Paper checking result

No	Parameter	Decision	Person in Charge	Comments
1	**Structure of Paper**	OK		
2.	**Title**	OK		
3.	**Abstract**	Revision	Author, (It could be help by clinical journal team if using our publication assistance)	Excessive words.
4.	**Keywords**	OK		
5.	**Introduction**	Revision	Author	Give a brief (suspected) key component of OleoprenCardio drug in introduction part.
6.	**Methods**	Revision	Author	Lack of patients detail, data collecting and analysis methods. See comments for the details.
7.	**Results**	Revision	Author (It could be help by clinical journal team if using our publication assistance)	Table serving, numbering and caption
8.	**Discussion**	Revision	Author (It could be help by clinical journal team if using our publication assistance)	Is not a real discussion part. Mention about treatments of CVD in the discussion section and the mechanism of OleoprenCardio in the treatment.
9.	**Conclusion**	Revision	Author	Missing conclusion in the main text
10.	**References**	OK		

*Please check comment on the manuscript

HIGHLY-EFFICIENT POLYPRENOL-BASED NATURAL COMPLEX FOR CARDIOVASCULAR SYSTEM RECOVERY

Keywords: BAA, prescription composition, quality, safety, regulated indicators, functional properties, efficiency

Abstract.

Scope of application: prevention and treatment of patients suffering from dyslipidemia and stage 1-2 hypertensive disease.

Objective: determine the regulated indicators of quality, including nutritional value; determine the effectiveness and functional focus of the Oleopren Cardio biologically active additive (BAA).

Methods and results: 60 patients suffering from dyslipidemia and stage 1-2 hypertensive disease were observed. All patients under study received OleoprenCardio BAA at a dosage of 1 capsule, 2 times a day, for 30 days (OC group) alongside complex classical treatment (statins, hypotensive drugs, diuretics). 30 people with a similar pathology did not receive the BAA and served as a comparison group (control group). The average age of the patients was 56.8 ± 5.3 years.

As a result of the studies, we obtained positive dynamics of the following quality of life indicators: vigor, pain, emotional state, sleep, social isolation, and physical activity. Quality of life was statistically significantly lower in the control group by the indicators vigor, pain, emotional state, physical activity and total score. The best results were noted in the patients taking OleoprenCardio BAA.

The differences between the comparison parameters were considered statistically dissimilar at $p \leq 0.05$. Full-scale tests were carried out in accordance with the principles of the Helsinki Declaration of the World Medical Association (as amended in 2000, with explanations given at the WMA General Assembly, Tokyo, 2004), the rules of the Quality Clinical Practice of the International Conference on Harmonization (ICS OCR), ethical principles laid down in EU Directive 2001/20 / EC and the requirements of Russian legislation. Each patient signed an informed consent form to participate in the research.

The tests were carried out at the central research laboratory of Kemerovo State Medical University and the day patient department of Municipal Clinical Hospital No. 2 in Kemerovo.

Diagnoses were made based on the patients' history, the results of physical examination, and laboratory and instrumental examination methods.

The intensity of subjective ailments was assessed using the Giessen "Pressure of Somatic Complaints" questionnaire developed at the psychosomatic clinic of Giessen University (Germany). The questionnaire reveals the intensity of

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emotionally-tinged complaints of physical health which correlate with masked depression. Using the questionnaire, the total indices of the ailments on the following scales are calculated: "exhaustion"; "gastric complaints"; "pains in various parts of the body" or "rheumatic factor"; and "heart complaints". The effectiveness of treatment was assessed by the immediate results after 30 days of treatment.

Conclusions: Complex treatment of patients suffering from dyslipidemia and hypertensive disease of stage 1-2 using OleoprenCardio BAA favorably influences the clinical manifestations of the disease.

OleoprenCardio BAA is well tolerated by patients and does not cause any side effects.

1. Introduction

Nutrition plays an important role in the prevention and comprehensive treatment of various diseases. Priority is given to natural biologically active complexes. They are not inferior in terms of efficacy to the effects of drugs and lack the negative consequences that can be observed when using drugs obtained by chemical synthesis [1,2,8,9,13].

Cardiovascular diseases (CVD), which remain the root cause of disability and mortality, occupy the first place by the prevalence among the population of economically developed countries. The wide spread of cardiovascular diseases makes it necessary to talk about the CVD epidemic - a penalty for the negative processes that accompany the progress and development of civilization. The growth of heart and vascular diseases is typical for highly developed industrial countries, which is associated with such factors as population concentrtion in cities (urbanization), changes in the rhythm of life and the nature of work, increased emotional tension, violation of rational and balanced nutrition principles, and restriction of physical activity.

According to the World Health Organization (WHO), in 2006, 17.5 million people died of CVD worldwide (30% of all the diseases) and that figure has continued to grow over the last 10 years. The primary cause of death is ischemic heart disease (IHD) - 12.2%, followed by cerebrovascular pathology - 9.7%. According to the WHO prognosis, by 2030 the death rate from IHD will increase by 30%. Today, this disease has gained new strength. In Russia, CVD mortality is 56% of total mortality - 940 thousand people. [3-6].

Two important components of preventive measures is dietary correction and observing food culture. It is necessary to inform the population about a healthy lifestyle: balanced, rational nutrition; physical activity; and bad habits (alcohol, smoking, etc.).

The accumulated domestic and international experience shows that one of the most available and effective ways to reduce the negative impact of most risk factors for the development and poor outcome of these diseases is supplementing the diet with specialized products, including biologically active additives with targeted functional properties [7, 11, 12 , 14-19].

2. Material and Methods

The OleoprenCardio poleprenol-based complex biologically active additive was developed for cardiovascular system recovery. The prescription composition of the specialized product is scientifically justified by evaluating the pharmacological orientation and synergistic properties of the active characteristics of the raw components:

Polyprenols are biologically active components extracted from needles of pine, fir, spruce and other plant sources. Their high effectiveness associated with the correction of metabolic disorders, and prevention and treatment of various diseases has been proven in numerous studies by domestic and foreign authors. At the same time, most pathological conditions are connected with a disruption of the normal functioning of the dolicholphosphate cycle (DPhC) at the cell membrane level, which is accompanied by an increase in the output of dolichol from the body and the development of their deficiency. In turn, dolichols occupy key positions in the DPhC, providing biosynthesis of glycoproteins and gucoaminoglucans, the process of glycolizing membrane proteins, preventing their protolysis. Dolichol level can be recovered through dietary supplementation with specialized products containing plant polyprenols, which are biotransformed in the liver into dolichols.

Due to polyprenols and the support of the dolicholphosphate path for cell repair and stabilization of cell membranes, this product stimulates the regenerative potential of the myocardium and vascular wall cells.

Lycopene. Normalizes cholesterol metabolism, prevents the development of atherosclerosis, strengthens blood vessel and capillary walls. Its antioxidant properties help prevent the oxidation of low-level lipoprotein, that is, "bad cholesterol", which leads to atherosclerosis and coronary artery disease. Unlike other carotenoids, lycopene is characterized by a stable content level in blood when the organism is exposed to alcohol and tobacco.

L – Carnitin. In the mitochondrial membrane, carnitin receives the fatty acid from coenzyme A and transfers it through the inner membrane, passing the acid to another molecule of coenzyme A. This biochemical relay enables the cell energy exchange and normal functioning of the cardiovascular system, as well as other body systems.

Coenzyme Q10 (ubiquinone). The discovery of the role of ubiquinone in the electron transfer chain, i.e., its energy-forming functions, was awarded with the Nobel Prize. Iin ATP synthesis, at the final stage of substrate oxidation, the

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What were the inclusion and exclusion criteria?
How was the sample size generated?
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electrons are transferred from the mitochondrial matrix to the intermembrane space through the respiratory chain to oxygen by means of Q10.

Being a vitamin-like substance, ubiquinone has another important function. It is an antioxidant - it catches free radicals, preventing destructive oxidation processes. Another indirect antioxidant effect is the prevention of the formation of phenoxyl radicals, alpha-tocopherol, and, consequently, the prevention of its possible prooxidant effect.

Coenzyme Q is synthesized by the human body in the endoplasmic reticulum and Golgi apparatus. It can be regenerated from the oxidized form, which distinguishes it from other antioxidants, including vitamins (E, C, beta-carotene).

Tocopherol acetate is a fat-soluble form of vitamin E, which has synergistic antioxidant properties with ubiquinone.

Analysis of the pharmacological characteristics and synergistic properties of the initial components made it possible to develop the quantitative and qualitative composition of the BAA formula (Table 2.1).

Table 2.1. Formulation of OleoprenCardio BAA

#	Component name	Content, mg/1 capsule	Content, mg/2 capsules	% of the recommended daily intake in 2 capsules
1	**L-Carnitin**	**22.5**	**45**	15
2	**Polyprenols 75 % mixture** *Sum of polyprenols*	**6.7** *5*	**13.4** *10*	100
3	**Lycopene 10%** *Lycopene*	**6.25** *0.625*	**12.5** *1.25*	25
4	**Tocopherol acetate 98%** *Tocopherol acetate*	**3.83** *3.75*	**7.65** *7.5*	50
5	**Coenzyme Q10**	**3.75**	**7.5**	25

The BAA is a soft, red gelatin capsule with a specific taste and odor. Sediment is possible inside the capsule. The average weight is 790 mg (711-869).

The content of toxic elements, pesticides, and microbiological contamination was studied according to the requirements of the normative documentation [10]. Pathogenic microorganisms, including salmonella, were not detected. The results of sanitary and toxicological studies are presented in Table 2.2 and show the hygenic safety of the product.

Table 2.2. Safety indicators of OleoprenCardio BAA (averaged indicators, n = 6).

Indicator name		Content, mg/kg, no more than	
		Rated value	Actual content
Toxic elements	Lead	0.1	0.02
	Arsenic	0.1	0.03
	Cadmium	0.05	0.01
	Mercury	0.05	Not detected
	Iron	1.5*	0.09
	Copper	0.1	0.07

Continuation of table 2.2.

Indicator name		Content, mg/kg, no more than	
		Rated value	Actual content
Pesticides	HCCH (sum of isomers)	0.05	Not detected
	DDT and its metabolites	0.1	Not detected
	Heptachlor	not allowed (<0.002)	Not detected
	Aldrin	not allowed (<0.002)	Not detected

Upon expiry of the storage period, the peroxide content of the capsule (without the capsule coating) was determined at 4 mmol of active Q_2/kg (norm 10). The acid number of the refined sunflower oil used as the source raw material was 0.3 mg/KOH/g (permissible - no more than 0.6).

The obtained data made it possible to set a sell-by period of 24 months under the above-mentioned conditions with the necessary safety margin of three months.

We determined the regulated indicators of nutritional value (Table 2, 3).

Table 2.3. Nutritional value of OleoprenCardio BAA

Name of indicator	**Content of characteristics**
Coenzyme Q10, mg	3.75 (from 3.0 to 4.5)
L-carnitin, mg	22.5 (from 18 to 27)
Lycopene, mkg	625 (from 500 to 750)
Vitamin E, mg	3.75 (from 2.6 to 4.9)
Polyprenols, mg, no less than	5.0

Nutrient composition per g/100 g of the dry product was determined at: carbohydrates - 0; proteins - 21; fats - 68; sugar alcohols (excluding erythritol) - 6. The energy value is 710 kcal.

Due to the pharmacological characteristics and synergistic properties of the formulation components and their acting principles, the specialized product helps maintain the integrity of the vascular wall, reduce the level of lipoproteins of low

and very low density, has an anti-aggregation effect, protects the myocardium cells from the damaging effect of free radicals, and activates the regeneration and restoration of cardiac muscle function (after heart attacks or surgical interventions). The BAA feeds the myocardium by delivering long-chain fatty acids to the mitochondria of cardiocytes. It stimulates the regenerative potential of the myocardium and vascular wall cells (activation of membrane repair and protection of young cardiocytes) due to polyprenols and the support of the dolicholphosphate path for cell regeneration and stabilization of cell membranes. Overall, the functional properties of the specialized product are aimed at:

- restoring and stabilizing the membranes of cardiocytes and vascular wall cells, reducing cytolysis and cell death, inhibiting myocardial ischemia;
- blocking oxidative stress, reducing the damaging effect of free radicals, cytolysis, and cell death on the cell, increasing the blood supply and energy supply of the myocardium;
- stimulating the growth and protection of young cardiocytes, improving the nutrition and providing the energy potential of the heart muscle.

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3. Results

We carried out clinical studies on the efficacy and functional orientation of the developed product.

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Prior to treatment, patients presented a variety of complaints: general weakness and increased fatigue, headaches, memory loss, depression, and sleep disorders. The anamnesis included dyslipidemia - an increase of total cholesterol, triglycerides, and low-density lipoproteins. All the patients had established diagnoses of hypertensive disease and dyslipidemia over a period of 6 months.

30 days after the treatment, positive dynamics were observed in most clinical symptoms in both groups. A positive clinical effect was recorded for patients who had been treated and took OleoprenCardio BAA for the following symptoms: weakness, headaches, sleep disorders, memory impairment, and dizziness. Upon evaluation of the immediate treatment results, statistically significant differences in clinical data were seen between the patients in the control and the OC groups: headaches were several times less frequent in the patients in the OC group and the dynamics of such indicators as general weakness, dizziness, and memory state were more favorable.

In the course of treatment, the indicators for all scales of psychosomatic complaints of the Giessen questionnaire were characterized by a significant decrease in pressure of complaints, which was more eminent in the patients taking dietary therapy in addition to classical treatment. The results of the study are presented in Table 3.1.

Table 3.1. Pressure of somatic complaints according to the Giessen questionnaire in patients suffering from dyslipidemia and stage 1-2 hypertensive disease in the control and OC groups

Indicator	Before the treatment, points	30 days after the treatment, points	
		control, p=30	OK, p =30
Fatigue	13.9±0.4	8.1+0.7*	6.9+0.8*
Gastric complaints	8.9±1.2	7.3+0.9	6.7+0.9
Pain in different parts of the body	11.6±2.3	9.3±1.3	7.2+0.9
Heart complaints	21.3±1.2	15.3+0.7*	9.2+0.9*
Pressure (intensity) of complaints	55.7+2.2	40.0+1.3*	30.0+1.6*

Note: * - the differences are reliable compared to pre-treatment results at P<0.05.

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Table 3.2 presents the results of a point assessment of the quality of life of both patient groups.

Table 3.2. Quality of life of patients suffering from dyslipidemia and stage 1-2 hypertensive disease in the control and OC groups

Indicator	Before the treatment, points	30 days after the treatment, points	
		control, p=30	OK, p=30
Vitality	56.9±0.8	44.5+1.1	31.6+0.7*
Pain	89.3±1.6	62.1+1.0*	49.5+1.2*
Emotional state	46.3±1.0	32.3+1.4	28.6+1.3*
Sleep	76.3+1.1	52.1+0.8*	42.6+0.9*
Social isolation	34.6+1.4	26.5+1.2	25.1+1.1*
Physical activity	69.8+1.6	46.1+1.0*	33.2+0.9*
Total score	373.2+4.2	263.6+4.0*	210.6+3.7*

Note: * - the differences are reliable compared to pre-treatment results at P<0.05

Добавлено примечание ([A8]): What is control and what is OK group?

The stages in the dynamics of lowering the levels of total cholesterol, triglycerides, and the atherogenic index in the control group were 5.0%, 18.5%, and 11.5%, respectively. Additional intake of OleoprenCardio BAA strengthened the lipid-lowering effect of statins: the above indicators were 10.0%, 29.0% and 20.0%, respectively (Table 3.3).

Table 3.3. Lipidogram indices in patients suffering from dyslipidemia and

stage 1-2 hypertensive disease in the control and OC groups.

Indicator	Before treatment, points	30 days after treatment, points	
		control, p=30	OC, p=30
Total cholesterol, mmol/l	6.5+0.4	6.2+0.7 (5%)	5.9+0.5 (10%)*
Low-density lipoproteins, mmol/l	3.5+0.8	2.9+0.7	2.6+0.3 *
High-density lipoproteins, mmol/l	1.42+0.7	1.53+0.3	1.57+0.6
Triglycerides (TG), mmol/l	3.8+01	3.1 ±0.3 (18.5%)	2.7+0.5
Atherogenicity coefficient	3.5+0.3	3.1+0.5 (11.5%)	2.8+0.4

Note: * - the differences are reliable compared to pre-treatment results at P<0.05

By the end of the observation period, the blood pressure in the control group decreased: SBP by 5.3 mm Hg, DBP by 4.1 mm Hg, and in the OC group: by 6.8 and 5.4 mm Hg, respectively, which also shows the positive effect of the specialized product on blood pressure level.

We conclude that the product stimulates the regenerative potential of the myocardium and vascular wall cells due to polyprenols and the support of the dolicholphosphate path for the cell repair and stabilization of cell membranes.

4. Discussion

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The obtained materials give justification for recommending OleoprenCardio BAA as an additional factor for increasing the body's resistance to adverse environmental effects, stressful situations, psycho-emotional and physical stress, and for the prevention of dyslipidemia and hypertension.

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The recommended dosing scheme is 1 capsule 2 times a day for 30 days. Similar courses of the BAA intake should be repeated at least twice a year to prevent dyslipidemia and arterial hypertension and in cases of adverse environmental effects, hypodynamia, increased psychoemotional stress, and stressful situations.

The product formulation and technology have been tested in the production facilities at the company ArtLife (Tomsk). The stability of consumer properties, including the functional properties of the developed product, is ensured by the quality and safety management system implemented at the company's enterprises per the requirements of the ISO 9001 and 22000 international standards and the GMP rules.

Contribution of the Authors

M.M. Shamova[1] – research;
A.N. Astrievsky[1] – research;
N.A. Pleshkova[2] – research;
A.D. Toshev[2] – analysis of obtained results;
B.M. Kisimov[2] – analysis of obtained results;
V.M. Poznyakovskiy[2] – research advisor.

Conflict of interests

The authors state that they do not have competing interests.

References

1. Avstrievskikh, A.N. Healthy food products: new technologies, quality assurance, application efficiency/A.N. Avstrievskikh, A.A. Vekovtsev, V.M. Poznyakovskiy. - Novosibirsk: publishing house of Siberian University, 2005.- 416p.
2. Gerasimenko, N.F. Healthy nutrition and its role in ensuring the life quality / N.F. Gerasimenko, V.M. Poznyakovskiy, N.G. Chelnakov // Technologies of the Food and Processing Industry of the Agroindustrial Complex – Healthy Products. - 2016. - No.4 (12). - P. 52-57.
3. Demographic Yearbook of Russia. 2015. Statistical compilation. / M: Rosstat, 2015. - 727 p.
4. Health of Russia: Atlas / Edited by L.A. Bokeria. 8th ed. - M.: A.N. Bakoulev Scientific Center for Cardiovascular Surgery of the Russian Academy of Medical Sciences, 2012. - 408 p.
5. Kochetkova, A.A. Theoretical and practical aspects of the development of specialized food products for diet therapy of cardiovascular diseases. Kochetkova, V.M. Vorobyova, I.S. Vorob'ev et al. // Food Industry. - 2016. - № 8. - P.8-12.
6. Pogozheva, A.V. Diet therapy of cardiovascular diseases. General principles/ A. V. Pogozheva, A. R. Bogdanov, S. A. Derbeneva // Practical Dietology. - 2015. - No. 4 (16). - P. 36-40.
7. Poznyakovskiy, V.M. Food ingredients and biologically active additives / B.M. Poznyakovskiy, O.V. Chugunova, M.Yu. Tamova. - Moscow: INFRA-M, 2017. - 143 p.
8. The policy of healthy eating. Federal and regional levels / V.I. Pokrovsky, G.A. Romanenko, V.A. V.A. Knyazhev, N.F. Gerasemenko, G.G. Onischenko, V.A. Tutelyan, V.M. Poznyakovsky. - Novosibirsk: Publishing house of Siberian University, 2002. - 344 p.

9. Order of the RF Government No. 559-r of 25.10.10 "Fundamentals of the State Policy of the Russian Federation in the Field of Healthy Nutrition of the Population for the Period till 2020".

10. Technology Regulations TS 027/2012 "On the safety of certain types of specialized food products, including dietary, therapeutic and dietary preventive nutrition".

11. Tutelyan, V.A. Biologically active components of cardiac patients' nutrition/V. A. Tutelyan, A. V. Pogozhev, A. K. Baturin. // M .: SvR-ARGUS, 2012. - 380 p.

12. Decree of the President of the Russian Federation of 01.12.2016, No. 642 "On the Strategy of Scientific and Technological Development of the Russian Federation"

13. Chereshnev, V.A. Problems of food safety: national and international aspects / V.A. Chereshnev, V.M. Poznyakovskiy // Food Industry. - 2016. - No. 1 (1). - P.6-14.

14. Shevchenko, V.P. Clinical Dietology/V. P. Shevchenko. - Moscow: GEOTAR-Media, 2014. - 256 p.

15. Kromhout, D. Omega-3 fatty acids and cardiovascular events after myocardial infarction/D. Kromhout [et al.] // N. Engl. J. Med. - 2010. - Vol. 363 (21). - P. 2015-2026.

16. Lazarus, S. Tomato extract inhibits human platelet aggregation in vitro without increasing basal cAMP levels/S. Lazarus, M. Garg // Int. J. Food Sci. Nutr. - 2004. - Vol. 55. P. 249-256.

17. Lee, J. H. Omega-3 fatty acids for cardioprotection/J. H. Lee, H. O'Keefe, C. J. Lavie et al. // Mayo Clin. Proc. - 2008. - Vol. 83. - P. 324-332.

18. Singh, R. B. Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction/R. B. Singh., N. S. Neki // Mol. Cll. Biochem. - 2003. - Vol. 264 (1-2). - P. 75-82.

19. Yamamoto, J. Tomatoes have natural antithrombotic effects/J. Yamamoto [et al.] // Br. J. Nutr. - 2003. - Vol. 90. - P. 1031-1038.