



## **The Role of Hyperhomocysteinemia in the Pathogenesis of Thromboocclusive Diseases**

**Ibragim Abdulganievich Yusupov<sup>1</sup>, Mubarik Dziaudinovna Akaeva<sup>2</sup>,  
Natalia Yurievna Stepanova<sup>2</sup>, Nikita Vladimirovich Slysarenko<sup>1</sup>,  
Omar Ruslanovich Gaidarbekov<sup>3\*</sup>, Eldar Abdurahmanovich Saidov<sup>1</sup>,  
KhavraAdamovna Dudugova<sup>3</sup>, Zaytun Said-Magomedovna Dikieva<sup>3</sup>  
and Alina Yuryevna Maslova<sup>4</sup>**

<sup>1</sup>Rostov State Medical University, Rostov-on-Don, Russia.

<sup>2</sup>Tyumen State Medical University, Tyumen, Russia.

<sup>3</sup>Chechen State University, Grozny, Chechen Republic, Russia.

<sup>4</sup>Socmedica, Skolkovo, Russia.

### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2021/v33i48A33229

#### **Editor(s):**

(1) Dr. Barkat Ali Khan, Gomal University, Pakistan.

#### **Reviewers:**

(1) C. Guillermo Yanowsky Reyes, Universidad de Guadalajara, México.

(2) Abha Chandra, Sri Venkateswara Institute of Medical Sciences, India.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/76381>

**Short Communication**

**Received 24 August 2021**  
**Accepted 29 October 2021**  
**Published 06 November 2021**

### **ABSTRACT**

Homocysteine is a sulfur-containing non-proteinogenic amino acid that is an intermediate product of methionine metabolism. With excessive accumulation of homocysteine in the body, a state of hyperhomocysteinemia occurs, which has attracted the attention of doctors since the middle of the last century and received a serious impetus for research after the publication of data on the role of hyperhomocysteinemia in the pathogenesis of thromboocclusive diseases. To date, there are more than 7.5 thousand scientific papers devoted to the study of hyperhomocysteinemia, monothematic international conferences on clinical and therapeutic aspects of hypermonocysteinemia are held every year. In the Russian Federation, a detailed study of the role of homocysteine and its side effects in excess is of particular interest due to the prevalence of cardiovascular pathologies

\*Corresponding author: E-mail: [ruslankalmykov777@yandex.ru](mailto:ruslankalmykov777@yandex.ru);

(according to statistics of the Ministry of Health of Russia-49.27% of deaths of Russians fall on this cohort of diseases). This is an important fact in Russian medicine, which deserves close attention from researchers and scientists.

**Keywords:** *Hyperhomocysteinemia; homocysteine; hypertension; cardiovascular disease; arterial hypertension; CBS gene.*

## 1. INTRODUCTION

Homocysteine is a sulfur-containing non-proteinogenic amino acid that is an intermediate product of methionine metabolism. That is, this amino acid is not part of proteins, it is not contained in food [1]. Metabolic transformations involving homocysteine occur in two ways: remethylation and transulfation. In the first case, the amino acid attaches a methyl group, forming methionine with the participation of folic acid and methylenetetrahydrofolate reductase and B12-dependent methyltransferase. An additional route of homocysteine methylation is through an independent B12-independent betaine-homocysteine methyltransferase [2]. Due to the limited tissue bioavailability of the latter, there is not a sufficient conversion of homocysteine, therefore, in the case of a defect in methylenetetrahydrofolate reductase or B12-dependent methyltransferase, the amino acid is not able to compensate for the disturbed metabolism [3,4]. In the process of transulfation, homocysteine combines, with the participation of B6-dependent cystathion- $\beta$ -synthase, with serine in a reaction to form a diaminodicarboxylic aliphatic sulfur-containing amino acid-cystathione. Cystathionine is an S-substituted cysteine. By the way, genetically determined disorders of cystathionine metabolism are the cause of hereditary diseases-cystathioninuria and homocystinuria [4].

To date, more than 55 mutations of the CBS gene are known. More than 9 different mutations of methylenetetrahydrofolate reductase have been described [5]. Two alleles are of practical importance: the thermolabile C677T and the A1298C allele. The mutation in the allele N677-O is inherited most often, and according to an autosomal recessive type, it occurs both in North America and in Europe in a homozygous carrier in 10-20% of the population, in a heterozygous carrier-in almost 40-60% of residents. It can be assumed that the same ratios are found in the Russian Federation [6].

The results of the Augusta University researchers showed that oxidative stress,

inflammation and epigenetic modifications are possible mechanisms of dysfunction of the external blood-brain barrier caused by hyperhomocysteinemia. The study also talks about hyperhomocysteinemia-induced inflammation of the brain, as a mechanism of dysfunction of the blood-brain barrier and the pathogenesis of Alzheimer's disease [7].

## 2. THE EFFECT OF HYPERHOMOCYSTEINEMIA ON THE CARDIOVASCULAR SYSTEM

The metabolism and "efficiency" of homocysteine metabolism depends on a number of factors: the amount of methionine consumed, the concentration of folic acid and B vitamins in the blood, the amount of S-adenosyl methionine in cells [8]. Since the kidneys are the organ of homocysteine excretion, in case of their damage, homocysteine increases in the blood [9]. Fact: in patients with type 2 diabetes mellitus, the level of homocysteine constantly exceeds the norm, and even the severity of microalbuminuria, a marker of kidney damage, depends on its initial concentration in the blood [10]. In patients with CRF who are on hemodialysis, hyperhomocysteinuria is detected in 100% of cases, and the concentration of the amino acid itself is from 25 mmol/l [11]. In general, the level of homocysteine in the blood is affected by a large number of various factors, including genetic mutations, age and gender (men, menopausal period in women, age over 55 years), nutrition, bad habits, lack of B vitamins, some nosologies (type 2 diabetes, malignant neoplasms, rheumatoid arthritis, SLE, hypothyroidism, cystic fibrosis, Alzheimer's disease, etc.), the effect of various pharmacological drugs [12].

Even a small excess of homocysteine cytotoxicity affects the endothelial vascular lining. It inhibits cyclooxygenase activity in endotheliocytes, minimizing the synthesis of prostacyclin, and thereby stimulating the production of thromboxane A2, with an increase in the amount of the latter, the aggregation activity of platelets increases, which is already a prerequisite for vascular pathology.

Hyperhomocysteinemia is accompanied by an increase in the synthesis of tissue factor, a decrease in the activity of natural anticoagulants and a tissue activator of plasminogen (the primary form of plasmin – an enzyme that restricts blood coagulation) [13].

Endotheliocytes and the nitrogen monoxide synthesized by them (hereinafter NO) are of significant importance in the exchange of homocysteine) [14]. In healthy people, an excess of this amino acid binds to NO in the bloodstream with the formation, as a result, of S-nitrosomocysteine – a substance that lacks a priori cytotoxic properties and has a vasodilator effect. And how it should be concluded: with hyperhomocysteinemia, endothelial NO-synthetase is blocked, NO production decreases rapidly, the formation of S-nitrosohomocysteine is disrupted [15]. Homocysteine has the ability to induce the activity of 3-hydroxy-3-methylglutaryl-COA reductase, which, in turn, leads to increased synthesis of cholesterol and its deposition in the places of the damaged endothelial layer. In addition to this trouble, with the growth of homocysteine in the blood, the growth of asymmetric dimethylarginine, an inhibitor of nitric oxide synthetase, also increases [16].

In researches of the effect of hyperhomocysteinemia on the cardiac system in laboratory conditions, it was found that in patients with coronary disease, this fact contributed to endothelial damage, which is confirmed by an increased level of endothelin 1 [17]. There is no doubt that hyperhomocysteinemia contributes to the formation of endotheliosis. Also, studies have shown that hyperhomocysteinemia affects the formation and maintenance of a systemic inflammatory response. This was shown by biochemical blood tests of cardiac patients, where overestimated markers of inflammation (interleukin-6, fibrinogen, CRP) were clearly demonstrated [18].

Next, we will consider clinical cases of coronary artery damage with obvious consequences for the myocardium, which were conducted on the basis of the Stavropol Regional Hospital.

When studying patients aged 46-65 years, 3-12 months before the study, who had suffered a myocardial infarction and concomitant diseases, such as arterial hypertension (stage 2-3), it was found that the average level of hyperhomocysteinemia in plasma was 24 microns/l. In the group of patients under 46 years of age, the average level of HZ was 17.6 microns/l. It was found that the latter values are close to those established for patients with unstable angina in the same age group. Samples with a methionine load (100 mg/kg) showed that the ratio of the resulting increase in the concentration of HC to its initial value fluctuated widely and the lower the level of post-loading HC, the less likely it was to repeat coronary disorders.

The significance of the concentration of HC in the blood of patients as a prognostic sign of postoperative complications and the adequacy of the vitamin profile after heart transplantation was demonstrated by the fact that the concentration of HC in patients of the examined group was higher than in the comparison group ( $20.1 \pm 13.0$  vs.  $10.0 \pm 4.0$  microns/l;  $p < 0.01$ ), and an increase in the level of HC was observed in 78% of recipients even before transplantation. The concentrations of folate and vitamin B6 in these patients before and after surgery were significantly lower than in the comparison group.

Post-transplant complications were noted in 69.3 % of patients with severe hyperhomocysteinemia. In our study, for most of these patients, an increase in the concentration of HC and a decrease in folate and vitamin B6 levels were observed (Table 1) before surgery. It is believed that the correction of these disorders could significantly reduce the number of post-transplant complications.

The HC concentration was also determined in 100 patients with confirmed coronary artery disease during subsequent angioplasty, compared with 110 subjects without coronary pathology. In this study, it was not possible to find a relationship between the level of HC in the blood and the classic manifestations of cardiovascular disease.

**Table 1. Average values of vitamin B6, homocysteine and folate in patients**

Name	Unit of measurement	Quantity
Vitamin B6 (pyridoxal-5-phosphate) in plasma	ng / ml	4,0
Vitamin B6 (pyridoxal-5-phosphate) in whole blood	ng / ml	3,6
Homocysteine	micromole/l	24,1

**Table 2. Platelet aggregation (max. significant, opt. units) on the first day of the disease, depending on the number of white blood cells in the blood of patients with acute disorders of cerebral circulation, m±σ**

<b>Name of the method research</b>	Total cholesterol	High-density lipoproteins	Low-density lipoproteins	Thyroglobulin	Coefficient of atherogenicity
<b>Lipidogram</b>	6,77 mmole/l	1,19 mmole/l	4,69 mmole/l	2,64 mmole/l	4,69

Studies to determine homocysteine used a chemiluminescence microparticle immunoassay (CMIA). Detection range: 1 - 500 μmol / L (Architect i2000SR analyzer, Abbott Diagnostics).

Additional blood tests were also conducted for platelet aggregation on the first day of the disease, depending on the number of white blood cells in the blood of patients (Table 2).

The systemic inflammatory reaction observed in hyperhomocysteinemia manifests itself in the form of induction of a pro-inflammatory phenotype in the arterial membrane [19]. This leads to the activation of adhesive molecules in the endothelium, the adhesion of monocytes and platelets and, ultimately, is manifested by atherothrombotic complications [20].

Homocysteine, as an amino acid, has the property of mitogenicity in relation to smooth muscle cells of the vessels of the circulatory system, contributing to their accelerated proliferation, which is manifested by thickening of the intima and copper vessels [21]. Mitogens are peptides or low molecular weight proteins that induce mitosis. Mutagenesis is the entry of a cell into the process of division under the action of a certain mutagen. Their action is provided by the translation of signals that turn on mitogen-activated protein kinases and lead to mitosis [22].

Currently, there is no generally accepted norm for the level of homocysteine in blood plasma, so it varies depending on the age category, ethnicity, nutrition, and so on. But it was found that with age, both men and women have homocysteine levels increasing. If the level of homocysteine in children does not exceed 6 mmol/l before puberty, then during puberty the level of this amino acid increases markedly, especially in males [23-25].

### 3. DETERMINATION OF LATENT HYPERHOMOCYSTEINEMIA

There is no single classification for hyperhomocysteinemia, because it is an extremely variable phenomenon that takes into account many conditions. After analyzing various literature, some researchers have attempted to create such a classification [26]. Athrombosis of different localization was significantly more common than in those with a lower amino acid level [28-30].

Among the commonly used methods for the level of homocysteine is a high-performance liquid chromatography immunoenzyme analysis [31]. The advantage of this method is not only in sensitivity and high accuracy (up to 1 mmol/l of total homocysteine in blood serum), but also accessibility. This method can be used in any laboratories where there is an enzyme immunoassay.

To determine the latent form of hyperhomocysteinemia, some authors suggest a test with a methionine load [32,33]. This manipulation allows us to see a hidden defect in the exchange of amino acids, including due to a heterozygous mutation of cystation-β-synthase. This is an outdated method, which, nevertheless, is often used.

The method consists in the fact that the patient is given methionine inside at the rate of 100 mg/kg of body weight. Then, after 2, 4, 6 and 8 hours, the concentration of homocysteine in the blood is determined, comparing it with the initial values. The most optimal test option is a 2-hour one. If, after a couple of hours, the amino acid concentration is 2 times higher than the initial level (by 2 standard deviations), then the sample is considered positive.

This method allows to identify an additional average of up to 30% of patients with latent hyperhomocysteinemia.

#### 4. THERAPY

For the treatment and reduction of homocysteine in the blood, combinations of group B drugs are used. The literature describes the ability to reduce high levels of homocysteine both by one representative of the vitamins of this group (this is B12), and in combination with folic acid [34]. Information on the positive use of B6 and B2 was reported. There is evidence that the use of folate even improves cognitive functions in people, especially in those with very high homocysteine levels [35].

#### 5. CONCLUSION

Hyperhomocysteinemia is one of the most important factors contributing to endothelial damage. Endometriosis is accompanied by a systemic inflammatory reaction, activation of platelet and coagulation hemostasis, stimulation of mitotic activity of vascular smooth muscle cells, which leads to the development of atherosclerosis and associated thromboocclusive vascular damage. The latent form of hyperhomocysteinemia can be identified by modern laboratory research methods, which should be resorted to in the case of additional examination, if no obvious causes of "chronic" thromboocclusive diseases have been found. Also, for such a thorough work, the treating specialist must have a deep understanding of biochemistry and molecular interactions at the cellular level in order to find the initial etiological factor, and not to treat the consequences of the disease already.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

#### REFERENCES

1. Esse R, Barroso M, Tavares de Almeida I, Castro R. The Contribution of Homocysteine Metabolism Disruption to Endothelial Dysfunction: State-of-the-Art. *Int J Mol Sci.* 2019;20(4):867. DOI: 10.3390/ijms20040867
2. Chen NC, Yang F, Capecci LM, Gu Z, Schafer AI, Durante W, Yang XF, Wang H. Regulation of homocysteine metabolism and methylation in human and mouse tissues. *FASEB J.* 2010;24(8):2804-17. DOI: 10.1096/fj.09-143651
3. Goetzl S, Teutloff C, Werther T, Hennig SE, Jeoung JH, Bittl R, Dobbek H. Protein Dynamics in the Reductive Activation of a B12-Containing Enzyme. *Biochemistry.* 2017;56(41):5496-5502. DOI: 10.1021/acs.biochem.7b00477
4. Baroni L, Bonetto C, Rizzo G, Bertola C, Caberlotto L, Bazzlerla G. Association Between Cognitive Impairment and Vitamin B12, Folate, and Homocysteine Status in Elderly Adults: A Retrospective Study. *J Alzheimers Dis.* 2019;70(2):443-453. DOI: 10.3233/JAD-190249
5. Wang J, Hegele RA. Genomic basis of cystathioninuria (MIM 219500) revealed by multiple mutations in cystathionine gamma-lyase (CTH). *Hum Genet.* 2003;112(4):404-8. DOI: 10.1007/s00439-003-0906-8.
6. Zhao H, Li Q, Wang J, Su X, Ng KM, Qiu T, Shan L, Ling Y, Wang L, Cai J, Ying J. Frequent epigenetic silencing of the folate-metabolising gene cystathionine-beta-synthase in gastrointestinal cancer. *PLoS One.* 2012;7(11):e49683. DOI: 10.1371/journal.pone.0049683
7. Tawfik A, Samra YA, Elsherbiny NM, Al-Shabrawey M. Implication of Hyperhomocysteinemia in Blood Retinal Barrier (BRB) Dysfunction. *Biomolecules.* 2020;10(8):1119. DOI: 10.3390/biom10081119.
8. Tchantchou F. Homocysteine metabolism and various consequences of folate deficiency. *J Alzheimers Dis.* 2006;9(4):421-7. DOI: 10.3233/jad-2006-9408
9. Perna AF, Ingrosso D. Homocysteine and chronic kidney disease: an ongoing narrative. *J Nephrol.* 2019;32(5):673-675. DOI: 10.1007/s40620-019-00622-1. Epub 2019 Jun 21
10. Glassock RJ. Is the presence of microalbuminuria a relevant marker of kidney disease? *CurrHypertens Rep.* 2010;12(5):364-8.

- DOI: 10.1007/s11906-010-0133-3. PMID: 20686930
11. Gonella M, Calabrese G, Scancarello M, Mengozzi A, Deambrogio P. Livelliplasmatici di omocisteina in pazienti in emodiafiltrazione [Plasma levels of homocysteine in patients on hemodiafiltration]. *Minerva UrolNefrol.* 2000;52(3):163-5. Italian
  12. Maayan-Metzger A, Lubetsky A, Kuint J, Rosenberg N, Simchen MJ, Kuperman A, Strauss T, Sela BA, Kenet G. The impact of genetic and environmental factors on homocysteine levels in preterm neonates. *Pediatr Blood Cancer.* 2013;60(4):659-62. DOI: 10.1002/pbc.24352. Epub 2012 Sep 28
  13. Raevskaya A I, Belyalova A A, Shevchenko P P, Karpov S M, Mishvelov A E, Simonov A N et al. Cognitive Impairments in A Range of Somatic Diseases Diagnostics, Modern Approach to Therapy. *Pharmacophore* 2020;11(1): 136-41
  14. Ranucci M, Romitti F, Costa E. Hyperhomocysteinemia, antithrombin consumption, and early venous graft closure in surgical coronary revascularization. *Minerva Anesthesiol.* 2008;74(7-8):439-42.
  15. Watts RN, Richardson DR. The mechanism of nitrogen monoxide (NO)-mediated iron mobilization from cells. NO intercepts iron before incorporation into ferritin and indirectly mobilizes iron from ferritin in a glutathione-dependent manner. *Eur J Biochem.* 2002;269(14):3383-92. DOI: 10.1046/j.1432-1033.2002.02987.x.
  16. Mutus B, Rabini RA, Staffolani R, Ricciotti R, Fumelli P, Moretti N, Martarelli D, Mazzanti L. Homocysteine-induced inhibition of nitric oxide production in platelets: a study on healthy and diabetic subjects. *Diabetologia.* 2001;44(8):979-82. DOI: 10.1007/s001250100581
  17. Li H, Lewis A, Brodsky S, Rieger R, Iden C, Goligorsky MS. Homocysteine induces 3-hydroxy-3-methylglutaryl coenzyme a reductase in vascular endothelial cells: a mechanism for development of atherosclerosis? *Circulation.* 2002;105(9): 1037-43. DOI: 10.1161/hc0902.104713.
  18. Salvio G, Ciarloni A, Cutini M, Balercia G. Hyperhomocysteinemia: Focus on Endothelial Damage as a Cause of Erectile Dysfunction. *Int J Mol Sci.* 2021;22(1):418. DOI: 10.3390/ijms22010418.
  19. Al Mutairi F. Hyperhomocysteinemia: Clinical Insights. *J Cent Nerv Syst Dis.* 2020;12:1179573520962230. DOI: 10.1177/1179573520962230.
  20. Chakraborty RK, Burns B. Systemic Inflammatory Response Syndrome. 2021 Jul 28. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
  21. da Costa Martins P, van den Berk N, Ulfman LH, Koenderman L, Hordijk PL, Zwaginga JJ. Platelet-monocyte complexes support monocyte adhesion to endothelium by enhancing secondary tethering and cluster formation. *Arterioscler Thromb Vasc Biol.* 2004;24(1):193-9. DOI: 10.1161/01.ATV.0000106320.40933.E5. Epub 2003 Nov 13.
  22. Majors AK, Sengupta S, Jacobsen DW, Pyeritz RE. Upregulation of smooth muscle cell collagen production by homocysteine-insight into the pathogenesis of homocystinuria. *Mol Genet Metab.* 2002;76(2):92-9. DOI: 10.1016/s1096-7192(02)00030-6.
  23. Westwood JT, Wagenaar EB, Church RB. Synthesis of unique low molecular weight proteins during late G2 and mitosis. *J Biol Chem.* 1985;260(2):695-8.
  24. Zhou Z, Liang Y, Qu H, Zhao M, Guo F, Zhao C, Teng W. Plasma homocysteine concentrations and risk of intracerebral hemorrhage: a systematic review and meta-analysis. *Sci Rep.* 2018;8(1):2568. DOI: 10.1038/s41598-018-21019-3.
  25. Blinov AV, Siddiqui SA, Nagdalian AA, Blinova AA, Gvozdenko AA, Raffa VV, et al. Investigation of the influence of Zinc-containing compounds on the components of the colloidal phase of milk. *Arab J Chem.* 2021;14(7):103229
  26. Boraeva TT, Vadaeva MA, Matveeva UV, Revazova AB, Albegova BZ, Kanukoeva DT, Mishvelov AE, Povetkin SN. Dynamics of Diseases of the Upper Digestive Tract in Children, *Journal of Pharmaceutical Research International.* 2021; 33(38B): 48-57. DOI: 10.9734/jpri/2021/v33i38B32098
  27. Harmon DL, Woodside JV, Yarnell JW, McMaster D, Young IS, McCrum EE, Gey KF, Whitehead AS, Evans AE. The common 'thermolabile' variant of methylene tetrahydrofolate reductase is a major determinant of mild hyperhomocysteinemia. *QJM.* 1996; 89(8):571-7.

- DOI: 10.1093/qjmed/89.8.571.
28. Guthikonda S, Haynes WG. Homocysteine: role and implications in atherosclerosis. *CurrAtheroscler Rep.* 2006 Mar;8(2):100-6. DOI: 10.1007/s11883-006-0046-4.
29. Božič-Mijovski M. Hyperhomocysteinemia and thrombophilia. *ClinChem Lab Med.* 2010;48Suppl 1:S89-95. DOI: 10.1515/CCLM.2010.365. Epub 2010 Nov 25.
30. Rzhepakovskiy, SiddiquiS.A., AvanesyanS., BenlidayiM., DhingraK., DolgalevA., ErukashvilyN., FritschT., HeinzV., KocherginS., NagdalianA., SizonenkoM., TimchenkoL., VukovicM., PiskovS., GrimmW-D. Anti-arthritic effect of chicken embryo tissue hydrolyzate against adjuvant arthritis in rats (X-ray microtomographic and histopathological analysis). *FoodScience&Nutrition* 2021;00:1-22. Available:<https://doi.org/10.1002/fsn3.2529>
31. Goyette P, Sumner JS, Milos R, Duncan AM, Rosenblatt DS, Matthews RG, Rozen R. Human methylenetetrahydrofolate reductase: isolation of cDNA, mapping and mutation identification. *Nat Genet.* 1994;7(2):195-200. DOI: 10.1038/ng0694-195. Erratum in: *Nat Genet.* 1994 Aug;7(4):551.
32. Cavazzini A, Pasti L, Massi A, Marchetti N, Dondi F. Recent applications in chiral high performance liquid chromatography: a review. *Anal ChimActa.* 2011 Nov 14;706(2):205-22. DOI: 10.1016/j.aca.2011.08.038. Epub 2011 Sep 22.
33. van der Griend R, Biesma DH, Banga JD. Postmethionine-load homocysteine determination for the diagnosis hyperhomocysteinemia and efficacy of homocysteine lowering treatment regimens. *Vasc Med.* 2002 Feb;7(1):29-33. DOI: 10.1191/1358863x02vm407ra.
34. Blinov A V., Kravtsov AA, Krandievskii SO, Timchenko VP, Gvozdenko AA, Blinova AA. Synthesis of MnO<sub>2</sub> Nanoparticles Stabilized by Methionine. *Russ J Gen Chem.* 2020; 90(2):283-6.
35. Kotsoeva G A, Esiev R K, Toboev G V, Zakaeva R S, Kulova A A, Tsokova L V, et al. Phytoadaptogenic Cocktail Use "Biorithm-E" In The Complex Treatment Of Odontogenic Inflammatory Diseases Of The Maxillofacial Region. *Ann. Dent. Spec.* 2021;9(2):52-57. Available:<https://doi.org/10.51847/PyVv83OTGt>
36. Loria-Kohen V, Gómez-Candela C, Palma-Milla S, Amador-Sastre B, Hernanz A, Bermejo LM. A pilot study of folic acid supplementation for improving homocysteine levels, cognitive and depressive status in eating disorders. *Nutr Hosp.* 2013;28(3):807-15. DOI: 10.3305/nh.2013.28.3.6335.

© 2021 Yusupov et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*  
The peer review history for this paper can be accessed here:  
<https://www.sdiarticle4.com/review-history/76381>