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ANTIOXIDANT AND ANTI-CYTOLYTIC ACTIVITY OF PARSNIP (*Pastinaca sativa L.*) HERB THICK EXTRACT IN CONDITIONS OF CATECHOLAMINE MYOCARDIODYSTROPHY IN RATS

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The aim: to study the antioxidant and anticytolytic activity of the parsnip herb thick extract (PHTE) in conditions of catecholamine myocardial dystrophy in rats.

Materials and methods. Catecholamine myocardial dystrophy was reproduced in rats by a single subcutaneous injection of 0.18 % adrenaline hydrochloride solution at a dose of 0.5 mg/kg (0.28 ml/kg) of body weight. The experiment used 36 white male rats with an initial weight of 220–250 g, 4–4.5 months of age. The tested drugs were PHTE at doses of 100 and 200 mg/kg and the reference drug (RD) “Tricardin” were administered intragastrically in a therapeutic and prophylactic regimen for 7 days, the last time on the day of the experiment 1 hour before the administration of cardiotoxin. The activity of the studied agents was assessed by the survival rate of the animals, the functional state of the myocardium (ECG studies), by the effect on the heart mass ratio (HMR), the activity of aspartate aminotransferase (ASAT), the level of active products interacting with thiobarbituric acid (TBA-AP) and the content of reduced glutathione (RG) in the heart homogenate.

Results. The study of the effect of PHTE on the lipid peroxidation / antioxidant protection (LPO / AOP) system showed that a pronounced antioxidant effect of the tool was found at a dose of 200 mg/kg: there was an increase in VG at the trend level ($0.05 < p < 0.10$) and a significant decrease ($p < 0.05$) the content of TBK-AP in 1.85 times compared with the group of positive control (PC). A similar effect was found in the comparison drug “Tricardin”. PHTE at a dose of 100 mg/kg was less influential. The use of PHTE in both doses and the comparison drug “Tricardin” reduced the severity of cytolytic processes: the activity of the enzyme AST – a marker of cardiocytolysis, was lower than in the PC group. PHTE at doses of 100 and 200 mg/kg contributed to a certain normalization of some ECG parameters compared to PC: a slight insignificant decrease in heart rate and a significant decrease ($p < 0.05$), QT interval, systolic index (SI) and decreased ischemia marker – ST segment displacement. The comparison drug “Tricardin” showed a similar effect to PHTE on the functional state of the myocardium in adrenaline intoxication.

Conclusions. Parsnip herb thick extract exhibits antioxidant and anticytolytic activity, improves the functional state of the myocardium, prevents a decrease in the severity of alterative processes in the organ under conditions of adrenaline myocardial dystrophy

Keywords: catecholamine (adrenal) myocardial dystrophy, parsnip herb thick extract (PHTE), antioxidant and anticytolytic activity

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1. Introduction

Cardiovascular diseases occupy a leading position in terms of mortality among other diseases. In the genesis of their development, an important place is given to stress as a risk factor, the initiation of which involves the pathogenic effects of catecholamines, namely adrenaline [1, 2]. Adrenaline has both a direct negative effect on the myocardium and mediated by significant metabolic disorders, which leads to irreversible damage to cardiomyocytes [3, 4]. Superphysiological levels of catecholamines in blood plasma, above all, contributes to the violation of myocardial lipid homeostasis and causes disruption of

lipid metabolism in the heart, which in turn enhances lipotoxicity and lipid peroxidation (LPO) [5]. Against the background of LPO intensification in the myocardium, cytolytic processes are also intensified, which leads to cardiac dysfunction. Determinant under such conditions is the state of the antioxidant system that counteracts the processes of LPO [6, 7].

Given the above, the use of antioxidants, in particular plant phenolic compounds, which inhibit the formation of free radicals and increase the activity of antioxidant protection [7, 8] in catecholamine cardiopathy, is appropriate. Promising in this regard are prepara-

tions obtained from plant raw materials of parsnip (*Pastinaca sativa* L.). Recent studies have shown that biologically active substances (including furocoumarins – remove) parsnips have the ability to dilate peripheral vessels and coronary vessels of the heart, eliminate spasms of the bronchi and smooth muscles of the abdominal cavity, have a moderate sedative effect [9, 10]. However, the antioxidant properties of biologically active substances of parsnip have been insufficiently covered in the scientific literature, in particular in catecholamine cardiomyodystrophy.

The aim of the work – study of antioxidant and anticytolytic activity of parsnip herb thick extract (PHTE) in catecholamine myocardial infarction in rats.

2. Planning (methodology) of research

Catecholamine myocardial infarction in rats is a well-reproduced model of myocardial damage, similar to that in patients with stress-induced cardiomyopathy, which is a very common cardiovascular disease [1, 2]. Given this, the study used this experimental model using the basic principles of the concept of Quality by design [11].

3. Materials and methods

The tests were conducted in the autumn of 2021. White laboratory rats obtained from the vivarium of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy, Kharkiv were selected for the study. Animals were kept in a room with controlled microclimate parameters: air temperature +18–22 °C, relative humidity 50–65 %, light regime “12 hours day / night” in accordance with the rules of laboratory animals [12]. Animals were treated in accordance with the rules of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes” [13]. The draft research plan was approved by the NUPh Bioethics Commission (Minutes No. 6 of 08.06.2021). The study was conducted in accordance with the guidelines [14], in compliance with the requirements of Good Laboratory Practice [15].

The experiment used 36 white male rats with an initial weight of 220–250 g, aged 4–4.5 months. Animals were divided into 4 groups: group 1 – intact control (IC); group 2 – positive control (PC); group 3 – animals receiving PHTE at a dose of 100 mg/kg; group 4 – animals receiving PHTE at a dose of 200 mg/kg; group 5 – animals that received the comparison drug (CD) “Tricardin” [16] (1 ml of drops contains: valerian tincture (tinctura Valerianae) (1: 5) (extractant ethanol 70 %) – 0.34 ml, hawthorn tincture (tinctura Crataegi) (1:10) (extractant ethanol 70 %) – 0.33 ml, nettle (motherwort) tincture (tinctura Leonuri) (1: 5) (extractant ethanol 70 %) - 0.33 ml, produced by LLC “Ternopharm”, Ukraine) at a dose of 5 drops/kg body weight (calculated on the total weight of animals, the number of drops of the drug was diluted with distilled water to a volume of 1 ml/1 kg, then injected the resulting liquid at a rate of 0.1 ml / 100 g body weight animals). The drug “Tricardin” was used in the dose determined by transferring from the daily dose for humans to rats using the method of Ulanova I. P. [17]. The drug “Tricardin” was chosen as a comparative drug as an analogue in pharmacological action and origin.

Parsnip herb thick extract (PHTE) was obtained by scientists of NUPh in the phytochemical laboratory under the direction of the head of the Department of Chemistry of Natural Compounds and Nutrition, Doctor of Pharmacy, prof. Kislichenko V. S.

Previous pharmacognostic analysis showed that the resulting thick extract contains phenolic compounds, including coumarins, flavonoids, hydroxycinnamic acids, as well as polysaccharides, amino acids, volatile compounds, organic acids and other biologically active substances [18, 19].

The extract is produced from the terrestrial part of *Pastinaca sativa* L. by triple fractional maceration from crushed raw materials using 70 % ethanol extractant at a raw material-extractant ratio (1:5) followed by evaporation under vacuum [18]. A “Specification” for the obtained thick extract was developed according to the following indicators: production, description, identification (phenolic compounds), weight loss during drying, quantification of polyphenolic compounds in terms of gallic acid, storage and shelf life included in the “Methods of quality control” for the obtained substance [18, 19].

In addition, we have added the following quality indicators to the updated part of the “Specification” and “Quality Control Methods” (QCM) on “Parsnip herb thick extract”, set out in version II: solubility, total ash, heavy metals and microbiological purity

In accordance with the requirements of the developed QCM on parsnip herb thick extract (*Pastinacae sativae herbae extractum spissum*) plant substance is a viscous mass of brown color with a fragrant odor, which is easily soluble in water, soluble in ethanol, practically insoluble in glycerol plants and mineral and insoluble in chloroform and ethyl acetate.

Identification of phenolic compounds was performed by TLC. As the mobile phase was used: ethyl acetate P-acetic acid P-formic acid P-water P (100:11:11:25). Hyperoside was identified in the PHTE by the presence of a comparison solution of the fluorescent yellow-brown zone in PHTE, and chlorogenic acid by the presence of a blue fluorescent zone [19].

The weight loss during drying in the studied samples of the thick extract is 22.0 %; total ash – 7.8 %; heavy metal content – 0.001 % (1000 ppm), which corresponds to the established standards specified in the developed regulations. The substance also passes the test for microbiological purity. The total number of aerobic microorganisms (TAMC) is not more than 10⁴ CFU/g. The total number of yeasts and molds (TYMC) is not more than 10² CFU/g. No more than 10² tolerant to bile gram-negative bacteria in 1.0 g. Absence of *Salmonella* in 25.0 g. Absence of *E. coli* in 1.0 g.

According to the results obtained on the study of solubility in the obtained samples of PHTE (Table 1) and determination of dry residue and pH level (Table 2), it should be concluded that PHTE has a pronounced hydrophilic nature: practically insoluble in hexane, petroleum ether, chloroform, mineral and vegetable oils, ethanol; easily soluble in purified water, water-alcohol mixtures (40–70 % alcohol), glycerin, propylene glycols, PEO-400.

Table 1

The results of the study of the solubility of experimental samples of PHTE

No.	The name of the solvent	PHTE solubility
1	Hexane	Practically insoluble
2	Chloroform	Practically insoluble
3	Petroleum ether	Practically insoluble
4	Glycerin	Practically insoluble
5	Vaseline oil	Practically insoluble
6	Vegetable oils	Practically insoluble
7	Purified water	Easily soluble
8	Ethanol 96 % v/v	Soluble
9	Ethanol 70 % v/v	Easily soluble
10	Ethanol 40 % v/v	Easily soluble
11	Propylene glycol	Easily soluble
12	PEO-400	Easily soluble

According to the results of determining the dry residue in the plant substance PHTE (Table 2), it was found that this indicator ranges from 76 to 80 %, which meets the requirements of the general monograph “Extracts” SPbU [20].

The results of the study of the pH of the PHTE solution (Table 2) showed that the pH is in the range from 4.70 to 6.30 depending on the series of the drug. The

content of heavy metals in the studied series of PHTE is less than 0.01 %, which also meets the requirements of SPbU [20]. According to the results of quantitative determination, the content of polyphenolic compounds in the studied PHTE samples is 10.5 %.

PHTE samples were used at doses of 100 and 200 mg/kg, for which the ability to normalize heart rate in adrenaline was found in previous studies [21].

Table 2

Dry residue content and pH level in experimental and industrial samples of plant substance PHTE

No. PHTE sample	Dry residue, %	pH
011020	76.23±1.24	5.70±0.08
021020	78.25±1.45	6.20±0.02
031020	79.12±1.09	6.30±0.04
041020	77.82±1.51	4.70±0.01
051020	78.56±1.35	5.90±0.05

The study drugs were administered intragastrically in the treatment-and-prophylactic mode for 7 days, the last time on the day of the experiment 1 hour before the introduction of cardiotoxin. Pathology was reproduced in all experimental rats except the intact control group. Adrenaline-induced pathology was initiated by a single subcutaneous injection of 0.18 % solution of epinephrine hydrochloride at a dose of 0.5 mg/kg (0.28 ml/kg) of body weight [22].

The effect on the myocardium of cardiotoxin and the studied drugs was evaluated by the survival of animals, the functional state of the myocardium (ECG study), the effect on the relative coefficient of body mass (BM) of the heart by the formula:

$$\text{Heart BM} = (m_{\text{organ}} (\text{g}) / M_{\text{animal}} (\text{g})) \times 100 \%$$

and biochemical parameters in blood serum and heart homogenate. After 24 hours of administration of epinephrine hydrochloride in animals under mild chloroform anesthesia, cardiovascular performance was recorded using an EC1T 03M electrocardiograph, after which they were removed from the experiment by euthanasia.

In the homogenate of the heart was determined by the activity of the marker enzyme cardiocytolysis - aspartate aminotransferase (AST) using the Lachema test kit (Czech Republic). The cardioprotective effect of the drugs was also evaluated by the effect on lipid peroxidation

(LPO) and antioxidant protection (AOP): the level of active products that interact with thiobarbituric acid (TBA) [23] and the content of reduced glutathione (RG) [24].

Performance indicators of the cardiovascular system were recorded using an electrocardiograph EK1T 03M in the II standard lead. The following indicators were taken into account when interpreting the electrocardiogram: R-R – duration of the complete cardiac cycle; the duration of the interval P-Q, which characterizes the atrioventricular conduction; duration of ventricular QRS complex and electrical ventricular systole – QT interval; voltage of teeth P, T and R. Calculated the following indicators: heart rate (heart rate, beats / min) as the ratio of time (60 s) to the duration of the cardiac cycle RR and systolic index (SP) as the ratio of the duration of the QT interval to the duration of the cardiac cycle RR (QT/RR, %) [14].

Experimental data were processed by methods of variation statistics (mean value and its standard error, $M \pm m$) using parametric (one-way analysis of variance ANOVA) and nonparametric methods of analysis (Kruskal-Wallis test). Accepted significance level $p < 0.05$. The standard STATISTICA software package (version 6) was used to obtain statistical conclusions.

4. Results

When modeling the pathology as a result of subcutaneous adrenaline, one rat from the PC group died, the

survival rate of animals in this group was 86 %, which is consistent with the literature [25]. According to the data (Table 3), it could be argued that the surviving PC animals developed myocardial infarction, characterized by changes in many indicators of the cardiovascular system, determined by ECG 24 hours after the initiation of pathology.

The development of cytolytic processes in the myocardium of PC rats was accompanied by a significant increase in 1.62 times the level of the marker enzyme cytolysis AST in the serum relative to group IC (Table 3). Probable increase in heart rate indicates the development

of myocardial infarction, accompanied by increased alternative processes, tissue damage, destruction of myocardial cells [26, 27]. An imbalance in the lipid peroxidation system / antioxidant protection (LPO/AOP) was observed in the myocardial tissues of PC animals, as evidenced by a significant ($p < 0.05$) increase in TBA content by 1.8 times compared to IC. Statistically significant in comparison with the IC group 2.26-fold decrease in the level of RG in the heart tissue indicate the depletion of antioxidant protection in the case of adrenaline-induced pathology (Table 4).

Table 3

The effect of PHTE and the comparison drug “Tricardin” on the course of adrenaline myocardial infarction in rats (M±m)

Indicators	Study conditions				
	Intact control (n=6)	Positive control (n=5)	PHTE, 100 mg/kg (n=6)	PHTE, 200 mg/kg (n=6)	Tricardin, 5 drops/kg (n=6)
Survival, %	100	86	100	100	100
Heart MK, %	0.31±0.01	0.37±0.01*	0.35±0.01t*	0.32±0.01**	0.35±0.01t*
serum					
AST, mmol/(h•l)	1.67±0.08	2.71±0.22*	2.30±0.06*/**	2.10±0.09*/**	2.19±0.12*/**
homogenate of the heart					
RG, μmol/g	3.16±0.71	1.40±0.21 *	2.52±0.22	2.80±0.22t**	2.34±0.21t**
TBA, μmol/g	28.63±1.19	51.79±3.70*	46.58±1.03*/**/#	27.99±2.30**	31.84±2.46**

Note: * – differences are significant compared to intact control, $p < 0.05$; ** – differences are significant compared to the positive control, $p < 0.05$; *** – differences are significant compared to PHTE at a dose of 200 mg/kg, $p < 0.05$; # – differences are significant compared to CD “Tricardin”, $p < 0.05$; t – the tendency to probable changes, $0.05 < p < 0.10$

The study of ECG parameters (Table 4) showed that animals from the PC group had a slight increase in heart rate ($p > 0.05$) against IC, and statistically significant according to the IC group increase in SP (64.07±1.92 % vs. 42.84±1.92 %, $p < 0.05$), as well as a decrease in the QRS interval (0.013±0.001 s vs. 0.017±0.001 s, $p < 0.05$), an increase in the QT interval (0.086±0.004 s vs. 0.063±0.002 s, $p < 0.05$) and significant changes in the marker of myocardial ischemia – ST segment (0.050±0.003 s vs. 0.024±0.004 s, $p < 0.05$) were detected.

Such changes in ECG parameters do not correspond to the classical picture of the pacing effect of adrenaline but have a basis for explanation. It is known that at physiological (moderate) concentrations adrenaline acts on ventricular cardiomyocytes through the activation of β_2 -adrenoceptors and has a positive inotropic (increased strength of heart rate) and chronotropic (increased heart rate) effect. This effect of adrenaline is

realized through the activation of the cascade of reactions that are triggered during the conformation of Gs (stimulating) membrane protein. At high concentrations, adrenaline, namely those used in the experiment, is a traumatic agent, causing spasm of myocardial vessels, contributing to the development of ischemia, as evidenced by a significant displacement of the ST segment. It is known that in the affected myocardium significantly increases the density and activity of membrane Gi (inhibitory) protein compared to Gs (stimulating) protein. Against this background, the hormone-receptor complex Gs- β_2 -adrenoceptors-Gi blocks L-type calcium channels, leading to adverse heart reactions: decreased amplitude of the QRS complex, prolongation of the QT interval, indicating a decrease in myocardial excitability [28].

Thus, the established changes in the activity of the heart are a consequence of the cardiotoxic effects of adrenaline and the development of ischemia in PC rats.

Table 4

The effect of PHTE and the comparison drug “Tricardin” on the functional state of the myocardium in rats with a model of adrenaline myocardial infarction (M±m)

Indicators	Умови досліджу				
	Intact control (n=6)	Positive control (n=6)	PHTE, 100 mg/kg (n=6)	PHTE, 200 mg/kg (n=6)	Tricardin, 5 drops/kg (n=6)
HR, bts/min	405.36±8.34	448.35±8.08	421.11±14.54	415.61±12.36	427.20±17.31
SP, %	42.84±1.92	64.07±1.92*	53.67±1.72*/**	49.76±2.98t*/**	53.69±3.63*/**
QT, c	0.063±0.002	0.086±0.004*	0.077±0.002*/**	0.072±0.003*/**	0.075±0.002*/**
PQ, c	0.046±0.002	0.048±0.004	0.047±0.003	0.045±0.002	0.047±0.002
QRS, c	0.017±0.001	0.013±0.001*	0.015±0.001t*	0.016±0.001t*	0.015±0.001
R, mV	0.54±0.03	0.67±0.02	0.55±0.04t**	0.49±0.03**	0.60±0.06
P, mV	0.06±0.01	0.11±0.01	0.10±0.02	0.08±0.02	0.063±0.01
T, mV	0.13±0.02	0.20±0.03	0.17±0.01	0.14±0.02	0.18±0.02
Offset ST, s	0.024±0.004	0.050±0.003*	0.035±0.004**	0.030±0.005**	0.037±0.003**

Note: * – differences are significant compared with the IC group, $p < 0.05$; ** – differences are significant compared to the PC group, $p < 0.05$; *** – differences are significant compared to the group CD “Tricardin”, $p < 0.05$; t – the tendency to probable changes, $0.05 < p < 0.1$

Under the influence of PHTE at doses of 100 and 200 mg/kg, some normalization of some ECG parameters compared to PC was observed: slight insignificant decrease in heart rate and significant decrease ($p < 0.05$) in QT interval, which characterizes ventricular systole 0.077 ± 0.002 s and 0.072 , respectively. ± 0.003 s against 0.086 ± 0.004 s in the PC group), which contributed to a significant decrease in the rate of SP (respectively 53.67 ± 1.72 % and 49.76 ± 2.98 % against 64.07 ± 1.92 % in the PC group), and the positive dynamics before the normalization of the tooth R. PHTE in both doses contributed to a decrease in the displacement of the ST segment (respectively 0.035 ± 0.004 s (at a dose of 100 mg/kg) and 0.030 ± 0.005 (at a dose of 200 mg/kg) against 0.050 ± 0.003 in the PC group), which indicates its ability to reduce the cardiotoxic effects of adrenaline and the severity of ischemia. The comparison drug "Tricardin" showed a similar effect to PHTE on the functional state of the myocardium in adrenaline intoxication.

Significant ($p < 0.05$) reduction of cardiac BM occurred against the background of PHTE at a dose of 200 mg/kg, which indicates a decrease in the severity of alternative processes in the body. Under the influence of PHTE at a dose of 100 mg/kg and the comparison drug, an increase in cardiac BM was observed compared with intact control at the trend level ($0.05 < p < 0.1$), which was almost at the PC level. The use of PHTE in both doses and the comparison drug "Tricardin" reduced the severity of cytolytic processes: the activity of the enzyme AST – a marker of cardiocytolysis, was lower than in the PC group: respectively 2.30 ± 0.06 mmol/(h•l) under the influence of PHTE at a dose of 100 mg/kg and 2.10 ± 0.09 /(h•l) under the influence of PHTE at a dose of 200 mg/kg and 2.19 ± 0.12 under the influence of CD against 2.71 ± 0.22 mmol/(h•l) in the PC group.

A study of the effect of PHTE on the LPO/AOP system showed that the drug showed a more pronounced antioxidant effect at a dose of 200 mg/kg: there was a tendency to increase RG levels and a significant decrease in TBA in 1.85 times compared to the PC group. A similar effect was found in the comparison drug "Tricardin". PHTE at a dose of 100 mg/kg was less effective. It is obvious that the containment of disorders in the LPO/AOP system affected the functional state of the myocardium: under the influence of PHTE there is a tendency to decrease heart rate and a significant decrease in systolic index compared to the PC group.

5. Discussion of research results

It is known that adrenaline in high doses has an excessive stimulating effect on the myocardium, which leads to increased oxygen demand, hypoxia, ischemia, disorders of plastic and energy metabolism in the myocardium [3, 4]. Violations of lipid metabolism in the myocardium, increased lipotoxicity [5], which creates conditions for disruption in the LPO / AOP system [6, 7], as evidenced by increased TBA LPO and decreased levels of the antioxidant system RG in the myocardium of rats from PC.

Phenolic compounds of plants are known antioxidants and show cytoprotective activity [26, 27]. Our results allow us to assert the pronounced anticytolytic

and antioxidant properties of PHTE, as evidenced by a decrease in the marker of cytolysis of AST and LPO/TBA products and an increase in RG concentration in rats with a model of adrenaline myocardial infarction. The anticytolytic and antioxidant properties of PHTE were more pronounced at a dose of 200 mg/kg. The described dynamics of the studied parameters along with the normalization of heart rate and functional state of the heart proves the effectiveness of PHTE in catecholamine-induced heart disease, in particular those occurring under stress, as stress is accompanied by increased levels of catecholamine adrenaline [1, 2].

The comparison drug "Tricardin" had a similar effect to PHTE on cytolytic processes and the state of the LPO/AOC system in the myocardium. Biologically active substances contained in the roots and rhizomes of valerian (ester of borneol and isovaleric acid, borneol, isovaleric acid, alkaloids, tannins, sugars), reduce the excitability of the CNS, reduce stress and irritability in the psyche, hypnotic, antispasmodic properties. Biologically active substances contained in the herb nettle (essential oil) (essential oil, saponins, tannins, alkaloids), reduce the processes of excitation in the CNS, contribute to the normalization of blood pressure. Biologically active substances contained in hawthorn fruits (flavonoids, choline, acetylcholine, tannins, phytosterols) have anti-hypertensive, cardioprotective, antispasmodic properties; increase blood circulation in coronary vessels and cerebral vessels, increase the contraction of the heart muscle and at the same time reduce its excitability [16].

The established anticytolytic, antioxidant and cardioprotective properties of the obtained parsnip of sowing grass extract justify the relevance of its further study in order to create on its basis drugs of cardioprotective action.

Study limitations. Only LPO products were studied in the experiment, but the evaluation of protein oxidation products, which are also markers of cardiomyocyte damage, is also relevant.

Prospects for further research. In the future it is planned to study the level of protein oxidation products as markers of cardiomyocyte damage in catecholamine myocardial infarction.

6. Conclusions

1. Pasternak grass seed extract is a thick extract under the conditions of therapeutic and prophylactic administration to rats with a model of adrenaline myocardial infarction exhibits antioxidant and anticytolytic activity, which improves myocardial function and reduces the severity of alternative processes in the body.

2. The severity of the cardioprotective effect of PHTE at a dose of 200 mg/kg is not inferior to the comparison drug "Tricardin".

Conflict of interests

The authors declare that they have no conflicts of interest.

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