dionex, Germany). The mobile phase was a 0.1 mol / L NaCl solution, an Ultrahydrogel Column, 250, 6 μm, 7.8 mm X 300 mm.

The yield and monosaccharide composition of the obtained polysaccharides are presented in table. 1.

Table 1

Characteristics of polysaccharides (PS) of hawthorn, birch, alfalfa

	PS hawthorn	PS birch	PS alfalfa
Output, %	1.8 ± 0.2	3.4 ± 0.4	3.7 ± 0.3
Uronic acids,%	19.1 ± 0.6	55.9 ± 3.4	20.9 ± 0.9
Glucose,%	17.41 ± 0.92	-	12.19 ± 0.73
Galactose,%	38.88 ± 2.00	9.58 ± 0.52	9.96 ± 0.52
Xylose,%	2.05 ± 0.11	-	-
Arabinose,%	12.24 ± 0.75	1.44 ± 0.09	48.31 ± 3.86
Rhamnose,%	-	26.42 ± 2.25	-
M_w, kDa	413.7 ± 19.9	310.2 ± 15.1	366.8 ± 14.9

Experimental animals and experimental conditions

To study the hypolipidemic activity of new substances, a method for simulating hyperlipidemia with the help of prolonged (5–6 weeks) feeding of experimental animals with a high-fat diet rich in cholesterol is widely used [21].

The experiments were carried out on 48 female Wistar rats weighing 200–240 g of the first conventional category obtained from the Department of Experimental Biological Models of the V.I. E. D. Goldberg "(Tomsk). The animals were kept under standard conditions with free access to water and food (air temperature in the vivarium - 20 ± 2 ° C, humidity - no more than 80%). To simulate chronic hyperlipidemia in rats, a special food was prepared providing 45% of energy from animal fat (2.5% cholesterol; 0.5% cholic acid; 0.1% 2-thiouracil), as follows: 2.5 g cholesterol (Sigma-Aldrich, USA); 0.5 g of cholic acid (Sigma-Aldrich, USA) and 0.1 g of 2-thiouracil (Sigma-Aldrich, USA) were dissolved in 16 g of ghee (98% animal fat) and mixed with 81 g of a standard feed.

The experimental rats received an atherogenic diet for 28 days. On the 29th – 42nd day of the experiment, the rats of the corresponding groups received an atherogenic diet with the addition of birch, hawthorn, or alfalfa polysaccharides (1.5 g / 100 g of atherogenic food) to the feed, respectively. The reference drug simvastatin (Sigma-Aldrich, USA) was administered orally to the animals at a dose of 10 mg / kg. The rats of the control group received standard laboratory food for 42 days.

On the 15th day after the start of feeding the animals with a high-fat diet with the addition of polysaccharides or oral administration of simvastatin after fasting for 12 h, the rats were decapitated after CO_2- asphyxiation. In the blood serum, the level of total cholesterol, cholesterol in low-density lipoproteins (LDL-C) and high (HDL-C) density lipoproteins was determined. Based on the experimental data obtained, the atherogenic index (IA) was calculated using the formula according to [22]: IA = (total cholesterol - HDL-cholesterol) / HDL-cholesterol.

RESULTS

In the blood serum of animals that received an atherogenic diet for 6 weeks, the total cholesterol content increased by 5 times, mainly due to an increase in LDL-C. At the same time, the level of HDL cholesterol in the blood serum increased 2.6 times (Table 1). The presence of cholic acid (0.5%) in the food received led to a decrease in the metabolism of cholesterol to bile acids. In addition, cholic acid stimulates the emulsification of fat in the intestine, promotes the assimilation of exogenous fat, and affects the transcription of genes involved in the regulation of lipoprotein metabolism [23]. The atherogenic index calculated by the formula against the background of hyperlipidemia induced by an atherogenic diet was 3.06 ± 0.35, which significantly exceeded its value in animals receiving a standard diet (1.13 ± 0.15) (Fig. 1).

The comparison drug simvastatin reduced the serum cholesterol level elevated against the background of an atherogenic diet by 46.2%, which is mainly due to inhibition of HMG-CoA reductase, as well as the ability of statins to increase its excretion in faeces. Simvastatin significantly reduced (63.4%) the level of LDL-C, increased against the background of an atherogenic diet, and did not significantly change the level of HDL-C (Table 2).

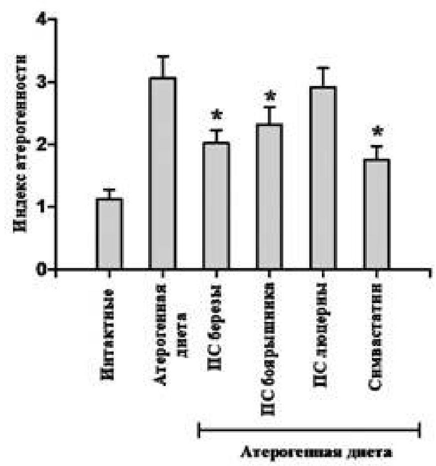
table 2

The effect of the course use of birch, hawthorn, alfalfa polysaccharides (14 days, 1.5 g / 100 g feed) and simvastatin (14 days, 10 mg / kg) for total cholesterol and cholesterol in lipoproteins of low (LDL) and high (HDL) density in the blood serum of rats with experimental chronic hyperlipidemia caused by an atherogenic diet

(X ± m, n = 8)

Experimental groups	General cholesterol, mmol / l	Cholesterol LDL, mmol / l	Cholesterol HDL, mmol / l
Standard laboratory diet	1.54 ± 0.07	0.25 ± 0.02	0.72 ± 0.07
Atherogenic diet	7.77 ± 0.38 *	1.23 ± 0.15 *	1.91 ± 0.28 *
atherogenic diet + birch polysaccharides	4.69 ± 0.49 *	0.60 ± 0.05 *	1.55 ± 0.24
Atherogenic diet + hawthorn polysaccharides	5.65 ± 0.55 *	0.89 ± 0.09 *	1.70 ± 0.21
Atherogenic Diet + Alfalfa Polysaccharides	6.84 ± 0.59	1.08 ± 0.11	1.75 ± 0.31
Atherogenic diet + simvastatin	4.18 ± 0.36 *	0.45 ± 0.05 *	1.52 ± 0.15

Note: * - p <0.05 for an atherogenic diet versus a standard diet, for polysaccharides and simvastatin versus an atherogenic diet; n - the number of animals in the group



Rice. 1. Influence of course use of polysaccharides (PS) of birch, hawthorn, alfalfa(14 days, 1.5 g / 100 g feed) and simvastatin (14 days, 10 mg / kg) on the atherogenic index in rats with experimental chronic hyperlipidemia caused by an atherogenic diet (X ± m, n = 8)

The addition of birch polysaccharides to the atherogenic feed led to a decrease in the level of total cholesterol by 39.6% (p <0.05) and, to a greater extent, in the pro-atherogenic fraction of low density lipoproteins (50.4%) (Table 2). The concentration of cholesterol in the antiatherogenic fraction of high density lipoproteins decreased to a lesser extent, while the atherogenic index significantly decreased and amounted to 2.02 ± 0.21 (Fig. 1). Hawthorn polysaccharides had a less pronounced lipid-lowering effect. When using them, the atherogenic index was 2.32 ± 0.28. Alfalfa polysaccharides did not have a hypolipidemic effect against the background of an atherogenic diet (Table 2; Fig. 1).

DISCUSSION

It was carried out comparative study hypolipidemic activity polysaccharides isolated from the leaves of the blood-red hawthorn Crataegus sanguinea Pall., the leaves of silver birch and downy birch Betula pendula Roth., Betula pubescens Ehrh. and the aerial part of alfalfa sowing Medicago sativa L. It was found that birch polysaccharides against the background of an atherogenic diet in rats, like simvastatin, reduce the level of total cholesterol in the blood serum, and, to a greater extent, of proatherogenic LDL-C. Hawthorn polysaccharides exhibited a less pronounced lipid-lowering effect, while alfalfa polysaccharides did not.

The ability of polysaccharide complexes and individual substances obtained from plants to have a hypolipidemic effect has been shown in a number of works.

In research in vivo hypolipidemic and hypotensiveactivity of polysaccharides in cactus fruits (Opuntia ficus indica Fruits) [24]. It was shown that the levels of total cholesterol and LDL-C were significantly reduced in groups of animals receiving the polysaccharide for 3 weeks. The polysaccharide complex isolated from Cyclocarya paliurus has a pronounced lipid-lowering activity in a mouse model with hyperlipidemia treated with a high-fat emulsion. The authors associate the main mechanism of the revealed activity with the high antioxidant potential of these compounds [17]. Polysaccharides extracted from the fruits of pumpkin (Cucurbita moschata) and consisting of galactose, glucose, arabinose, xylose and glucuronic acid exhibit various types of biological activity: detoxifying, antioxidant, hypotonic, and hypolipidemic [25]. Research results show that the addition of the pumpkin polysaccharide complex to a high-fat diet lowers the levels of triacylglycerols, LDL-C and increases the plasma levels of HDL-C in experimental rats. This increases the excretion of cholesterol and triacylglycerols with feces [25]. The ability of the black tea polysaccharide complex to maintain the lipid profile of the blood within the normal range, as well as to reduce excess body weight, was assessed [26, 27]. In a comprehensive study of the hypolipidemic properties of tea polysaccharides, their ability to effectively reduce the levels of total triacylglycerols and LDL-C and increase the concentration of HDL-C in blood plasma was established, which, together with a decrease in the concentration of total cholesterol in the liver of rats, indicates that

Potential mechanisms of the hypolipidemic action of polysaccharides are currently being discussed. It is assumed that pectin polysaccharides of various plants can inhibit the absorption of dietary cholesterol by increasing the viscosity of the intestinal contents and thickening the mucin layer on the intestinal surface or preventing the formation of micelles [29]. Indeed, the excretion of bile acids in the faeces increased in rats fed with crude tea polysaccharides [29]. The black tea polysaccharide complex exhibited the ability to bind cholesterol [28]. Considering that the synthesis of bile acids is regulated by a negative feedback mechanism, chelation of bile acids in the intestinal lumen reduces reabsorption and suppresses their enterohepatic circulation.de novo from cholesterol, which leads to a decrease in its concentration in the liver and, therefore, toa decrease in the level of LDL-C (Shi et al., 2016). Another possible mechanism of hypolipidemic action is shown for soy polysaccharides, which inhibit the key enzyme of lipid absorption, pancreatic lipase [31].

Along with the composition of polysaccharide complexes, the structure of polysaccharide chains is of great importance. Straight-chain polysaccharides have been shown to have a greater potential for selective adsorption of hydrophobic bile salts than resin-based sequestrants [30]. The main advantage of this class of compounds is a more pronounced ability for ionic and hydrophobic interactions [30].

CONCLUSION AND CONCLUSIONS

A comparative study of the hypolipidemic effect of polysaccharide complexes of the leaves of the blood-red hawthorn Crataegus sanguinea Pall was carried out. silver birch leaves and downy birch Betula pendula Roth., Betula pubescens Ehrh. and the aerial part of alfalfa cultivar Medicago sativa L. in a model of hyperlipidemia caused by prolonged feeding of Wistar rats with a high-fat diet rich in cholesterol. The addition of birch polysaccharides (1.5%) to atherogenic feed led to a decrease in the level of total cholesterol and, to a greater extent, in the pro-atherogenic fraction of low density lipoproteins. The concentration of cholesterol in the antiatherogenic fraction of high density lipoproteins decreased to a lesser extent, while the atherogenic index decreased significantly. Hawthorn polysaccharides had a less pronounced lipid-lowering effect.

To identify the mechanisms of the hypolipidemic action of polysaccharides isolated from the leaves of silver birch and downy birch Betula pendula Roth., Betula pubescens Ehrh., Further studies are required, including the study of their effect on the binding of bile acids and the expression of genes for the metabolism of bile acids and cholesterol.

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