UDC 615.31'857.4:577.115].015:616-092.9
DOI: 10.14739/2310-1210.2021.3.207465

Study on the influence of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkanic acid derivatives on the lipid metabolism in experiment

I. M. Bilai *[A,C,E,F], M. I. Romanenko [B,C], D. H. Ivanchenko [B,C]

Zaporizhzhia State Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words: xanthines, hyperlipidemia, lipoproteins.

Zaporozhye medical journal 2021; 23 (3), 412-417

***E-mail:** belay250455@gmail.com

Statin side effects are not a rare occurrence, in particular dyspeptic disorders, insomnia, headache, skin erythema, rash are often noted. All of this determines scientists to find new effective and low-toxic hypolipidemic agents. Various natural and synthetic xanthine derivatives have been recognized as therapeutically potential compounds and reported to control various diseases. Therefore, the study of new xanthine derivatives and their hypolipidemic effects, which would have a significant therapeutic effect with minimal side effects, is relevant.

The aim of the study was to examine the effect of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkanic acid derivatives on lipidogram parameters in experimental laboratory rats.

Materials and methods. The objects of the study were 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkanic acid derivatives. The experiments were performed in white laboratory Wistar rats weighing 180–220 g. Experimental modeling of hyperlipidemia – tween model: intraperitoneal administration of tween-80 at a dose of 200 mg/100 g body weight. The test compounds were administered orally, simultaneously with tween, at a dose of 1/10 of LD_{50} (previously calculated by Prozorovsky express method) for 6 days. The following indicators of lipidogram were determined: total cholesterol (TC), high-density lipoprotein cholesterol (HDL cholesterol), low-density lipoprotein cholesterol (LDL cholesterol), triglycerides (TG) and atherogenic index of plasma: TC – HDL cholesterol / HDL cholesterol. The experiments were carried out with respect to Bioethical rules and norms.

Results. The studies have shown data on the hypolipidemic activity of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkane acid derivatives. According to the conditional efficiency index Σ, which included the overall percentage of the following indicators – total cholesterol, low-density lipoprotein cholesterol and triglycerides, the leading compounds were 2439 (87.47 %), 6047 (82.30 %). The reference drug atorvastatin had a value of 82.98 %.

Conclusions. The major compound was 2439 identified among all compared to the control group. The prospect of further research is a more detailed study on the ability of xanthine derivatives to exhibit hypolipidemic effects and to influence oxidative stress in various hyperlipidemic models.

Ключові слова: ксантини, гіперліпідемія, ліпопротеїди.

Запорізький медичний журнал. 2021. Т. 23, № 3(126). С. 412-417

Дослідження впливу похідних 7-β-гідрокси-γ-арилоксипропілксантиніл-8-тіоалканових кислот на показники ліпідограми в експерименті

І. М. Білай, М. І. Романенко, Д. Г. Іванченко

Побічні ефекти статинів – нерідке явище, часто визначають диспепсичні розлади, безсоння, головний біль, еритему шкіри, висип. Це спонукає науковців до пошуку нових ефективних і малотоксичних гіполіпідемічних засобів. Різні природні та синтетичні похідні ксантину визнані терапевтично активними сполуками, описані як засоби для боротьби з різними захворюваннями. Тому актуальним є вивчення нових похідних ксантину та їхніх гіполіпідемічних ефектів, які б мали значущий терапевтичний ефект при мінімальній побічній дії.

Мета роботи – вивчення впливу похідних 7-β-гідрокси-γ-арилоксипропілксантиніл-8-тіоалканових кислот на показники ліпідограми в експерименті в лабораторних щурів.

Матеріали та методи. Об'єкти дослідження – похідні 7-β-гідрокси-γ-арилоксипропілксантиніл-8-тіоалканових кислот. Експерименти виконали на білих лабораторних щурах лінії Вістар масою 180–220 г. Експериментальне моделювання гіперліпідемії – твінова модель: внутрішньоочеревинне введення твін-80 у дозі 200 мг/100 г ваги. Досліджувані речовини вводили перорально одночасно з твіном протягом 6 днів у дозі 1/10 від LD_{50} (попередньо обрахована за експрес-методом Прозоровського).

Визначали показники ліпідограми: рівень загального холестерину (ЗХС), холестерин ліпопротеїдів високої щільності (ХС ЛПВЩ, α-ХС), холестерин ліпопротеїдів низької щільності (ХС ЛПНЩ), тригліцериди (ТГ), холестериновий індекс атерогенності (ХІА) за формулою: ХІА = ЗХС – ХС ЛПВЩ / ХС ЛПВЩ. Під час експерименту дотримувалися біоетичних правил і норм.

Результати. У результаті досліджень отримали дані щодо гіполіпідемічної активності похідних 7-β-гідрокси-γ-арилоксипропілксантиніл-8-тіоалканових кислот. За даними експерименту, за показником умовного індексу ефективності Σ, який включав суму відсотків таких показників, як загальний холестерин, холестерин ліпопротеїдів низької щільності та тригліцериди, сполуками-лідерами визначено речовини 2439 (87,47 %), 6047 (82,30 %). Препарат-порівняння аторвастатин мав значення 82,98 %.

Висновки. Сполука-лідер порівняно з контрольною групою – речовина 2439. Перспективи подальших досліджень передбачають детальніше вивчення похідних ксантину щодо наявності гіполіпідемічної дії та здатності впливати на показники оксидативного стресу на різних моделях гіперліпідемії.

Исследование влияния производных 7-β-гидрокси-γ-арилоксипропилксантинил-8-тиоалкановых кислот на показатели липидограммы в эксперименте

Ключевые слова: ксантины, гиперлипидемия, липопротеиды.

Запорожский медицинский журнал. 2021. Т. 23, № 3(126). С. 412-417

И. М. Белай, Н. И. Романенко, Д. Г. Иванченко

Побочные эффекты статинов – нередкое явление, часто отмечают диспепсические расстройства, бессонницу, головную боль, эритему кожи, сыпь. Это мотивирует ученых к поиску новых эффективных и малотоксичных гиполипидемических средств. Различные природные и синтетические производные ксантина признаны терапевтически сильнодействующими соединениями, описаны как средства для борьбы с различными заболеваниями. Поэтому изучение новых производных ксантина и их гиполипидемических эффектов, которые имели бы значительный терапевтический эффект при минимальном побочном действии, является актуальным.

Цель работы – изучение влияния производных 7-β-гидрокси-γ-арилоксипропилксантинил-8-тиоалкановых кислот на показатели липидограммы в эксперименте на лабораторных крысах.

Материалы и методы. Объекты исследования – производные 7-β-гидрокси-γ-арилоксипропилксантинил-8-тиоалкановых кислот. Эксперименты проведены на белых лабораторных крысах линии Вистар массой 180–220 г. Экспериментальное моделирование гиперлипидемии – твиновая модель: внутрибрюшинное введение твин-80 в дозе 200 мг/100 г веса. Исследуемые вещества вводили внутрь одновременно с твином в течение 6 дней в дозе 1/10 от LD_{50} (предварительно рассчитана по экспресс-методу Прозоровского). Определяли показатели липидограммы: уровень общего холестерина (ОХС), холестерина липопротеидов высокой плотности (ХС ЛПВП, α-ХС), холестерин липопротеидов низкой плотности (ХС ЛПНП), триглицериды (ТГ) и холестериновый индекс атерогенности (ХИА) по формуле: ХИА = ОХС – ХС ЛПВП / ХС ЛПВП. В ходе эксперимента придерживались биоэтических правил и норм.

Результаты. В результате исследований получены данные о гиполипидемической активности производных 7-β-гидрокси-γ-арилоксипропилксантинил-8 тиоалкановых кислот. По данным эксперимента, по показателю условного индекса эффективности Σ, который включал сумму процентов таких показателей, как общий холестерин, холестерин липопротеидов низкой плотности и триглицериды, соединениями-лидерами определены вещества 2439 (87,47 %), 6047 (82,30 %). Препарат-сравнения аторвастатин имел значение 82,98 %.

Выводы. Преобладающее по сравнению с контрольной группой соединение – вещество 2439. Перспективы дальнейших исследований предусматривают более глубокое изучение производных ксантина относительно способности проявлять гиполипидемическое действие и влиять на показатели оксидативного стресса на разных моделях гиперлипидемии.

According to the World Health Organization Expert Committee, atherosclerosis is a variable combination of changes in the intima of arterial vessels that includes the accumulation of lipids, lipoproteins, complex carbohydrates, fibrous tissue, blood components, calcifications and concomitant changes in the vascular tunica media. The vessels of elastic and muscular-elastic type are damaged mostly (aorta, brain vessels, coronary arteries) and less often – vessels of the lower extremities. The term "atherosclerosis» was firstly formulated in 1904 by Felix Jacob Marshand [1].

Nowadays, according to the 2019 recommendations of the European Atherosclerosis Association, the following groups of medicines are used to treat dyslipidemia: inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase (statins), inhibitors of intestinal cholesterol absorption (ezetimib), bile acid sequestrants (cholestyramine, colestipol), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (alirocumab, evolocumab) [2], selective inhibitors of microsomal triglyceride-transferring protein (lomitapide), ω-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) (icosapentyl ethyl), nicotinic acid and cholesterol-ester protein inhibitors (dalcetrapib) [1,3].

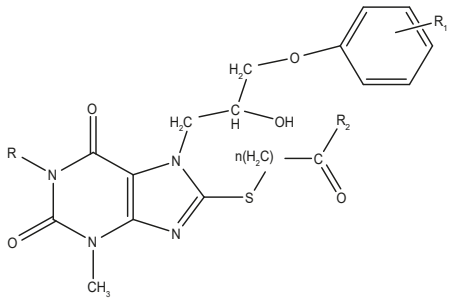
The most effective and popular hypolipidemic medicines from the 90s to the present time are statins. During this time, the great number of clinical studies were conducted to investigate statins. The main ones are: ALLHAT, PROSPER, WOSCOPS, PROVE-IT, CARE – to study pravastatin, HPS, IDEAL, A to Z, 4S – simvastatin, ASCOT LLA, CARDS – atorvastatin, AF-CAPS – lovastatin, LIPS – fluvastatin, CORONA, JUPITER – rosuvastatin. IMPROVE-IT, FOURIER and ODYSSEY studies have formed the database to enhance low-density lipoprotein (LDL) cholesterol lowering therapy in addition to statins [1,4].

Statins are usually used for a long time and are relatively well tolerated. However, the side effects of statins are not rare, in particular, dyspeptic disorders, insomnia, headache, erythema of the skin, rash. Dose-dependent side effects – hepatotoxicity (with or without elevated transaminases) – can be caused by the all types of statins. The most severe side effect of all statins is myopathy, which is manifested by the development of skeletal muscle myodystrophies and others. All of that has led scientists to discover new effective and low-toxic lipid-lowering medicines [5–7].

A promising direction in this regard is the search for effective and low-toxic hypolipidemic medicines, in particular, on the basis of xanthine derivatives. Among the alkaloids, xanthine and its derivatives occupy one of the leading positions in the field of medical care. These compounds are natural heterocyclic alkaloids based on purine, which were firstly discovered in 1817 by German chemist Emil Fischer, and later in 1899, the designation «xanthine» was introduced. The structural similarity to two important purine derivatives, adenine and guanine, makes xanthine an interesting therapeutic molecule. Xanthines are known for their diverse biological role, including inhibition of various cellular signaling enzymes and exhibition of polysystemic pharmacological activity, such as antidepressant, antibacterial, metabolic drugs, etc. Natural xanthine derivatives such as caffeine, theophylline and theobromine, are nitrogenous compounds based on purine, which have broad medicinal properties [8].

Various natural and synthetic xanthine derivatives have been recognized as therapeutically potent compounds and have been described to fight various diseases. As for the potential health benefits, interest in these compounds is constantly growing from the sides of scientists, medical

Table 1. Structural formula of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkane acid derivatives



№	Compound code	R	R_1	n	R_2
1	2439	H	CH_3-o	1	NH_2
2	2486	H	CH_3-o	1	OH
3	2487	H	CH_3-o	2	OH
4	5705	CH_3	OCH_3-п	1	OH
5	6042	H	CH_3-п	1	OH
6	6043	H	CH_3-м	1	OH
7	6047	CH_3	CH_3-o	1	OH
8	6049	CH_3	CH_3-м	1	OH
9	6286	CH_3	CH_3-п	1	OH
10	8402	H	$C(CH_3)_3$-п	1	OH
11	8403	CH_3	$C(CH_3)_3$-п	1	OH

professionals and consumers. Therefore, the study on new xanthine derivatives and their hypolipidemic effects, which would have a significant therapeutic effect with minimal side effects, is relevant [9].

Aim

The aim of the study was to investigate the effects of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkane acid derivatives on the lipid profile in laboratory rats experimentally.

Materials and methods

The objects of the study were 11 derivatives of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkane acids (*Table 1*), synthesized at the Department of Biological Chemistry of Zaporizhzhia State Medical University headed by Professor M. I. Romanenko, which are promising in search for hypolipidemic medicines. A number of modern physicochemical methods of analysis confirmed the structure of the compounds: IR-, PMR-spectroscopy, mass-spectrometry. The experiments were performed in 112 white laboratory Wistar rats aged between 6-8 months, weighing 180–220 g. The rats were divided into groups: group 1 (normal) – intact animals; group 2 (control) – animals with experimental hiperlipidemia (without treatment); groups 3–13 – animals with hiperlipidemia and tested compounds; group 14 – comparison drug – atorvastatin. Each group consisted of 8 animals. The rats were obtained from the animal farm of the State Institution "Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine". The animals were kept on the standard diet in natural light regime "day and night".

The tween model as an experimental hyperlipidemia was used: intraperitoneal administration of the tween-80 in a dose of 200 mg/100 g body weight. Tested compounds were administered orally, simultaneously with tween, for 6 days. 12 hours after the last administration of tween-80 or tested compounds, the animals underwent laparotomy under ether narcosis, blood was taken from glomerular artery, centrifuged to obtain a serum. This model is advantageous since leads to a rapid (8–10 hours) increase in blood lipids (especially triglycerides) and a decrease in HDL cholesterol. The tested compounds were administered at the dose of 1/10 of the LD_{50} (previously calculated by the express method of Prozorovsky) [10]. The comparison option was the medicine from the group of statins – atorvastatin ("Atorvastatin" (Ananta Medicare (India)) at the dose of 20 mg/kg body weight.

The level of total cholesterol (TC) was determined by colorimetric, enzymatic methods, diagnostic kits Cormay (Poland) (mmol/l), HDL cholesterol (α-cholesterol) – by colorimetric and precipitating methods, HDL cholesterol – precipitating reagent 1 × 50 ml, (Cormay, Poland) (mmol/l), LDL cholesterol – colorimetric and precipitating methods, LDL cholesterol – precipitating reagent 1 × 20 ml (Cormay, Poland) (mmol/l), TG – colorimetric, enzymatic methods, diagnostic kits 150 ml (Cormay, Poland) (mmol/l) and cholesterol atherogenic index (CAI) (conventional units) × according to the formula:

$$CAI = TC - HDL\ cholesterol / HDL\ cholesterol.$$

Laboratory tests were carried out on the semi-automatic biochemical analyzer "Screen point" (Italy).

For the integral assessment of the derivative hypolipidemic action, the conditional efficacy index Σ (EI) was used representing the generalized value of lipid metabolism (sum of reductions in percentages of TC, LDL cholesterol, TG: EI = TC (%) + LDL cholesterol (%) + TG (%) [11].

During the experiment, the rules and regulations were followed according to the Protocol no. 5 (April 17, 2019) of the Commission on Bioethics Session of ZSMU.

The results of the study were processed on a personal computer using the statistical package of the licensed program Statistica, version 13 (Copyright 1984-2018 TIBCO Software Inc. All rights reserved. License No. JPZ8041382130ARCN10-J). The normality of the quantitative variables distribution was analyzed using the Shapiro–Wilk test. Descriptive statistics was provided in the form of a median with interquartile range – Me [Q_{25}; Q_{75}], because the parameters had the distribution different from the normal. The Mann–Whitney test was used to find differences between the groups. A level of $P < 0.05$ was considered statistically significant.

Results

The studies have demonstrated the data on the hypolipidemic activity of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkane acid derivatives (*Tables 2, 3*).

The highest hypolipidemic activity (TC) relative to the control group was shown by compounds 6043 (27.5 %), 6047 (27.1 %) and 2439 (25.3 %). The value of comparison drug atorvastatin, relative to the control group, was 23.6 %. The most effective derivatives to increase the HDL-cholesterol levels were: 8402 (67.1 %), 6286 (54.4 %), 6042 (50.6 %), compounds with moderate

Table 2. The value of lipid parameters in experimental rats, Me [Q_{25}; Q_{75}]

№	Compound code	TC, mmol/l	HDL-cholesterol, mmol/l	LDL-cholesterol, mmol/l	TG, mmol/l	CAI, c. u.
1	Intact group	2.15 (1.80; 2.70)*	1.29 (1.10; 1.60)*	0.69 (0.46; 0.95)*	1.05 (0.70; 1.50)	0.72 (0.27; 1.45)*
2	Control group	2.83 (2.30; 3.40)	0.99 (0.80; 1.20)	1.20 (0.93; 1.41)	1.30 (1.00; 1.70)	1.87 (1.41; 2.38)
3	2439	2.11 (1.80; 2.70)*	1.28 (0.90; 1.80)*	0.79 (0.61; 1.12)*	0.94 (0.60; 1.40)*	0.69 (0.35; 1.11)*
4	2486	2.18 (2.00; 2.30)*	1.31 (0.70; 1.50)	0.87 (0.56; 1.38)*	0.95 (0.40; 1.40)*	0.74 (0.40; 1.86)*
5	2487	3.10 (2.40; 3.70)	1.75 (1.30; 2.50)*	1.10 (0.86; 1.74)	1.25 (0.70; 1.80)	0.87 (0.14; 1.61)*
6	5705	2.73 (2.00; 3.30)	1.08 (0.50; 1.50)	1.08 (0.74; 1.34)	1.53 (0.80; 1.90)	1.72 (0.93; 3.00)
7	6042	3.00 (2.70; 3.30)	1.49 (0.70; 2.40)*	1.42 (0.66; 2.22)	1.24 (0.60; 1.70)	1.24 (0.25; 3.28)*
8	6043	2.05 (1.80; 2.30)*	1.30 (0.70; 1.70)*	0.69 (0.33; 1.00)*	1.31 (0.70; 1.70)	0.66 (0.28; 1.71)*
9	6047	2.06 (1.70; 2.50)*	1.21 (0.70; 1.90)	0.84 (0.57; 1.13)*	0.98 (0.60; 1.50)*	0.80 (0.31; 1.86) *
10	6049	2.14 (1.80; 2.40)*	1.38 (1.10; 1.60)*	1.17 (0.73; 1.67)	1.65 (1.30; 2.00)*	0.57 (0.19; 0.90)*
11	6286	2.94 (2.00; 3.50)	1.53 (0.90; 2.10)*	0.77 (0.57; 0.90)*	1.05 (0.80; 1.50)*	1.03 (0.11; 2.11)*
12	8402	2.17 (1.80; 2.60)*	1.65 (1.20; 2.20)*	0.66 (0.40; 0.90)*	1.45 (0.80; 1.80)	0.33 (0.19; 0.53)*
13	8403	2.23 (1.90; 3.00)*	0.75 (0.60; 1.00)*	0.90 (0.78; 1.45)*	1.49 (1.01; 1.90)	2.02 (1.33; 3.29)
14	Atorvastatin	2.16 (1.70; 2.80)*	1.15 (0.90; 1.50)*	0.64 (0.30; 0.92)*	1.14 (0.60; 1.50)	0.93 (0.53; 1.54)*

*: veraciously according to the control group.

Table 3. The value of lipid parameters in experimental rats, according to the control group (%)

№	Compound code	TC, mmol/l	HDL-cholesterol, mmol/l	LDL-cholesterol, mmol/l	TG, mmol/l	CAI, c. u.	EI Σ, %
1	Intact group	-28.27 %	30.38 %	-42.47 %	-19.23 %	-61.35 %	-89.97
3	2439	-25.32 %	30.38 %	-34.27 %	-27.88 %	-63.22 %	-87.47
4	2486	-23.11 %	32.91 %	-28.14 %	-26.92 %	-60.35 %	-78.17
5	2487	9.60 %	77.22 %	-8.41 %	-4.40 %	-53.39 %	-3.21
6	5705	-3.66 %	8.86 %	-10.59 %	17.31 %	-7.70 %	3.05
7	6042	6.06 %	50.63 %	17.96 %	-4.81 %	-33.38 %	19.22
8	6043	-27.53 %	31.65 %	-42.47 %	0.96 %	-64.41 %	-69.04
9	6047	-27.08 %	22.78 %	-30.22 %	-25.00 %	-56.65 %	-82.30
10	6049	-24.43 %	39.24 %	-2.80 %	26.92 %	-69.33 %	-0.31
11	6286	3.85 %	54.43 %	-36.34 %	-19.23 %	-44.94 %	-51.72
12	8402	-23.55 %	67.09 %	-44.96 %	11.54 %	-82.09 %	-56.97
13	8403	-21.34 %	-24.05 %	-24.82 %	14.42 %	8.83 %	-31.73
14	Atorvastatin	-23.55 %	16.46 %	-46.94 %	-12.50 %	-50.29 %	-82.98

activity – 2486 (33.0 %) and 2439 (30.4 %), relative to the control group.

The best results in the lowering of LDL-cholesterol relative to the control group were shown by derivatives: 8402 (45.0 %), 6043 (42.5 %), 6286 (36.3 %) and 2439 (34.3 %). Compounds 6047 (30.2 %) and 2486 (28.1 %) exhibited moderate activity in respect of this value.

The most effective hypotriglyceridemic activity was shown by compounds 2439 (27.9 %), 2486 (26.9 %), 6047 (25.0 %). Derivative 6286 was characterized by moderate activity (19.2 %) relative to the control group.

When assessing the CAI, the most active compounds, compared to the control group, were 8402 (82.1 %), 6049 (69.3 %), 6043 (64.4 %), 2439 (63.2 %), 2486 (60.4 %), 2487 (53.4 %). Compounds 6047 (56.7 %) and 6286 (45.0 %) showed moderate activity, compound 6042 (33.4 %) had a slight effect.

By the generalized value of lipid metabolism indicator – EI Σ, the best hypolipidemic effect, relative to the control group, had compounds 2439 (87.5 %), 6047 (82.3 %). Compounds 2486, 6043, 8402 and 6286 were characterized by moderate effect 78,2 %, 69,0 %, 57.0 % and 51.7 %, respectively. Compound 8403 had a slight effect (31.7 %). The comparison drug atorvastatin had a value of 83.0 %.

Analyzing the dependence of lipid profile on the structure of the tested derivatives, we were able to draw some preliminary conclusions. O-methyl-substituted derivatives of 3-methylxanthine (compounds 2439, 2486) and theophylline (compound 6047) showed the highest activity. Moreover, the amide (compound 2439) was more active than acids (derivatives 2486 and 6047). Elongation of the carbon chain in the thioalkanoic acid residue at position 8 of the xanthine molecule practically led to loss of hypocholesterolemic and hypolipidemic effect (compound 2487). Similar effects occurred when the methyl was replaced by the methoxy group (compounds 5705 and 6042). The significant decrease in hypolipidemic activity was observed in a large aromatic substitution (compounds 8402, 8403). For the more detailed analysis of the dependence in the series "structure-action", it is necessary to expand significantly the chemical library of the tested compounds.

Discussion

In recent years, heterocyclic compounds, including xanthine derivatives, have received considerable attention due to their importance in pharmacological research. In particular, the data obtained by us are confirmed by the research results of D. H. Ivanchenko and N. Singh: the use of 3,7-dimethylxanthine (theobromine) is associated with a reduced risk of cardiovascular disease. The main rationale for this is that theobromine has a beneficial effect on fasting serum lipids. It can be associated with inhibition of

phosphodiesterases, which, by destroying cellular cyclic adenosine monophosphate (cAMP), increase the activity of ABCA1 (a gene encoding the protein that regulates cellular cholesterol and phospholipid homeostasis), which plays a role in a removal of cholesterol from macrophage foam cells to apolipoprotein A-I (the main apolipoprotein of HDL-cholesterol). Therefore, theobromine can increase HDL-cholesterol levels and have a cardioprotective effect [12–15].

Another generalized study that significantly confirms our results was that the compound KMUP-1 (7-[2-[4-(2-chlorophenyl)piperazinyl]ethyl]-1,3-dimethylxanthine), by inhibiting phosphodiesterase, modulates G-protein-coupled receptors (GPCR) to reduce hyperlipidemia and lose weight. KMUP-1 reduced the accumulation of triglycerides, indicating inhibition of adipogenesis in cells, and the expression of mitogen-activated protein kinase (MAPK) and immunoreactivity at the stage of adipogenesis. Appropriate biochemical reactions contributed to the inhibition of adipocyte differentiation. These data suggest that KMUP-1 may inhibit hyperadiposis in adipocytes [16].

In addition, literature data confirms that KMUP-1 can cause the decrease in liver fat. However, the mechanisms of KMUP-1 action in obesity-induced steatohepatitis remain unclear. Prolonged administration of KMUP-1 to mice on a high-fat diet reduced body weight, triglyceride and glucose levels, which is completely correlated with our data. Furthermore, KMUP-1 reduced the amount of MMP-9 (matrix metalloproteinase 9 – extracellular zinc-dependent endopeptidase capable of destroying extracellular matrix protein) and reactive oxygen species (ROS), and increased the content of anti-inflammatory cytokine IL-10 in the liver of mice on the high-fat diet. Thus, it was shown that KMUP-1 reduces the accumulation of lipids in liver tissue, which is the promising aspect in the fatty liver disease treatment [17–19].

What is more, according to X. Zhu, it was shown that incubation of preadipocytes with a solution containing xanthines significantly reduced the incorporation of triglycerides during adipogenesis without affecting cell viability. Finally, the active study of xanthine derivatives with hypolipidemic activity continues [16].

Conclusions

1. The studies provided the data on the hypolipidemic activity of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkane acid derivatives. The highest hypolipidemic activity (TC) relative to the control group was shown by compounds 6043 (27.5 %), 6047 (27.1 %) and 2439 (25.3 %). The most effective derivatives to increase the HDL-cholesterol levels were: 8402 (67.1 %), 6286 (54.4 %), 6042 (50.6 %).

2. The best results in LDL-cholesterol lowering relative to the control group were shown by derivatives: 8402 (45.0 %), 6043 (42.5 %), 6286 (36.3 %) and 2439 (34.3 %). The most effective hypotriglyceridemic activity was shown by the compounds 2439 (27.9 %), 2486 (26.9 %), 6047 (25.0 %).

3. When assessing the CAI, the most active compounds, relative to the control group, were 8402 (82.1 %), 6049 (69.3 %), 6043 (64.4 %), 2439 (63.2 %), 2486 (60.4 %), 2487 (53.4 %). By the generalized value of lipid metabolism indicators – EI Σ, the best hypolipidemic effect, relative to the control group, had compounds 2439 (87.5 %), 6047 (82.3 %).

4. The results of experimental studies clearly indicate the feasibility and prospects for further search on original lipid-lowering drugs among xanthine derivatives.

The prospect for further research is the study of 7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioalkane acid derivatives on the ability to enhance a hypolipidemic effect and to influence the values of oxidative stress in various models of hyperlipidemia.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 19.02.2021
Після доопрацювання / Revised: 17.03.2021
Прийнято до друку / Accepted: 19.03.2021

Information about authors:
Bilai I. M., MD, PhD, DSc, Professor, Head of the Department of Clinical Pharmacy, Pharmacotherapy, Pharmacognosy and Pharmaceutical Chemistry, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0002-7574-4093
Romanenko M. I., PhD, DSc, Professor of the Department of Biological Chemistry, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0003-4213-7841
Ivanchenko D. H., PhD, DSc, Associate Professor of the Department of Biological Chemistry, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0001-9858-2659

Відомості про авторів:
Білай І. М., д-р мед. наук, професор, зав. каф. клінічної фармації, фармакотерапії, фармакогнозії та фармацевтичної хімії, Запорізький державний медичний університет, Україна.
Романенко М. І., д-р фарм. наук, професор каф. біологічної хімії, Запорізький державний медичний університет, Україна.
Іванченко Д. Г., д-р фарм. наук, доцент каф. біологічної хімії, Запорізький державний медичний університет, Україна.

Сведения об авторах:
Белай И. М., д-р мед. наук, профессор, зав. каф. клинической фармации, фармакотерапии, фармакогнозии и фармацевтической химии, Запорожский государственный медицинский университет, Украина.
Романенко Н. И., д-р фарм. наук, профессор каф. биологической химии, Запорожский государственный медицинский университет, Украина.
Иванченко Д. Г., д-р фарм. наук, доцент каф. биологической химии, Запорожский государственный медицинский университет, Украина.

References

[1] Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., Chapman, M. J., De Backer, G. G., Delgado, V., Ference, B. A., Graham, I. M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T. R., Riccardi, G., Richter, D. J., Sabatine, M. S., Taskinen, M. R., Tokgozoglu, L., … ESC Scientific Document Group. (2020). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European Heart Journal, 41*(1), 111-188. https://doi.org/10.1093/eurheartj/ehz455

[2] Steffens, D., Bramlage, P., Scheeff, C., Kasner, M., Hassanein, A., Friebel, J., & Rauch-Kröhnert, U. (2020). PCSK9 inhibitors and cardiovascular outcomes. *Expert Opinion on Biological Therapy, 20*(1), 35-47. https://doi.org/10.1080/14712598.2020.1677604

[3] Baum, S. J., Toth, P. P., Underberg, J. A., Jellinger, P., Ross, J., & Wilemon, K. (2017). PCSK9 inhibitor access barriers-issues and recommendations: Improving the access process for patients, clinicians and payers. *Clinical Cardiology, 40*(4), 243-254. https://doi.org/10.1002/clc.22713

[4] Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. *Pharmacy, 6*(1), Article 10. https://doi.org/10.3390/pharmacy6010010

[5] Brozin, D., & Raal, F. J. (2018). Novel approaches to lipid-lowering therapy. *South African Medical Journal, 108*(4), 262-265. https://doi.org/10.7196/SAMJ.2018.v108i4.13234

[6] Mach, F., Ray, K. K., Wiklund, O., Corsini, A., Catapano, A. L., Bruckert, E., De Backer, G., Hegele, R. A., Hovingh, G. K., Jacobson, T. A., Krauss, R. M., Laufs, U., Leiter, L. A., März, W., Nordestgaard, B. G., Raal, F. J., Roden, M., Santos, R. D., Stein, E. A., Stroes, E. S., … European Atherosclerosis Society Consensus Panel. (2018). Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *European Heart Journal, 39*(27), 2526-2539. https://doi.org/10.1093/eurheartj/ehy182

[7] Toth, P. P., Patti, A. M., Giglio, R. V., Nikolic, D., Castellino, G., Rizzo, M., & Banach, M. (2018). Management of Statin Intolerance in 2018: Still More Questions Than Answers. *American Journal of Cardiovascular Drugs, 18*(3), 157-173. https://doi.org/10.1007/s40256-017-0259-7

[8] Basu, S., Barawkar, D. A., Ramdas, V., Waman, Y., Patel, M., Panmand, A., Kumar, S., Thorat, S., Bonagiri, R., Jadhav, D., Mukhopadhyay, P., Prasad, V., Reddy, B. S., Goswami, A., Chaturvedi, S., Menon, S., Quraishi, A., Ghosh, I., Dusange, S., Paliwal, S., … Mookhtiar, K. A. (2017). A2B adenosine receptor antagonists: Design, synthesis and biological evaluation of novel xanthine derivatives. *European Journal of Medicinal Chemistry, 127*, 986-996. https://doi.org/10.1016/j.ejmech.2016.11.007

[9] Mikhalchenko, E. K., Aleksandrova, K. V., Levich, S. V., & Sinchenko, D. M. (2017). Synthesis and physical-chemical properties of 3-benzyl8-propylxanthinyl-7-acetic acid and its derivatives. *Current issues in pharmacy and medicine: science and practice, 10*(1), 14-19. https://doi.org/10.14739/2409-2932.2017.1.93430

[10] Mironov, A. N. (Ed.). (2012). *Rukovodstvo po provedeniyu doklinicheskikh issledovanii lekarstvennykh sredstv. Chast' pervaya [Guidance on non-clinical studies of pharmaceuticals. Part one]*. Grif i K. [in Russian].

[11] Ostapenko, A. A. (2012). *Hipolipidemichna aktyvnist novykh pokhidnykh 7-β-hidroksy-γ-(mono- ta dykhlorfenoksy)propilksantyniv pry eksperymentalnii hiperlipidemii*. (Avtoref. dis. … kand. farm. nauk). [Hypolipidemic activity of some derivatives of 7-β-hydroxy-γ-(mono- and dichlorophenoxy)propylxanthines in the experimental hyperlipidemy]. (Extended abstract of candidate's thesis). Kharkiv. [in Ukrainian].

[12] European Parliament, & European Council. (2010, October 20). Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes Text with EEA relevance. *Official Journal of the European Union, L 276*, 33-79. http://data.europa.eu/eli/dir/2010/63/oj

[13] Ivanchenko, D. G., Romanenko, N. I., & Kornienko, V. I. (2018). Synthesis and Antioxidant Activity of 8-bromo-7-(2-hydroxy-3-aryloxyprop-1-yl) theophyllines. *Chemistry of Natural Compounds, 54*(3), 532-534. https://doi.org/10.1007/s10600-018-2397-9

[14] Singh, N., Shreshtha, A. K., Thakur, M. S., & Patra, S. (2018). Xanthine scaffold: scope and potential in drug development. *Heliyon, 4*(10), Article e00829. https://doi.org/10.1016/j.heliyon.2018.e00829

[15] Cook, N. R., Mora, S., & Ridker, P. M. (2018). Lipoprotein(a) and Cardiovascular Risk Prediction Among Women. *Journal of the American College of Cardiology, 72*(3), 287-296. https://doi.org/10.1016/j.jacc.2018.04.060

[16] Zhu, X., Yang, L., Xu, F., Lin, L., & Zheng, G. (2017). Combination therapy with catechins and caffeine inhibits fat accumulation in 3T3-L1 cells. *Experimental and Therapeutic Medicine, 13*(2), 688-694. https://doi.org/10.3892/etm.2016.3975

[17] Wu, B. N., Kuo, K. K., Chen, Y. H., Chang, C. T., Huang, H. T., Chai, C. Y., Dai, Z. K., & Chen, I. J. (2016). Theophylline-Based KMUP-1 Improves Steatohepatitis via MMP-9/IL-10 and Lipolysis via HSL/p-HSL in Obese Mice. *International Journal of Molecular Sciences, 17*(8), Article 1345. https://doi.org/10.3390/ijms17081345

[18] El-Kalyoubi, S. A., Fayed, E. A., & Abdel-Razek, A. S. (2017). One pot synthesis, antimicrobial and antioxidant activities of fused uracils: pyrimidodiazepines, lumazines, triazolouracil and xanthines. *Chemistry Central Journal, 11*(1), Article 66. https://doi.org/10.1186/s13065-017-0294-0

[19] Liu, L., Nagai, I., Gao, Y., Matsushima, Y., Kawai, Y., & Sayama, K. (2017). Effects of catechins and caffeine on the development of atherosclerosis in mice. *Bioscience, Biotechnology, and Biochemistry, 81*(10), 1948-1955. https://doi.org/10.1080/09168451.2017.1364618