

## Way of manufacturing complex drug of nucleotides: production, properties, application

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### Abstract

The way of manufacturing complex nucleotide medicine encad from yeast ribonucleic acid is offered. Development of inexpensive and effective medicines of domestic production, studying the pharmacological properties of natural biologically active substances are among the priority areas of medical chemistry. The pancreatic hydrolyzate of yeast ribonucleic acid is a mixture of products of fermentative hydrolysis of yeast RNA containing pyrimidine nucleoside-3'-phosphates and oligoribonucleosides. The pancreatic hydrolyzate, complex nucleotide medicine enkad, is allowed for clinical use in hereditary eye diseases – tapetoretinal degeneration (retina abiotrophy) leading to blindness. The substance was produced on technology of enzymatic hydrolysis of RNA from yeast of *Torula* with bovine pancreatic ribonuclease earlier according to VPS 42-1758-87. In this paper, we propose the method for obtaining the substation of the nucleotide medicine based on the bakery yeast *Saccharomyces cerevisiae*, being secondary raw materials in production of alcohol and bakery products that could be an available source of the general pool of yeast RNA under conditions of complex processing of biomass of microbiological production.

The optimal conditions for the yeast RNA hydrolysis by pancreatic ribonuclease were chosen. It was shown that the use of ribonuclease inhibitor, mandelic acid, at the stage of ultra-concentration provided an increase in the yield of the product by 10-12% in comparison with the known technologies and that allowed to increase the stability of the final product composition while maintaining its nontoxicity and apyrogenicity.

The control of the obtained medicine at the Kharkov enterprise for the production of immunobiological and medicinal preparations of CJSC Biolek confirmed the compliance of the drug with the requirements in its specified pharmacopoeial article. The test data allowed recommending to obtain a substance enkad for medical assignment on the basis of purified RNA from industrial baker's yeast of the Russian production. The general analysis of the obtained nucleotide medicine composition was carried out; separate components being isolated and characterized. Based on the experimental data, assumptions about possible mechanisms of effect of the drug were formulated.

### References

- [1] V.M. Zemskov, M.Yu. Lidak, A.M. Zemskov. Low molecular weight RNA - production, hydrolysis and application in medicine. **1985**. *Zinatne, Riga*. 191p.
- [2] I.B. Chernikova, and M.S. Yunusov. Synthesis of uracil derivatives containing in their structure the remains of succinic and maleic acids. *Butlerov Communications*. **2015**. Vol.43. No.7. P.37-39. DOI: 10.37952/ROI-jbc-01/15-43-7-37
- [3] R. Hirashima, H. Michimae, H. Takemoto, [et al.]. Induction of the UDP-glucuronosyltransferase 1A1 during the perinatal period can cause neurodevelopmental toxicity. *Mol. Pharmacol*. **2016**. No.90. P.265-274.
- [4] S.F. Shershevskaya, F.G. Levina. *Vestnik of Acad. Science of the USSR. Medicine, Moscow*. No.10. P.40-43. (russian)
- [5] B.B. Fuks, S.F. Shershevskaya, L.M. Popova, [et al.]. Therapeutic effect of ribonucleotides in some diseases. *Bull. Exp. Biol. and Medicine*. **1969**. No.9. P.23-26. (russian)

- [6] A.P. Avtsyn, B.B. Fuks, M.E. Shabanova, [et al.]. Hereditary dystrophies of the retina in humans in connection with the results of their pathogenetic therapy. *Vestnik of Acad. Science of the USSR*. **1971**. No.7. P.63-69. (russian)
- [7] L.I. Katsnelson, K.V. Trutneva, N.E. Bogoslovsky [et al.]. The results of a long-term dynamic observation of the use of the enkad preparation for pigmentary tapetorinal abiotrophy. *Vestnik of Ophthalmology*. **1982**. No.2. P.28-29. (russian)
- [8] L.A. Saikova. Thesis of Doct. Sciences, *State Institution of Doctor Advanced Training*, **1993**. St. Petersburg. P.178. (russian)
- [9] M.D. Mashkovsky. *Medicines*, **2012**. *New Wave, Moscow*. 1216p. (russian)
- [10] US Patent 5064758: *Chem. Abstrs.* **1990**. Vol.113, 4710f.
- [11] Patent SU1703113: *Bul. Invention*. **1992**, 1.
- [12] Patent RU2016579: *Bul. Invention*. **1994**, 5.
- [13] T.L. Bunina, O.A. Khondkarian, T.S. Korshunova. Treatment of amyotrophic lateral sclerosis with ribonucleotides. *S.S. Korsakov Journal of Neuropathology and Psychiatry*. **1976**. Vol.LXXVI. P.166-174. (russian)
- [14] L.P. Grinio, B.V. Agafonov. Myopathy. **1997**. *Medicine. Moscow*. 213p. (russian)
- [15] L.I. Markusheva, Yu.V. Tikhonov, R.T. Toguzov. A metabolic pool of purine compounds in the epidermis and blood of patients with psoriasis with enkad. *Clinical Laboratory Diagnostics*. **1998**. No.8. P.43. (russian)
- [16] T.V. Ryasina, T.S. Korshunova., M.E. Shabanova, [et al.]. *Patent RU2016579* Antihypoxic agent for the treatment of ischemic disorders of cerebral circulation. **1994**. (russian)
- [17] M.E. Shabanova, I.A. Krylov. New possibilities of medical application of the domestic preparation of nucleotides. *Allergology and Immunology in Pediatrics*. **2006**. No.2-3 (9) P.94. (russian)
- [18] M.E. Shabanova, V.V. Kazaniev, M.M. Baurina. The possibility of enhancing the proliferative activity of the bone marrow. *Neuroimmunology*. **2007**. No.5. P.127. (russian)
- [19] E.F. Vasilyeva, V.G. Caleda, M.E. Shabanova. Optimization of psychotropic therapy of endogenous psychoses using pancreatic hydrolyzate of yeast RNA. Moscow International Scientific and Practical Conference "*Biotechnology: Ecology of Large Cities*", Moscow. **2010**. P.473-474.
- [20] E.F. Vasilyeva, V.G. Caleda, M.E. Shabanova. Optimization of psychotropic therapy of endogenous psychoses using pancreatic hydrolyzate of yeast RNA. Moscow International Scientific and Practical Conference "*Biotechnology: Ecology of Large Cities*", Moscow. **2010**. P.473-474.
- [21] M.E. Shabanova, M.M. Baurina, L.M. Yakubovich [et al.]. Medicine drug of a complex of nucleotides for treatment of neuromuscular diseases. International Symposium "*Biological Motility: from fundamental achievements to nano-technologies*", Pushino. **2010**. P.234-236.
- [22] V.A. Ageevets, K.V. Kvitko, M.E. Shabanova, M.M. Baurina. I. A study of the effect of a multicomponent composition of a nucleotide drug on its antiviral activity. Moscow International Scientific and Practical Conference "*Pharmaceutical and Medical Biotechnologies*". International Congress "*Biotechnology: state of the art and prospects of development*". 20-22, March. **2012**. Moscow. P.180.
- [23] M.E. Shabanova, V.V. Kazaniev, M.M. Baurina. Action of the nucleotide preparation as a radioprotective agent. XIX Russian National Congress "*The Man and the Medicine*", Moscow. **2012**. P.330-331.
- [24] M.E. Shabanova, M.M. Baurina, L.M. Yakubovich, L.P. Grinio. Application of the domestic medicinal preparation of nucleotides in neuralgic practice. International Symposium "*Biological Motility: Fundamental and Applied Science*", Pushino. **2012**. P.181-183.
- [25] M.E. Shabanova, Yu.V. Tikhonov, M.M. Baurina. Analysis of the composition of the drug of nucleotide - inducer of hemopoiesis. VII International Congress "*Biotechnology: state of the art and prospects of development*", Moscow. **2013**. P.139-140.
- [26] *Ophthalmology*. Ed. E.I. Sidorenko. *GEOTAR-Media. Moscow*. **2013**. 640p. (russian)
- [27] M.E. Shabanova, M.M. Baurina, S.I. Nikonov. New possibilities of using the drug of nucleotides. I Russian Conference on Medical Chemistry "*MedChem Russia-2013*" with international participation, Moscow. **2013**. P.181.
- [28] K.V. Kvitko, V.A. Ageevets, M.E. Shabanova, M.M. Baurina. Comparison of the antiviral effect of drugs of nucleic nature. VIII International Congress "*Biotechnology: state of the art and prospects of development*", Moscow. **2015**. Vol.1. P.165-167.
- [29] E.F. Vasilyeva, M.E. Shabanova, Yu.E. Shilov, M.M. Baurina. The effect of the drug on the nucleic nature of enkad on the cytotoxic activity of natural killer lymphocytes in patients with mental illness.

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- [30] M.E. Shabanova, M.M. Baurina. Mechanism of radioprotective action of the nucleotide preparation enkad, Russian scientific conference with international participation ToxRad-2015 "Medico-biological problems of toxicology and radiobiology". *St. Petersburg*. **2015**. P.169.
- [31] M.E. Shabanova, M.M. Baurina, L.M. Yakubovich. Antihypoxic agent for the treatment of ischemic disorders of cerebral circulation. XXIII Russian National Congress "*The Man and the Medicine*". *Moscow*. **2016**. P.96-97.
- [32] M.E. Gordeeva, A.A. Lapin, and A.Yu. Karuseva. The comparative analysis of chemical and biological indicators thresh fishes of different sites of the Volga spur of the Kuibyshev reservoir under conditions of anthropogenous influence. *Butlerov Communications*. **2015**. Vol.41. No.3. P.124-131. DOI: 10.37952/ROI-jbc-01/15-41-3-124
- [33] M.E. Shabanova, S.I. Nikonorov, M.M.Baurina, L.M. Yakubovich. Study of the influence of stress factors on the development of sturgeon fishes and ways to protect their larvae from extreme effects. V International Congress "*Biotechnology: state of the art and prospects of development*", Moscow. **2009**. P.129-131.
- [34] M.E. Shabanova, M.M. Baurina, S.I. Nikonorov. Increase of adaptive possibilities at application immunomodulator, the preparation enkad. VI International Scientific and Practical Conference "*Pharmaceutical and Medical Biotechnologies*", Moscow. **2014**. P.212-213.
- [35] G.Z. Sitdikova, E.Z. Fazlinurova. The state of development of the yeast industry. *NovaInfo.Ru*. Economic sciences. **2015**. No.31-2. P.93-95.
- [36] Yeast market. Current situation and forecast 2017-2021. *ACG*. **2017**. Vol.203 P.24.
- [37] Methods for the Study of Nucleic Acids, ed. A.N. Belozersky. *Moscow: Mir*. **1970**. 277p.
- [38] M.R. McDonald, *Ribonucleases*, in *Methods Enzymol*. **1955**. No.2. P.427-436.
- [39] *Dorland's Illustrated Medical Dictionary*, Ed. W.B. Saunders, Philadelphia, **1988**.
- [40] Patent Ru 2274658. *Bul. Invention*. **2006**. 11.