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Research article

Effects of yacon on carbohydrates and lipid metabolism, oxidative-nitrative stress markers changes in rats with experimental metabolic syndrome

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ABSTRACT

Background and aim: Smallanthus sonchifolius (Poepp. and Hendl.) H. Robinson, commonly known as yacon, is a medicinal species recognized for its therapeutic properties. The hypoglycemic and hypolipidemic effects of yacon root tubers have been well-documented across various models of metabolic syndrome. However, research on the effects of biologically active compounds derived from yacon leaves remains limited. The aim of the study was to evaluate the hypoglycemic, hypolipidemic and antioxidant effects of an aqueous extract of yacon leaves under the fructose-induced experimental metabolic syndrome.

Experimental procedure: In the study were used male Wistar white rats, in which metabolic syndrome was induced by consuming a 10 % fructose solution. Animals were given an aqueous extract of yacon leaves at a dose of 500 mg per kilogram of body weight for seven and fourteen days following the establishment of metabolic syndrome. Hypoglycemic (glucose and glycosylate hemoglobin concentrations) and hypolipidemic (plasma cholesterol, triglycerides, low-density lipoproteins and high-density lipoproteins levels) effects and antioxidant activity (activity of superoxide dismutase, catalase, glutathione peroxidase, NO-synthase, the content of nitrite anion (NO_2^-) and nitrate anion (NO_3^-), content of carbonyl groups and thiobarbituric acid reactive substances) of extract were then evaluated.

Results: The 14 days use of aqueous extract of yacon for the treatment of fructose-induced metabolic syndrome leads to a decrease of animals' body weight (59.94 %), glucose concentration (10.33 %), glycosylated hemoglobin content (61.58 %), blood plasma triglycerides (50.35 %), cholesterol (24.46 %), low-density lipoproteins (21.56 %), as well as to increase in high-density lipoproteins concentration (29.29 %), paraoxonase activity (56.03 %). In animals with experimental MetS yacon cause oxidative-nitrative stress indicators normalization: increase in SOD (47.85 %) and GPO activity (16.55 %); decrease in TBARS content (23.77 %) and proteins oxidative modification products of neutral character (52.56 %); decrease in NOS activity (12.30 %), which was accompanied by a decrease in nitrate content (10.44 %).

Abbreviations: CAT, catalase; GPO, glutathione peroxidase; HbA1c, glycated hemoglobin; HDL, high-density lipoproteins; LDL, low-density lipoproteins; MetS, metabolic syndrome; NOS, NO-synthase; PON, paraoxonase; SOD, superoxide dismutase; TBARS, hiobarbituric acid reactive substances.

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Conclusions: The aqueous extract of yacon demonstrates significant hypoglycemic and hypolipidemic effects in a fructose-induced model of experimental metabolic syndrome, contributing to the normalization of both prooxidant and antioxidant states in rat erythrocytes.

1. Introduction

Metabolic syndrome (MetS) is recognized as a complex risk factor for cardiovascular disease, characterized by elevated plasma glucose and triglyceride levels, decreased high-density lipoprotein cholesterol, increased blood pressure, and the development of hypertension, obesity, and insulin resistance [1,2]. Furthermore, MetS is classified as a chronic inflammatory condition that activates prothrombotic mediators and inflammatory cytokines, leading to elevated leptin levels and decreased adiponectin levels. These changes contribute to reduced antioxidant enzyme activity and increased lipid peroxidation [3], ultimately resulting in endothelial dysfunction. Clinical evidence supports the involvement of erythrocytes in the development of endothelial dysfunction related to cardiovascular complications of MetS [4]. In rat models of MetS, an increase in thiobarbituric acid reactive substances (TBARS) and carbonyl groups in neutral and basic proteins, along with a significant decrease in the activity of specific antioxidant enzymes, has been observed in erythrocytes [5].

The exploration of alternative medicine to restore balance in carbohydrate metabolism and lipid profiles, as well as to maintain oxidative balance, has led to the investigation of plants such as yacon (*Smallanthus sonchifolius* (Poepp. and Hendl.) H. Robinson). Yacon contains biologically active compounds that exhibit immunomodulatory, antioxidant, and anti-carcinogenic properties, thereby supporting processes such as lipid metabolism, hypoglycemia, and insulin sensitivity modulation [6]. The diverse biological effects of yacon are attributed to its rich composition of various bioactive substances, including oxalic acid, tannins, and carotenoids [7,8]. Additionally, yacon is abundant in flavonoids and phenolic compounds, including gallic acid, caffeic acid, rosmarinic acid, ferulic acid, p-coumaric acid, chlorogenic acid, protocatechuic acid, quercetin and terpenes (notably sesquiterpene lactones such as uvedalin, polymatin A/B, sonchifolin, and enhydrin) [9,10,11,12,13]. Moreover, yacon leaves contain unique compounds such as enhydrin, o-quinone derivatives, smallanthaditerpenic acids A, B, C, and D, as well as specific flavonols like 5,7-dihydroxy-4′-methoxyflavonol, 5,7,3′-trihydroxy-4′-methoxyflavonol, and 7,4′-dihydroxy-3,5′-dimethoxyflavone, along with ent-kaurenoic acid and other ent-kaurane derivatives [14,15].

Numerous studies have confirmed the hypoglycemic and hypolipidemic effects of yacon in various models of MetS [16,7,17,18]. However, most of this research has focused on the root tubers of the plant, with a limited investigation into the biological activity of yacon leaves. Specifically, the primary studies assessing the effects of yacon leaf bioactive compounds have been conducted in models of diabetes mellitus [6,19,20] rather than MetS. An exception is a study examining the antioxidant potential of yacon leaf extract in rats fed a hypercholesterolemic diet; however, this study utilized an ethanol extract [21]. Given the insufficient amount of experimental data on the effects of aqueous extracts from yacon leaves in carbohydrate-induced MetS models, the present study aimed to investigate the hypoglycemic effects (as measured by glucose and glycosylated hemoglobin concentrations), hypolipidemic effects (including levels of triglycerides, cholesterol, and low- and high-density lipoproteins), and antioxidant properties (evaluated by prooxidant and antioxidant balance of erythrocytes) of an aqueous extract of yacon leaves in a fructose-induced model of experimental MetS.

2. Materials and methods

2.1. Preparation of aqueous extract of yacon leaves and compounds identification

Raw materials of *Smallanthus sonchifolius* (Poepp. and Hendl.) H. Robinson (specimens No. 86–2014 and No. 187–2023) are stored in the collection of the Herbarium of the Research Station of Medicinal Plants at the Institute of Agroecology and Nature Management of the National Academy of Sciences of Ukraine (acronym: LBE, Index Herbariorum Ukrainicum). The aqueous extract was prepared from ground and air-dried yacon leaves. The leaves were infused in water at a ratio of 1:10 (dry weight) for 15 min at 100 °C, then cooled to room temperature for 45 min before being filtered. The filtrate was vacuum-evaporated using a rotary evaporator at a temperature of 60–65 °C, resulting in a thick, jam-like residue. The yield of the extract was measured after the infusion process and found to be approximately 12 %, indicating the amount of plant material extracted relative to the total mass of dried leaves used. This dry residue was then dissolved in water and administered to the animals at a dose of 500 mg per kg of body weight. This dosage was based on literature and our previous research. Preliminary studies in experimental diabetes mellitus did not confirm a hypoglycemic effect at the lower dose; thus, subsequent experiments utilized the 500 mg per kg dose, which demonstrated a pronounced sugar-lowering effect [22,23]. Given these findings, the 500 mg per kg dose was selected for potential efficacy in metabolic syndrome.

An Agilent Technologies 6890 N chromatograph with mass spectrometer detector 5979B was used to examine the extract. Analysis was performed conditions according to Nagalievska [24]. Chromatographic capillary column HP-5MS 30 m in length and inner diameter of 250 μm, 0.25 μm phase was used. Helium was used as carrier gas at a constant flow rate of 1.5 ml/min and sample volume of 1 ml. Injector 7683B, Split 20:1, evaporator temperature 250 °C. The thermostat programmed temperature of 75 °C (over 2 min) with heating 15 °C/min to 300 °C (within 9 min). Mass selective detector, interface temperature of 280 °C, ionization by electron impact, ionization energy 70 eV, ion source temperature of 230 °C, the quadrupoles temperature 150 °C. By comparing the mass spectra data with the mass spectral libraries NIST05a and WILEY, identification was accomplished.

2.2. Animal experiments

White outbred male rats weighing between 250 and 300 g were utilized for this study, totaling 42 animals. The animals were maintained in clean and dry polypropylene cages at controlled temperature of 25 ± 2 °C and 45–55 % relative humidity and a 12-h dark-light cycle in the animal house (Ivan Franko National University of Lviv). The animals consumed compound feed for laboratory animals, which contained protein (22.5–23 %), fat (6.0–6.3 %), fiber (5.5–6.0 %), ash (5.2 %), Phosphorus (0.75 %), Sodium (0.04 %), Lysine (1.3 %), Methionine + Cysteine (0.82 %), Calcium (0.84 %), Tryptophan (0.29 %), Threonine (0.9 %), as well as a vitamin-mineral complex. The metabolic energy of the feed was 3279 Kcal/1 kg. Animals in all groups had free access to food and water. To induce MetS, the rats were provided with a 10 % fructose solution to drink for 42 days [25], control animals consumed drinking water. To assess weight gain body mass was measured prior to fructose solution (for MetS group) and drinking water (for C group) consumption, as well as on the 42nd day of solution consumption. On the same day, the extract was administered daily for 7 and 14 days at the same time of day to both healthy animals and animals with metabolic syndrome. Changes in weight gain, glucose concentration, glycosylated hemoglobin levels, and the concentrations of triacylglycerols, cholesterol, and low- and high-density lipoproteins served as indicators of MetS development [26].

The experimental groups consisted of seven animals each, categorized as follows:

(1) control animals (C);
(2) control animals that were treated with yacon leave extract for 7 days (C + Y^7);
(3) control animals that were treated with yacon leaf extract for 14 days (C + Y^{14});
(4) animals with experimental metabolic syndrome (MetS);
(5) animals with MetS, which were treated with extract for 7 days (MetS + Y^7);
(6) animals with MetS, which were treated with extract for 14 days (MetS + Y^{14}).

The study protocol was conducted in compliance with the general ethical principles of animal experiments following the "General Principles of Work on Animals", approved by the Ist National Congress of Bioethics (Kyiv, Ukraine, 2001) and conforming to the guidelines from Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes and the Law of Ukraine "On Protection of Animals from Cruelty" from February 26, 2006, as well as approved by the Ethics Committee of Ivan Franko National University of Lviv, Ukraine (protocol № 40-11-2023 from November 14, 2023).

2.3. Collection of blood and obtaining of erythrocytes hemolysates

After the experimental period, the rats were fasted for 15 h, then anesthetized using deep diethyl ether and euthanized by decapitation. Erythrocytes and plasma were isolated through centrifugation at 1700*g* for 10 min. The erythrocytes were washed three to four times with an isotonic solution (0.9 % NaCl) until the supernatant became colorless. Hemolysates were prepared by mixing the erythrocytes with cold distilled water in a 1:3 ratio. To ensure the complete removal of cell membranes, the resulting solution was centrifuged at 3000 g for 5 min at 4 °C [27]. Blood plasma and hemolysates were subsequently stored at −20 °C for future analysis.

2.4. Determination of glucose concentration and glycosylated hemoglobin content

An analytical kit (HP009.02, Philisit-Diagnostics) was utilized for the enzymatic determination of glucose concentration in blood plasma, based on the glucose oxidase reaction.

The concentration of glycated hemoglobin (HbA1c) in erythrocyte hemolysates was measured using a colorimetric method. This procedure involves the acid hydrolysis of the ketoamine bond, facilitated by oxalic acetic acid, leading to the formation of 5-oxymethylfurfural. This compound then reacts with 2-thiobarbituric acid. The intensity of the resulting colored complex was quantified using a spectrophotometer [28].

2.5. Analysis of the lipid profile

Plasma levels of cholesterol (HP026.02, Philisit-Diagnostics), triglycerides (HP022.02, Philisit-Diagnostics), low-density lipoproteins (LDL) (HP026.05, Philisit-Diagnostics), and high-density lipoproteins (HDL) (HP026.04, Philisit-Diagnostics) were assessed using commercial reagent kits according to the manufacturer's standards.

2.6. The measurement of paraoxonase (PON) activity

The activity of paraoxonase (PON) was measured using 4-nitrophenyl acetate as a substrate. The enzymatic cleavage of 4-nitrophenyl acetate by paraoxonase produces colored 4-nitrophenol, the concentration of which was determined colorimetrically. Paraoxonase activity was expressed in units per liter (U/L) [25].

2.7. Determination of oxidative and nitrate stress markers

The activity of superoxide dismutase (SOD) was assessed using a method that involves the reduction of yellow nitroaniline

tetrazolium dye to dark purple formazan. Catalase (CAT) activity was determined by measuring the color intensity of the complex formed from the interaction of hydrogen peroxide (H_2O_2) with ammonium molybdate. The rate of glutathione oxidation in the presence of tertiary butyl hydroperoxide was utilized to measure glutathione peroxidase (GPO) activity [5]. The activity of nitric oxide synthase (NOS) was measured via a modified microplate assay employing the Griess reaction to detect nitrite production [29]. Protein concentration was quantified using the Lowry method.

Carbonyl group content in proteins was evaluated through the reaction of aldehyde and ketone groups of aliphatic amino acids with 2,4-dinitrophenylhydrazine, resulting in the formation of 2,4-dinitrophenylhydrazones with distinct absorption spectra. Neutral aldehydes and ketones were measured at 370 nm, while basic derivatives were detected at 430 nm. The determination of thiobarbituric

Table 1
Qualitative and quantitative analysis of biologically active substances in yacon aqueous extract.

Peak no	R.T., min	Name of the compound	Peak Area %
1	3.337	2-isopropyl-4,5-dimethyl-3-oxazoline	0.54
2	3.551	2-methylpiperidine hydrochloride	0.17
3	3.699	glycerin	0,21
4	3.919	2(R),3(S)-1,2,3,4-butanetetrol	0.08
5	4.401	N-chloromethyl-N-ethylpiperidinium chloride	0.30
6	4.496	piperidine, 2,3-dimethyl-	0.23
7	4.633	cycloheptane	0.36
8	4.918	not identified	0.34
9	5.632	4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	2.04
10	5.971	octanal	0.29
11	6.655	ketone, methyl 2-methyl-1,3-oxothi olan-2-yl	1.01
12	7.326	decane-1,2-d2	0.30
13	7.642	hydroperoxide, 1-methylbutyl	0.28
14	8.165	2,10,10-trimethyl-4-hydroxy-1,11-didehydro-tricyclo[6.3.0(1,8)0.0(2,6)]undecane	0.19
15	8.527	not identified	2.09
16	8.902	galacto-heptulose	0.93
17	9.342	2(4H)-benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-	0.27
18	9.580	2-acetylthiazole	0.08
19	9.859	3-deoxy-d-mannoic lactone	1.26
20	10.109	carveol 1	0.87
21	10.496	1,1'-(1,1′-cyclopropylidenediethylidene)disemicarbazide	0.52
22	10.936	dodecanoic acid	0.29
23	11.132	2(4H)-benzofuranone, 5,6,7,7a-tetrahydro-6-hydroxy-4,4,7a-trimethyl-	1.06
24	11.257	2-cyclopropylthiophene	0.21
25	11.453	D-glucose, 6-O-.alpha.-D-galactopyranosyl-	0.73
26	12.077	hexadecanoic acid, methyl ester	0.86
27	12.321	hexadecanoic acid	5.07
28	12.624	alpha.-gluco-octonic-1,4-lactone	0.25
29	13.177	9,12-jctadecadienoic acid, methyl ester	0.37
30	13.296	phytol isomer	1.27
31	13.457	9,12,15-octadecatrienoic acid, methyl ester, (Z,Z,Z)-	4.68
32	13.564	octadecanoic acid	0.74
33	14.420	vulgarol A	0.30
34	14.729	7,9-dimethyl-8-nitrobicyclo[4.3.1]decan-10-one	1.39
35	15.443	benzene, 1,1'-(2-butene-1,4-diyl)bis-	0.58
36	15.752	methanol, tris(methylencyclopropyl)-	3.08
37	16.002	1,4-Benzenediamine, N,N,N′,N′-tetramethyl-	0.88
38	16.138	isoeugenol 1	0.43
39	16.448	1,1,1,3,5,5,5-heptamethyltrisiloxane	0.43
40	16.501	4-dehydroxy-N-(4,5-methylenedioxy-2-nitrobenzylidene)tyramine	0.30
41	16.679	1,1,1,3,5,5,5-heptamethyltrisiloxane	0.87
42	16.888	1-methyl-2-cyano-2-methyl-3-ethyl-4-thiophenylpiperidine	2.80
43	17.179	propanedinitrile, dicyclohexyl	5.89
44	17.316	Not identified	2.76
45	17.387	1H-indole, 5-methyl-2-phenyl-	1.29
46	17.773	4,14-bis(hydroxymethyl)-[2.2]metacyclophane	0.60
47	17.922	2-butenoic acid	3.86
48	18.023	1H-indole, 5-methyl-2-phenyl-	0.78
49	18.130	propiophenone, 2'-(trimethylsiloxy)-	0.89
50	18.255	1,1,1,3,5,5,5-heptamethyltrisiloxane	0.43
51	18.481	propiophenone, 2'-(trimethylsiloxy)-	0.70
52	18.939	trimethyl[5-methyl-2-(1-me thylethyl)phenoxy]-	0.62
53	19.700	benzene, 1,4-bis(trimethylsilyl)-	0.34
54	19.801	1-[(hexadeuterio)phenyl]naphthalen	0.18
55	20.063	(E)-23-ethylcholesta-5,22-dien-3.beta.-ol	1.63
56	20.586	gamma.-sitosterol	1.85
57	20.746	gibberellin A3	0.25
58	21.014	2H-cyclopropa[a]naphthalen-2-one1,1a,4,5,6,7,7a,7b-octahydro-1,1,7,7a-tetramethyl-,	0.46

acid reactive substances (TBARS) was based on the reaction of thiobarbituric acid with malondialdehyde, yielding a red complex with an absorbance maximum at 532 nm [5]. The concentrations of nitrite (NO_2^-) and nitrate (NO_3^-) anions in blood plasma were spectrophotometrically determined using the Griess reagent [30].

2.8. Statistical analysis

A software Microsoft Excel XP processed the data statistically using the Student's t-test. The primary statistical parameters were determined using the quantitative data gathered from the investigation, and the results are shown as M ± m (M – arithmetic mean, m - standard deviation of the arithmetic mean). Dunnett's test was used for a one-way analysis of variance (ANOVA) in order to determine the significance of the difference. When $P < 0.05$, differences were counted as significant.

3. Results

3.1. Phytochemical analysis

In the yacon extract, 58 components that are presented in Table 1.

The predominant components are 4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl- (2.04 %), ketone, methyl 2-methyl-1,3-oxothi olan-2-yl (1.01 %), 3-deoxy-d-mannoic lactone (1.26 %), (4H)-benzofuranone, 5,6,7,7a-tetrahydro-6-hydroxy-4,4,7a-trimethyl- (1.06 %), hexadecanoic acid (5.07 %), phytol isomer (1.27 %), 9,12,15-octadecatrienoic acid, methyl ester, (Z,Z,Z)- (4.68 %), 7,9-dimethyl-8-nitrobicyclo[4.3.1]decan-10-one (3.08 %), 1-methyl-2-cyano-2-methyl-3-ethyl-4-thiophenylpiperidine (2.80 %), propanedinitrile, dicyclohexyl (5.89 %), 1H-indole, 5-methyl-2-phenyl- (1.29 %), 2-butenoic acid (3.86 %), (E)-23-ethylcholesta-5,22-dien-3.beta.-ol (1.63 %), and gamma.-sitosterol (1.85 %).

3.2. Body mass

In animal studies assessing metabolic alterations, body weight is commonly used as a primary metric due to its direct correlation with metabolic changes. For instance, in diet-induced obesity models, researchers often monitor body weight to evaluate the development of obesity and its associated metabolic effects [31]. The initial average weight of the animals that made up the control group was 257.50 ± 12.46 g, while the weight of the animals that were assigned to the metabolic syndrome group at the time of the start of fructose consumption was 251.00 ± 14.21 g. Our findings indicate that the consumption of fructose by animals over a 42-day period is associated with an average body weight increase of 51 g (302.50 ± 5.92 g), compared to a weight increase of 27 g (284.09 ± 15.34 g) in the control group during the same timeframe (Fig. 1). These observed changes suggest a possible development of obesity in the fructose-fed animals.

The administration of an aqueous yacon extract for the treatment of MetS resulted in a body weight reduction of 55.41 % after 7 days (274.00 ± 6.14 g) and 59.94 % after 14 days (271.64 ± 9.55 g). In healthy animals, an increase in body weight of 5.09 % (298.57 ± 17.24 g) was found when consuming an aqueous extract of yacon for 7 days, and 7.80 % (306.25 ± 22.95 g) in case of longer use of the studied extract (Fig. 1).

3.3. Glucose and glycated hemoglobin concentration

Along with central adiposity, to main traits included in MetS diagnosis belong hyperglycemia, and atherogenic dyslipidemia [32]. The development of MetS is accompanied by an increase in glucose concentration by 46.83 % (Fig. 2). An additional parameter for assessing the development of hyperglycemia is the determination of glycated hemoglobin content (HbA1c), which allows to estimate

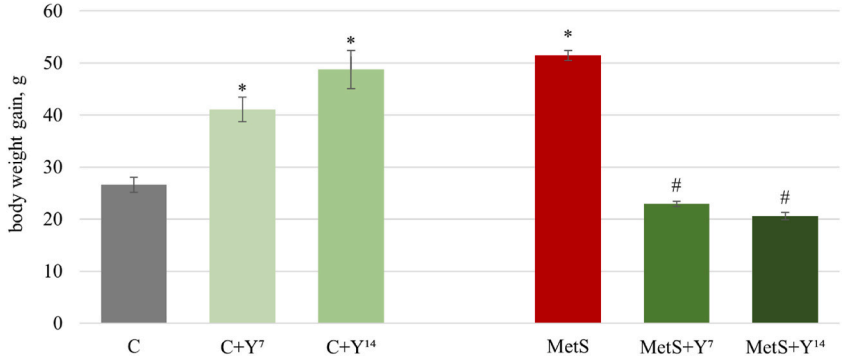

Fig. 1. Body weight gain of control animals (C), animals with experimental metabolic syndrome (MetS), and after treatment with yacon leaves aqueous extract for 7 days (C + Y^7, MetS + Y^7) and 14 days (C + Y^{14}, MetS + Y^{14}). * - significant difference compared with the control group ($P < 0.05$); # - significant difference compared with the MetS group ($P < 0.05$).

the average glucose concentration over a long period (3 months) depending on how long glycemic episodes last and how frequently they occur [33]. Against the background of increasing glucose concentration, we established a significant increase in HbA1c content by 220.04 % in MetS, compared to control values (Fig. 2).

The administration of yacon extract for 14 days in the context of experimental MetS resulted in a 10.33 % reduction in glucose concentration, accompanied by a significant decrease in HbA1c level by 61.58 % compared to the control group. In contrast, the use of the extract during the shorter studied period does not lead to significant changes in the studied parameters. In healthy animals, against the background of the use of the studied extract, an increase in glucose concentration by 44.72 % and a tendency to HbA1c increase was observed. A shorter period of yacon use did not cause significant changes in the studied indicators.

3.4. Lipid profile

Fructose-induced metabolic syndrome is characterized by a distinct pattern of lipid abnormalities in serum, including an increase in triglyceride level by 130.17 %, cholesterol level by 23.14 %, and low-density lipoprotein (LDL) level by 27.49 %. Concurrently, there was a notable decrease in high-density lipoprotein (HDL) concentration by 25.07 % (Table 2). This specific lipid pattern is indicative of "atherogenic dyslipidemia" [34].

The use of yacon extract for the treatment of MetS leads to a decrease in blood plasma triglycerides by 20.37 % (MetS + Y^7) and 50.35 % (MetS + Y^{14}) and a decrease in cholesterol by 7.87 % (MetS + Y^7) and 24.46 % (MetS + Y^{14}). In animals with experimental MetS, yacon causes an increase in HDL concentration by 12.84 % (MetS + Y^7) and 29.29 % (MetS + Y^{14}) against the background of a decrease in LDL content by 12.26 % (MetS + Y^7) and 21.56 % (MetS + Y^{14}). In healthy animals, the use of the studied extract leads to a decrease in triglycerides by 7.56 % (C + Y^7) and 11.35 % (C + Y^{14}), an increase in HDL content by 5.41 % (C + Y^{14}) without causing significant changes in the concentration of cholesterol and LDL (Table 2).

Dyslipidemia is an oxidative stress-associated process that is accompanied by low activity of PON, an antioxidant enzyme that is closely related to high-density lipoproteins [35]. A decrease in PON activity by 14.00 % in MetS compared to the control was established (Fig. 3).

The use of aqueous extract of yacon leads to an increase in paraoxonase activity by 60.91 % (MetS + Y^7) and 56.03 % (MetS + Y^{14}). No significant changes in PON activity were found when the extract was used in healthy animals.

3.5. Markers of oxidative-nitrative stress

To evaluate the antioxidant potential of yacon extract, we measured changes in the activity of key enzymes involved in the antioxidant defense system of red blood cells, specifically superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPO). The progression of metabolic syndrome was associated with a reduction in the activity of all enzymes examined, with SOD activity decreasing by 27.52 %, CAT by 44.32 %, and GPO by 16.55 % (Fig. 4).

The development of metabolic syndrome was accompanied by an increase in the number of oxidative modified lipids and proteins, as indicated by an increase in TBARS by 75.29 % and oxidized protein modification products of a neutral and basic nature by 38.16 % and 65.43 %, respectively (Fig. 5).

The administration of aqueous yacon extract resulted in a significant increase in SOD activity by 48.40 % (MetS + Y^7) and 47.85 % (MetS + Y^{14}). Concurrently, GPO activity also rose by 13.07 % (MetS + Y^7) and 16.55 % (MetS + Y^{14}). However, the treatment led to a further decline in CAT activity, by 18.24 % (MetS + Y^7) and 16.07 % (MetS + Y^{14}). A similar trend towards a decrease in CAT activity was observed when the extract was administered to healthy animals, in particular, a reduction in CAT activity of 36.92 % was observed in animals that were treated with extract for 14 days (C + Y^{14}) (Fig. 4). The observed increases in SOD and GPO activity underscore the antioxidant potential of the yacon extract. Additionally, this potential is further corroborated by a reduction of TBARS by 4.88 %

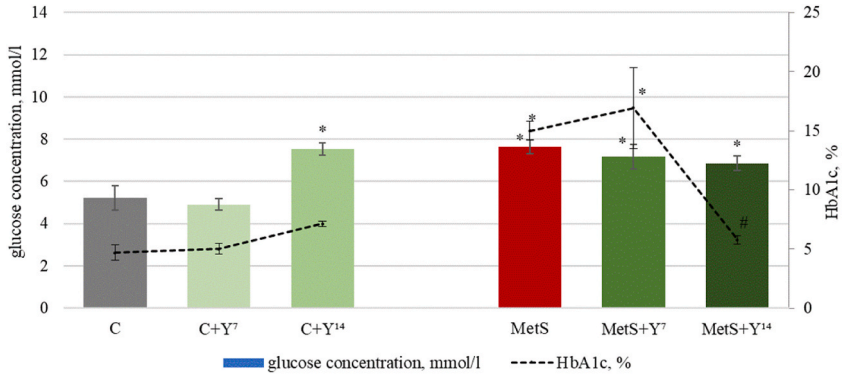

Fig. 2. Glucose concentration and glycated hemoglobin content in control animals (C), animals with experimental metabolic syndrome (MetS), and after treatment with yacon leaves aqueous extract for 7 days (C + Y^7, MetS + Y^7) and 14 days (C + Y^{14}, MetS + Y^{14}). * - significant difference compared with the control group ($P < 0.05$); # - significant difference compared with the MetS group ($P < 0.05$).

Table 2
Plasma lipid profile of control animals (C), animals with experimental metabolic syndrome (MetS), and after treatment with yacon leaves aqueous extract for 7 (C + Y^7, MetS + Y^7) and 14 days (C + Y^{14}, MetS + Y^{14}).

Animal groupsLipid concent-ration (mmol/l)	C	C + Y^7	C + Y^{14}	MetS	MetS + Y^7	MetS + Y^{14}
Triglycerides	0.739 ± 0.019	0.684 ± 0.013[a]	0.656 ± 0.011[a]	1.708 ± 0.075[a]	1.364 ± 0.059[a,b]	0.844 ± 0.027[b]
	1.063 ± 0.072	1.002 ± 0.021	1.000 ± 0.015	1.390 ± 0.120[a]	1.206 ± 0.058[a]	1.052 ± 0.037[b]
Cholesterol	0.738 ± 0.019	0.741 ± 0.017	0.777 ± 0.014[a]	0.553 ± 0.021[a]	0.624 ± 0.017[a,b]	0.715 ± 0.013[b]
HDL	0.211 ± 0.014	0.211 ± 0.002	0.210 ± 0.001	0.269 ± 0.003[a]	0.236 ± 0.007[b]	0.211 ± 0.001[b]
LDL						

[a] significant difference compared with the control group (P < 0.05).
[b] significant difference compared with the MetS group (P <0.05).

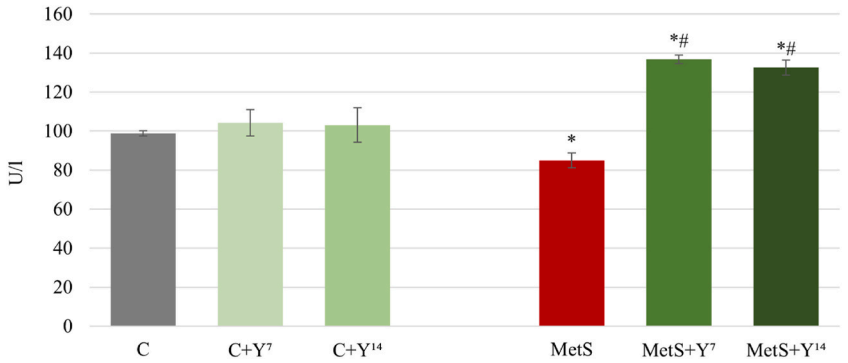

Fig. 3. Plasma paraoxonase activity of control animals (C), animals with experimental metabolic syndrome (MetS), and after treatment with yacon leaves aqueous extract for 7 days (C + Y^7, MetS + Y^7) and 14 days (C + Y^{14}, MetS + Y^{14}). * - significant difference compared with the control group (P < 0.05); # - significant difference compared with the MetS group (P <0.05).

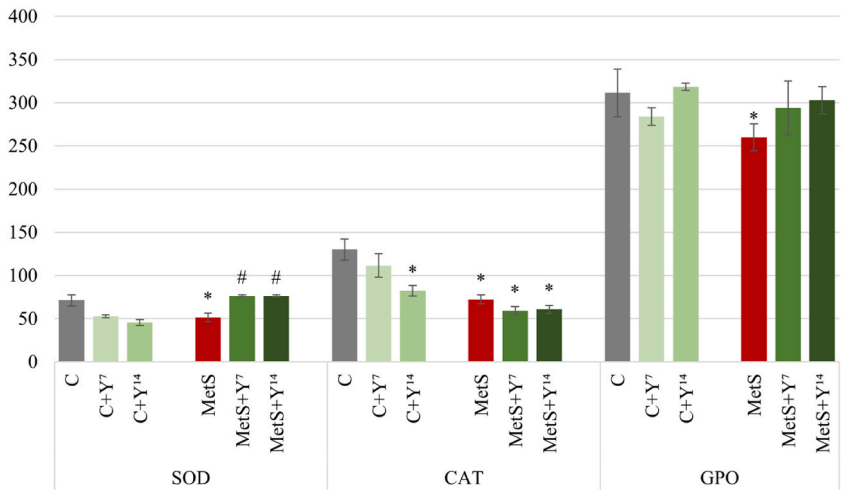

Fig. 4. Superoxide dismutase (SOD, % blocking of formazan), catalase (CAT, nM H_2O_2/min mg protein), and glutathione peroxidase (GPO, μM G-SH/min mg protein) activities in erythrocytes of control animals (C), animals with experimental metabolic syndrome (MetS), and after treatment with yacon leaves aqueous extract for 7 days (C + Y^7, MetS + Y^7) and 14 days (C + Y^{14}, MetS + Y^{14}). * - significant difference compared with the control group (P < 0.05); # - significant difference compared with the MetS group (P <0.05).

(MetS + Y^7) and 23.77 % (MetS + Y^{14}), along with a decrease in proteins oxidative modification products of neutral character by 45.46 % (MetS + Y^7) and 52.56 % (MetS + Y^{14}) (Fig. 5). The use of yacon in healthy animals did not cause any significant changes in the activity of SOD and GPO, and did not affect the studied indicators of protein and lipid peroxidation (Figs. 4 and 5).

The development of metabolic syndrome is accompanied by an increase in NOS activity by 41.16 %, compared to the control. The

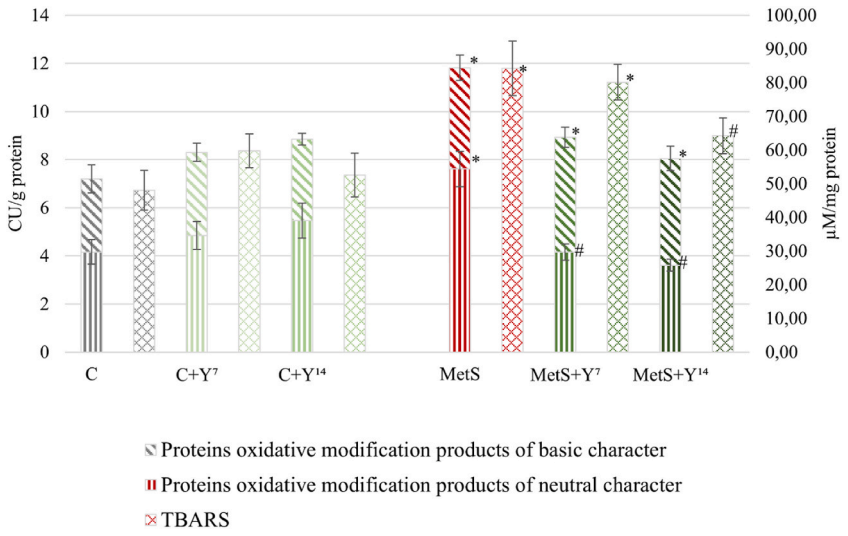

Fig. 5. Content of proteins oxidative modification products of neutral and basic character (CU/g protein) and TBARS (μM/mg protein) in erythrocytes of control animals (C), animals with experimental metabolic syndrome (MetS), and after treatment with yacon leaves aqueous extract for 7 days (C + Y^7, MetS + Y^7) and 14 days (C + Y^{14}, MetS + Y^{14}). * - significant difference compared with the control group ($P < 0.05$); # - significant difference compared with the MetS group ($P < 0.05$).

increase in NOS activity during metabolic syndrome leads to an increase in the content of nitrites and nitrates by 17.54 % and 19.34 %, respectively, relative to the control (Fig. 6).

The administration of aqueous yacon leaf extract resulted in a reduction of NOS activity by 20.49 % (MetS + Y^7) and 12.30 % (MetS + Y^{14}). This decrease was accompanied by a significant reduction in nitrate levels by 17.34 % (MetS + Y^7) and 10.44 % (MetS + Y^{14}). However, no significant changes in nitrite levels were observed following the administration of yacon extract to animals with MetS. In control animals, no significant changes in NOS activity and nitrite and nitrate content were observed when yacon extract was administered (Fig. 6).

4. Discussion

The onset of obesity in the group of rats with fructose-induced experimental MetS is evidenced by an increase in body weight gain. Obesity and insulin resistance may result from various pathological conditions, including alterations in lipid and glucose metabolism, the mobilization of free fatty acids from adipose tissue, impaired glucose uptake by muscle tissue, and inadequate insulin secretion from the pancreas. Additionally, chronic inflammation and the stress response play crucial roles in the development of these conditions [36].

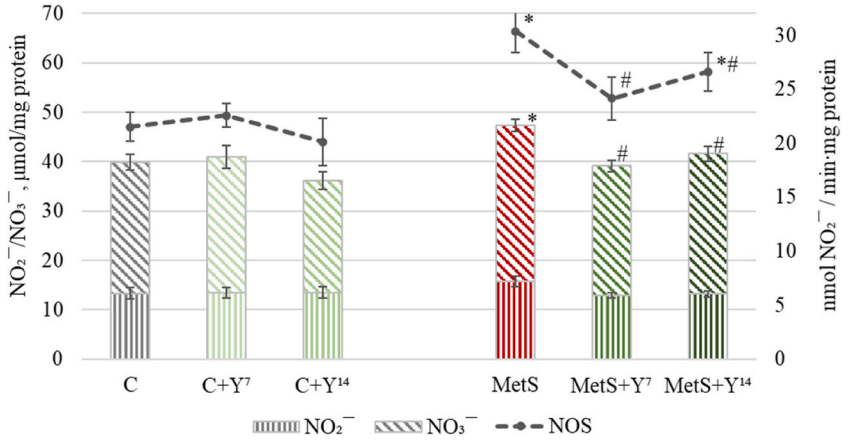

Fig. 6. Content of nitrites (NO_2^-) and nitrates (NO_3^-) (μmol/mg protein) and NOS activity (nmol NO_2^-/min•mg protein) in erythrocytes of control animals (C), animals with experimental metabolic syndrome (MetS), and after treatment with yacon leaves aqueous extract for 7 days (C + Y^7, MetS + Y^7) and 14 days (C + Y^{14}, MetS + Y^{14}). * - significant difference compared with the control group ($P < 0.05$); # - significant difference compared with the MetS group ($P < 0.05$).

Excessive consumption of fructose results in its enhanced absorption by hepatic cells. Within these cells, fructose is converted to fructose-1-phosphate through a reaction catalyzed by fructokinase in the presence of ATP. Subsequently, fructose-1-phosphate is cleaved into glyceraldehyde and dihydroxyacetone phosphate. Unlike glucose, fructose bypasses the initial regulatory phase of glycolysis, directly yielding two triose sugars. The fructose molecule is rapidly converted to acetyl-CoA, which is utilized for fatty acid synthesis instead of entering the tricarboxylic acid cycle when cellular energy levels are sufficient. Furthermore, fructose does not stimulate insulin secretion from pancreatic β-cells, likely due to the absence of the fructose transporter (GLUT5) in these cells. Consequently, excessive fructose consumption fails to trigger satiety signals in the brain by interfering with the release of gut hormones such as glucagon-like peptide-1 and peptide YY. This absence of satiety contributes to increased food intake and the subsequent development of MetS [37].

The administration of an aqueous extract of yacon in the treatment of MetS resulted in a reduction in body weight (Fig. 1). This observed effect may be attributed to the presence of phenolic compounds in yacon (Table 1) [38]. These phenolic compounds may contribute to obesity prevention through multiple mechanisms, including reduction of food intake, attenuation of inflammatory responses, suppression of oxidative stress, stimulation of fatty acid β-oxidation, inhibition of lipogenesis, enhancement of lipolysis, and limitation of adipocyte differentiation and proliferation [39]. The difference in weight responses between control and MetS animals treated with extract might seem contradictory. On the one hand, the increase in the weight of control animals against the background of the use of the extract can be explained by the normal weight gain of adult animals, and on the other hand, it may be due to the differential impact of the extract on metabolic pathways in animals with existing metabolic dysfunction compared to healthy controls. In the context of MetS, the extract may exert more pronounced beneficial effects on weight regulation due to the underlying pathological processes (such as insulin resistance, altered glucose lipid metabolism, and inflammation), whereas in healthy animals, the extract may only minimally affect these pathways.

In MetS, yacon leaf extract exhibits a significant hypoglycemic effect, as evidenced by a marked reduction in glycated hemoglobin levels. A similar effect has been reported in models of experimental diabetes mellitus [40,41]. This hypoglycemic action may be attributed to the presence of several bioactive compounds in yacon leaves, including caffeic acid, chlorogenic acid, ferulic acid, and procaechuic acid [9,6]. These compounds inhibit the activity of α-amylase and sucrase, thereby decreasing the amount of glucose absorbed by the cells of the gastrointestinal tract by blocking sodium-glucose transporters I and II (S-GLUT1 and 2) [42]. Furthermore, polyphenols found in yacon leaves have been shown to activate hepatic peroxisome proliferator-activated receptor gamma (PPARγ), which facilitates glycogen synthesis and reduces gluconeogenesis [43]. In addition, yacon leaves also contain lactone compounds such as cynarin. These compounds have been reported to interact with carbohydrate-digesting enzymes, such as α-amylase and sucrase, potentially contributing to the hypoglycemic effects observed in yacon-treated animals. Lactones may enhance the plant's ability to regulate blood glucose by inhibiting the breakdown of starches and disaccharides, leading to a reduced glycemic response [6]. Contradictory effects between the weight gain and blood sugar level in treated animals (MetS + Y^7) may stem from the treatment's selective effects on metabolic pathways. In some cases, plant extracts might primarily promote weight reduction by targeting pathways involved in lipid metabolism, fat oxidation, or energy balance, rather than directly influencing glucose regulation. This selective action could explain the lack of significant changes in blood glucose concentrations, despite measurable decreases in body weight [44,45].

The observed increase in glucose levels in the control animals that consumed the extract is an important and potentially contradictory finding. One possible explanation is that the extract may have a temporary effect on glucose metabolism in healthy animals, leading to an increase in circulating glucose levels. This could be due to altered insulin sensitivity, increased glycogen mobilization, or changes in metabolic pathways that temporarily elevate blood glucose, even in the absence of insulin resistance.

The administration of an aqueous extract derived from yacon leaves has been shown to normalize the lipid profile in experimental models of MetS. These findings align with previous research indicating that treatment with yacon significantly reduces plasma cholesterol and triglyceride levels in alloxan-induced rat models [20]. Comparable outcomes regarding lipid profile normalization have also been observed in hypercholesterolemic rats [21] and in models of MetS induced by a high-fructose diet [46]. The beneficial effects observed in yacon-treated animals, especially regarding lipid metabolism, can be attributed to the presence of bioactive compounds in the leaves, such as phenolic acids (e.g., caffeic acid, chlorogenic acid) and lactones (e.g., cynarin) [9,6], as well as its substantial polyphenol content [21].

The development of MetS was associated with a reduction in PON activity. Elevated low-density lipoprotein (LDL) can inactivate PON by interacting with the enzyme's free sulfhydryl groups [26], which is exacerbated by oxidative stress that surpasses the enzyme's antioxidant capacity in MetS conditions [35]. Notably, PON deficiency has been linked to increased insulin resistance in mice subjected to a high-fat diet [47]. The significant increase in PON activity observed in the study (MetS + Y^7, MetS + Y^{14}) is an important indicator of the antioxidant effects of yacon leaf extract in the context of metabolic syndrome. By enhancing PON activity, the extract may help to reduce oxidative stress, modulate inflammation, and improve lipid metabolism. The observed increase in paraoxonase activity following the administration of an aqueous extract from yacon may be related to the phenolic compounds present in yacon leaves [48]. Furthermore, numerous phytochemicals, including quercetin, resveratrol, and curcumin, as well as extracts from *Ilex paraguariensis, Punica granatum*, and *Berberis vulgaris*, have been shown to enhance PON gene expression and activity, thereby contributing to a reduction in oxidative stress levels [49].

Reactive oxygen and nitrogen species can interact with nearly all biomolecules, leading to oxidative damage when produced in excessive amounts. Patients with MetS exhibit elevated levels of oxidative damage markers, such as lipid peroxidation, alongside reduced plasma antioxidant enzyme activity, creating a state of oxidative stress. This increased oxidative stress may contribute to the pathogenesis of MetS by promoting thrombosis, atherosclerosis, and inflammation, thereby adversely affecting vascular function and leading to vascular disease [50]. Our previous research has demonstrated that assessing the erythrocyte redox balance in animals with MetS is a practical and effective approach for evaluating the body's prooxidant-antioxidant status [5].

A decline in antioxidant enzyme activity in MetS is attributable to the rapid consumption and depletion of these enzymes during the scavenging of excessive free radicals generated by diet-induced MetS, as well as the formation of crosslinks with malonic dialdehyde resulting from lipid peroxidation [51]. This decrease in antioxidant enzyme activity is paralleled by an increase in oxidative-modified lipids and proteins, collectively indicating the onset of oxidative stress. These alterations are also associated with increased activity of NOS, leading to elevated levels of nitrites and nitrates. Once formed, nitric oxide (NO) is quickly oxidized to nitrite (NO_2^-) and nitrate (NO_3^-). Both blood and tissues are capable of recycling nitrate and nitrite to synthesize NO and other bioactive nitrogen oxides [52]. In the context of MetS, NOS activity can be influenced by inflammatory cytokines such as leptin, tumor necrosis factor, and interleukin-6, as well as by elevated glucose and free fatty acids [53]. The iNOS gene is upregulated upon activation of the leptin/STAT3 signaling pathway, while the Akt-mediated eNOS activity is stimulated through the leptin/JAK2/IRS-1 pathway [54]. Consequently, the increase in NOS activity and the concentration of stable metabolites of nitric oxide indicate that MetS is associated with the development of nitrative stress.

Administration of yacon aqueous extract to animals with MetS resulted in increased activity of SOD and glutathione peroxidase GPO, as well as a reduction in NOS activity and levels of oxidatively modified proteins and lipids in red blood cells, indicating the antioxidant potential of the extract. A decrease in CAT activity was observed in animals following treatment with the extract. A similar reduction in CAT activity has also been reported in liver and kidney homogenates from diabetic rats treated with yacon [55]. This decrease in CAT activity may be attributed to a reduction in its substrate, potentially resulting from the increased activity of SOD on one hand, and the antioxidant effects of the yacon extract on the other. Previous studies have confirmed the pronounced antioxidant effects of yacon extract in vitro, as assessed using DPPH, ABTS, and FRAP assays. This antioxidant potential is largely attributed to its high content of phenolic compounds, including caffeic acid and its derivatives, chlorogenic acid, protocatechuic acid, and ferulic acid [40, 56]. These bioactive compounds effectively scavenge a range of reactive species, such as N_2O_3, organic free radicals, hypochlorous acid, superoxide anion (O_2^-), hydroxyl radicals (•OH), peroxynitrite ($ONOO^-$), and peroxy radicals, leading to the formation of stable products that do not generate free radicals. Additionally, yacon is rich in flavonoids, which exert antioxidant effects by donating hydrogen atoms to transition metals, thereby reducing their oxidative potential and mitigating their prooxidative effects [6,41].

5. Conclusions

In conclusion, the administration of aqueous yacon extract for 14 days in the treatment of fructose-induced metabolic syndrome resulted in significant reductions in body weight, glycated hemoglobin levels, and normalization of the lipid profile in rats. Additionally, yacon extract enhanced the activities of superoxide dismutase and glutathione peroxidase in erythrocytes of rats with metabolic syndrome, which contributed to a decrease in the levels of oxidative protein modification products and thiobarbituric acid reactive substances. Furthermore, the extract's ability to reduce nitric oxide synthase activity led to lower concentrations of stable nitrogen oxide metabolites (NO_2^- and NO_3^-). The present study demonstrates that yacon leaf extract possesses anti-diabetic and lipid-lowering properties, which can be beneficial for individuals suffering from or at risk of metabolic syndrome. Given the increasing prevalence of metabolic syndrome worldwide, incorporating yacon leaf extract into functional foods or dietary supplements could offer a natural, adjunctive strategy to help manage these conditions, particularly when combined with a balanced diet and lifestyle modifications.

Despite the hypoglycemic and hypolipidemic potential of yacon extract, as well as its capacity to mitigate oxidative-nitrosative stress in erythrocytes, the results obtained do not provide a comprehensive assessment of the extract's effects on the entire body. Therefore, it would be prudent for future studies to investigate the impact of this extract on organs most affected by metabolic syndrome, particularly the liver, kidneys, and heart, as well as to investigate broader range of doses, including lower doses and longer treatment periods to better understand the dose-time-response relationship. Further studies investigating bioavailability enhancement, safety evaluation, and mechanisms of action, are essential to fully assess the therapeutic potential of yacon leaf extract in MetS and other metabolic disorders.

CRediT authorship contribution statement

Mariia Nagalievska: Writing – review & editing, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Khrystyna Vilkiv:** Writing – original draft, Methodology, Investigation, Formal analysis. **Lidiya Mishchenko:** Writing – review & editing, Resources, Methodology. **Nataliia Sybirna:** Writing – review & editing, Resources, Methodology, Conceptualization.

Data availability statement

Data are available from the authors upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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