Tropical Journal of Pharmaceutical Research November 2019; 18 (11): 2233-2240
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v18i11.1

Original Research Article

Prospects for intranasal drug delivery systems with Ginkgo biloba in the treatment of cerebral circulatory disorders

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Sent for review: 24 May 2019 *Revised accepted: 28 October 2019*

Abstract

Purpose: *To analyze the range of currently available nasal medicines, and to study extant information on the use of Ginkgo biloba herbal complexes for the treatment of cerebral circulatory disorders of different etiologies. The study dwelt on the features and prospects of intranasal drug administration. Currently, intranasal administration is used primarily for the treatment of local symptoms. However, it has a much higher potential: the mucous membrane of the nasal cavity offers an opportunity for non-invasive treatment using systemic administration.*

Methods: *The study involved the analysis of materials from information-retrieval systems, library databases, patent databases, and scientific information repositories such as e-Library. PubMed, Scopus, Google Scholar, as well as materials from the websites of manufacturers of herbal medicinal products and other herbal substances.*

Results: *Herbal medicinal products have great potential in terms of intranasal administration. This is especially true of herbal medicines obtained through extraction of leaves of Ginkgo biloba, which have a broad spectrum of action, i.e., anti-aggregatory, venotonic, nootropic, anti-hypoxic, antioxidant, anti-inflammatory, membrane-stabilizing, and capillary-protective effects. The range of Ginkgo biloba-based medicines calls for expansion, and this testifies to a good potential of these products in terms of further research and use. The analysis of literature and technical information showed the existence of a wide range of nasal medicines currently in use. However, only few drugs are used for the treatment of cerebrovascular diseases. Furthermore, there are no herbal medicines among these drugs, despite obvious advantages of herbal products such as ease of use, high bioavailability, and systemic action potential.*

Conclusion: *The current status of research on nasal dosage forms of Ginkgo biloba herbal complexes warrants further development involving biopharmaceutical and pharmacological studies.*

Keywords: *Nasal dosage forms, Cerebral circulation disorder, Ginkgo biloba*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Intranasal administration is one of the routes of drug delivery. The mucous membrane of the nasal cavity may be used as a non-invasive means of systemic drug administration.

Nasal medicines may be classified based on site of action: local action, systemic action, targeted delivery to the brain, and delivery to the lungs, bronchi, or the respiratory system. Examples of nasal medicines intended for local administration include products belonging to the following pharmacologic groups: decongestants, antihistamines and glucocorticoids [**Error! Reference source not found.**-**Error! Reference source not found.**].

Intranasal administration is currently considered a promising route for the delivery of systemic drugs belonging to different pharmacologic classes. The main advantages of intranasal drug administration have been identified [5, 6]. These advantages are:

- ease of administration for patients of all ages, implying less complex and less traumatic procedure, unlike injections; and better patient compliance. Intranasal administration does not usually require the participation of medical personnel;
- high bioavailability and fewer adverse reactions due to avoidance of first-pass hepatic metabolism;
- potential for central action (e.g. the drugs can reach the brain directly from the nasal cavity); and
- rapid systemic effects resulting from active absorption of some drug components that are decomposed in the gastrointestinal tract, and short time taken to attain maximum blood concentration of drugs.

Moreover, intranasal administration has advantages when it is necessary to relieve severe symptoms e.g. intranasal administration of triptanes (for treating migraine), fentanyl (for pain relief in cancer patients), or ondansetron (for treating nausea). In such cases, one might use single-dose systems or multidose pumps equipped with unit-registering or blocking mechanisms that reduce the risk of accidental overdose or misuse.

The possibility of administering medicines by bypassing the gastrointestinal tract makes it possible to deliver even peptide hormones.

The disadvantages of this route of administration include:

(a) inter-individual physiological differences in nasal mucosa;
(b) potential effect of some diseases on the bioavailability of drugs;
(c) potential of some active substances or excipients (e.g. surfactants and preservatives) to cause irritation of the nasal mucosa;
(d) frequent use of medicines might lead to changes in the nasal mucosa;
(e) intranasal delivery is used mostly for substances that possess certain physico-chemical properties (lipophilicity, molecular weight) that ensure their penetration into the blood circulation in amounts required to achieve therapeutic effects;
(f) adverse reactions associated with the inability to provide continuous, steady concentration of a drug in the blood;
(g) formulations include excessive amounts of active substances due to the fact that only a small portion of the drug penetrates the blood circulation, and this may increase the cost of the drug;
(h) some substances undergo modifications (hydrolysis, oxidation, isomerization or polymerization) in the nasal cavity during intranasal administration, which reduces their effects [**Error! Reference source not found.**-**Error! Reference source not found.**].

However, adequate composition of a nasal dosage form compensates for these shortcomings. Nevertheless, the physiological characteristics of the nasal mucosa need to be taken into account. The aim of this study was to examine and analyze literature data on the range of currently available nasal herbal medicines, and to study materials on the use of nasal herbal mixtures based on *Ginkgo biloba* leaves for the treatment of cerebral circulatory disorders of different etiologies.

METHODS

The study involved the analysis of materials from information-retrieval systems, library databases, patent databases, and scientific information repositories such as e-Library, PubMed, Scopus and Google Scholar, as well as materials from the web-sites of manufacturers of herbal medicinal products and herbal substances.

RESULTS

The area of nasal mucosa in an average person is about 150 cm^2. It has a *dense network of capillaries* which ensures rapid absorption of

most drugs, leading to high drug concentrations in the systemic circulation, and it helps to avoid the first-pass hepatic metabolism that needs to be taken into account when administering drugs orally [**Error! Reference source not found.**-**Error! Reference source not found.**].

Over the past decade, more than 100 animal studies have been devoted to the investigations of nasal transport of low and high molecular weight substances into the brain. Some of these studies include comparative studies that demonstrated the advantages of nasal administration (in terms of delivery of substances to the central nervous system) over intravenous administration [**Error! Reference source not found.**-**Error! Reference source not found.**].

The studies also demonstrated the advantages of this route of administration over subcutaneous or intraperitoneal administration. Tests on animal models showed that the nasal delivery of neuroprotective agents reduced brain damage after acute conditions such as stroke and subarachnoid hemorrhage. Some studies demonstrated the efficacy of rapid transportation of biologically active peptides through the olfactory and trigeminal nerves to the central parts of the brain [**Error! Reference source not found.**-**Error! Reference source not found.**]. The publications discussed three possible ways of drug transportation to the CNS in intranasal administration: transportation through the olfactory bulbs (olfactory epithelium) along the olfactory nerve, through the respiratory epithelium along the trigeminal nerve, and by primary absorption into the bloodstream.

Transportation of substances along the olfactory tracts and trigeminal nerve involves intracellular and extracellular mechanisms. The intracellular mechanism involves absorption of substances by olfactory sensory neurons, diffusion and endocytosis. However, the intracellular transport is a slow process requiring at least several hours, or even days. In contrast, extracellular transport is fast, as evidenced by rapid actions of some drugs administered intranasally [**Error! Reference source not found.**-**Error! Reference source not found.**]. These transport routes allow for bypass of the blood-brain barrier due to direct transportation of substances from the nose to the brain.

The third route is the absorption of substances into the systemic circulation and penetration through the blood-brain barrier into the CNS. During primary absorption, a substance passes through 3 barriers: the mucus layer, epithelial membrane and tight junctions (intercellular space). After that, the substance enters the venous bloodstream, and then passes through the blood-brain barrier.

Most drugs intended for intranasal use are peptide-based. Their pharmacological actions are similar to those of hormones such as thyroid hormone (regulator of calcium-phosphorus metabolism), gonadotropin-releasing hormone (similar to vasopressin), as well as immunosuppressive, nootropic (similar to neuropeptides), anxiolytic and anti-migraine agents [**Error! Reference source not found.**-**Error! Reference source not found.**]. For example, Semax provides neuroprotective, neurometabolic, nootropic and antiasthenic effects, and promotes the synthesis of important brain neurotrophic factors. After nasal instillation, 70% of the drug (Semax) is absorbed through the nasopharyngeal mucosa within 5 minutes. Animal studies showed that the drug is subjected to more intensive hydrolysis in blood than in brain tissue [**Error! Reference source not found.**,**Error! Reference source not found.**].

There are other advantages of nasal medicines used in clinical practice. For instance, Imigran (sumatriptan) in the form of a nasal spray, is intended for patients with severe epigastrium discomfort who cannot take tablets during a migraine attack. The effect of a nasal spray occurs faster than that of other dosage forms. A drug administered in the form of a spray enters the body bypassing the gastrointestinal tract, where the gastric emptying slows down during a migraine attack [**Error! Reference source not found.**].

Brain disorders are a common problem. Most often, cerebral circulation disorders occur in patients suffering from atherosclerosis or hypertension. The more pronounced these diseases are, the more severe the cerebral circulation disorders. Cerebrovascular disorders also evolve with underlying chronic fatigue syndrome. This disorder may lead to endocrine, digestive and cardiovascular problems. Stressful situations lead to nervous breakdowns, nervous system dysfunctions, and ultimately, to cerebrovascular disorders and hypertension.

Intranasal use of benzodiazepines (midazolam and lorazepam) is considered an alternative method of drug administration, especially in pediatric patients, for relieving prolonged seizures in out-of-hospital settings without the help of medical staff [**Error! Reference source not found.**,**Error! Reference source not found.**].

Complications associated with drug delivery to the target site are the main obstacles to the development of drugs for the treatment of CNS disorders. In normal conditions, the blood-brain barrier plays an important role in brain protection by preventing the penetration of high- and low-molecular weight substances, thereby becoming a major barrier to drug substances in CNS treatment [**Error! Reference source not found.**,**Error! Reference source not found.**].

Drugs based on *Ginkgo biloba* have positive effects on blood rheology (viscosity, levels of microelements, vascular flow or blood flow properties) by preventing the formation of blood clots. They increase blood flow to the brain and ensure normal functioning of the vascular, nervous and endocrine systems. The scope of their application covers vascular diseases of different etiologies and cerebrovascular disease in particular; inner ear damage, eye problems, and colorectal diseases (hemorrhoids). It was demonstrated that *Ginkgo biloba* improved cognitive performance and enhanced brain activity, not only in the elderly, but also in young people [**Error! Reference source not found.**]. Experiments showed that a *Ginkgo biloba* herbal complex inhibited the development of Alzheimer's disease, which in orthodox medicine, is virtually untreatable; and significantly decreased the likelihood of heart attacks and strokes; improved the conditions of retina vessels, liver, and kidneys in diabetic patients, and had positive effects in the treatment of allergic diseases and neurotic disorders. A *Ginkgo biloba* herbal complex easily eliminated vasospasms, enhanced microcirculation, improved vascular permeability, relieved brain tissue edema, and protected vascular walls from free radical-induced damage.

Ginkgo biloba-based medicines have been very popular in oriental medicine since ancient times, but they were approved as official medicines only in 1960s. Currently, extracts of *Ginkgo biloba* leaves are among the most popular herbal medicines in the world [**Error! Reference source not found.-Error! Reference source not found.**].

The herb contains a vast array of phytochemicals such as terpene lactones [diterpenes - ginkgolides A, B, C, J (0.06 - 0.23)] and sesquiterpene [bilobalide A (NMT 0.26 %)]; flavonoids [flavonols (aglycones: isorhamnetin, kaempferol, quercetin, myricetin (0.2 - 1.4%), flavanols (catechin), flavones and biflavones (amentoflavone, ginkgetin and isoginkgetin)]; catechins, procyanidins, triterpenes (steroids and phytosterols); carotenoids, polyprenols, volatile terpenes, organic acids (including ginkgolic acid); waxes, and lipids [22-24].

According to the Register of Medicinal Products classification, *Ginkgo biloba* leaves and *Ginkgo biloba* dry extract are vasoprotectors and regulators of microcirculation, and therapeutic agents for cerebrovascular disorders.

The pharmacological effects of *Ginkgo biloba* extracts include anti-aggregatory, venotonic, nootropic, anti-hypoxic, antioxidant, microcirculation-improving, anti-inflammatory, membrane-stabilizing, and capillary-protecting effects [23-25].

Ginkgo biloba extract normalizes metabolism in cells, and positively affects vasomotor responses of blood vessels, rheological properties of blood, and microcirculation. It improves cerebral blood circulation and supply of oxygen and glucose to the brain. It has a dose-dependent vasoregulative effect, stimulates release of endothelial relaxing factor, dilates small arteries, and increases vein tone by regulating the filling of blood vessels. It inhibits phosphodiesterase, which leads to a decrease in arteriolar tone and arteriolar spasms, increase in microcirculatory blood flow, and accumulation of cGMP in arteriole smooth muscle cells. The extract suppresses the aggregation of platelets and erythrocytes; it has a pronounced anti-edema effect (on brain and peripheral tissues) and reduces the permeability of the vascular wall. It has antioxidant and anti-hypoxic properties, and it prevents lipid peroxidation and free radicals formation [**Error! Reference source not found.**,**Error! Reference source not found.**,**Error! Reference source not found.**].

Preclinical studies on *Ginkgo biloba* medicines have focused on different aspects: effects on cognitive function and microcirculation, and examination of neuroprotective as well as cardioprotective, hepatoprotective and nephroprotective properties [**Error! Reference source not found.-Error! Reference source not found.**].

Ginkgo biloba leaf extract has a protective effect against neuronal damage. Studies conducted in various models of ischemic stroke revealed that the effect of *Ginkgo biloba* extracts was due to combination of increased blood flow, neuroprotective and neurorestorative properties.

Studies in experimental models of Alzheimer's disease have demonstrated the inhibitory effects of *Ginkgo biloba* extract on β-amyloid oligomerization and caspase-3 (a key mediator of

apoptosis), and its capacity to increase cell proliferation [**Error! Reference source not found.**-**Error! Reference source not found.**].

The therapeutic indications for the use of a *Ginkgo biloba* extract have been identified [25 30]. They include:

- dyscirculatory encephalopathy as a result of stroke, traumatic brain injury, and old age manifested in inability to concentrate, and/or derangement of memory, reduced intellectual abilities, sleep disorders, anxiety and fear;
- dementia, including Alzheimer's disease;
- need for improvement of memory and attention in patients of any age, including young people;
- neurosensory disorders manifested in dizziness, tinnitus, hypacusia, as well as senile macular degeneration and diabetic retinopathy;
- asthenic syndromes: neurotic or psychogenic conditions caused by traumatic brain injury;
- peripheral circulation and microcirculation disturbances, including arteriopathy of lower limbs, and Raynaud syndrome.

One of the beneficial clinical effects of drugs containing *Ginkgo biloba* is improvement of memory and cognitive function. A number of studies showed that such medicines improve attention, memory, delayed recall, mental flexibility, and ability to switch between tasks.

There are evidence of the efficacy of the extract in the recovery period after an ischemic stroke. It was demonstrated that a course of therapy led to clinical improvement of the general condition of patients and their cognitive functions. Quantitative EEG showed a reduction in the relative power of slow rhythms and an increase in the relative power of alpha rhythm [**Error! Reference source not found.**-**Error! Reference source not found.**].

Studies also demonstrated that *Ginkgo biloba* reduces the severity of vestibular ataxia, headache, sleep disturbances, tinnitus, visual disturbances, and symptoms of vegetative dysfunction and emotional-affective disorders.

Ginkgo biloba medicines were shown to have a positive effect on peripheral circulation disorders: diabetic microangiopathy, obliteration of atherosclerosis of lower limbs, retinopathy, and other conditions involving chronic ischemia of peripheral tissues [**Error! Reference source not found.**-**Error! Reference source not found.**].

These findings imply that the development of nasal formulations based on *Ginkgo biloba* herbal complexes is advantageous to modern medicine. Most popular nasal dosage forms that produce systemic effects are sprays and drops. Modern types of nasal formulations include liquid nasal dosage forms, powders, aerosols, and gels. Hydrophilic nasal formulations are the most physiologic types. They have very little effect on the function of ciliated epithelium. The disadvantages of aqueous solutions include a potentially short action period. In order to increase the time of contact with the mucosa, they often use prolongators and moistening agents to keep the active principles in the nasal cavity for 20-25 min.

Another important issue is therapeutic concentration: how the drug dosing will be achieved (total dosage of the drug in the nasal cavity, and frequency of administration). This issue is one of the most problematic considerations today. For example, when using buserelin spray for the treatment of endometriosis, the daily dose is administered in equal portions, one spray into each nostril 3 times a day at regular intervals (6-8 h) in the morning, afternoon and evening. The recommended dose for relief of migraine attacks for Imigran® is 20 mg into one nostril [16].

The pH of the nasal cavity affects the rate and extent of drug absorption. The average pH of the human nasal cavity is about 6.3, while the pH of nasal sprays is in the range of 3.5-7.0. The optimum pH range for nasal formulations is 4.5-6.5. Values of pH < 3 or > 10 may damage the nasal mucosa. It should be noted that pH may also affect the stability of the drug during storage. Another feature to be taken into account during nasal development of formulations is osmolarity. Studies have demonstrated that hypotonic nasal sprays increase the permeability of the nasal mucosa. Some sprays have osmolarity values in the range of 300-700 mOsm/kg. An isosmolar solution (280 mOsm/kg) or hyposmolar solution (<50 mOsm/kg) may improve drug absorption, but may also increase the risk of epithelial damage. A hyperosmolar solution (> 900 mOsm/kg) increases the secretion of mucus. Studies have shown that in order to ensure passive diffusion, a drug should be hyperosmolar, but should not dry the mucous membrane.

An important characteristic of nasal formulations is viscosity. Most commercial medicines contain excipients which modify viscosity and surface tension and, thus, indirectly affect the efficacy of nasal sprays with respect to characteristics such as particle size, spray angle and the residence time of the formulation after delivery to the nasal cavity. A spray must have minimum number of particles smaller than 10 µm in size, so that upon administration, particles do not get into the lungs and rest in the nasal cavity.

The choice of optimal formulations in terms of consistency depends on the results of rheological studies. One of the stages in the development of nasal medicines is the choice of an optimal drug delivery system, and it depends mainly on the type of medicine. When the size of particles is larger than 10 µm, the medicine does not get into the lungs and produces effect in the nasal cavity. The formation of drops with particle sizes larger than 150 µm should be avoided since they tend to flow out of the nasal cavity immediately after spraying [**Error! Reference source not found.**-**Error! Reference source not found.**].

CONCLUSION

Analysis of literature suggests that nasal formulations are frequent subjects of studies. This means that they arouse interest, have good prospects and good commercial potential. *Ginkgo biloba* is a valuable raw material whose pharmacological efficacy has been convincingly demonstrated. Therefore, the search for optimal formulations of *Ginkgo biloba* herbal complexes is quite relevant. The use of nasal medicines may significantly increase the popularity of *Ginkgo biloba* in the pharmaceutical market, expand its pharmacological range, facilitate the development of a new medicinal compositions and production technology with improved biopharmaceutical characteristics and modern technological production schemes.

DECLARATIONS

Acknowledgement

This publication was prepared with the support of the “Russian Academic Excellence Project 5-100” (“Sechenov First Moscow State Medical University Program 5-100”).

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors equally contributed to this study.

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REFERENCES

1. *Marx D, Birkhoff M, Williams G. Intranasal drug administration – an interesting past and a fascinating future. Pharmaceutical technologies and packaging 2015; 5: 70-77.*
2. *Upadhyay S, Parikh A, Joshi P, Upadhyay UM, Chotai NP. Intranasal drug delivery system-A glimpse to become maestro. Journal of applied pharmaceutical science 2011; 1(03): 34-44.*
3. *Leskova N. The shortest rout of the drug. In the world of science («Scientific American» in Russian) 2016; 05/06: 115-117 [in Russian].*
4. *Madah-Amiria D, Clausena T, Lobmaiera P. Rapid widespread distribution of intranasal naloxone for overdose prevention. Drug and alcohol dependence 2017; 173: 17-23.*
5. *Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases: an anatomic, physiologic, and delivery technology overview. Therapeutic Delivery 2014; 5(6): 709-733.*
6. *Parvathi M. Intranasal drug delivery to brain: an overview. International journal of research in pharmacy and chemistry 2012; 2(3): 889-895.*
7. *Ruigrok MJ., de Lange EC. Emerging insights for translational pharmacokinetic and pharmacokinetic-pharmacodynamic studies: towards prediction of nose-to-brain transport in humans. The AAPS Journal 2015; 17 (3): 495-505.*
8. *Pandey PK, Sharma AK, Gupta U. Blood brain barrier: An overview on strategies in drug delivery, realistic in vitro modeling and in vivo live tracking. Tissue Barriers 2016; 4 (1): 1-14.*
9. *Chapman CD, Frey WH, Craft S, Danielyan L, Hallschmid M, Schiöth HB, Benedict C. Intranasal treatment of central nervous system dysfunction in humans. Pharm Res; 2013; 30: 2475-2484.*

10. Kumar NN, Gautam M, Lochhead JJ, Wolak DJ, Ithapu V, Singh V, Thorne RG. Relative vascular permeability and vascularity across different regions of the rat nasal mucosa: implications for nasal physiology and drug delivery. Scientific reports 2016; 6: 31732
11. Morimoto BH. Intranasal drug delivery: drug development considerations. Applied translational medicine 2015; 6. [cited 2019 Mar 6]. Available from: https://www.celerion.com/wp-content/uploads/2015/05/Celerion_050515_TIDES_Intranasal-Drug-Delivery.pdf
12. Cheng YS, Liao TY, Lin C, Shen HCH, Wang YH, Chang CW, Tu, PH. An intranasally delivered peptide drug ameliorates cognitive decline in Alzheimer transgenic mice. EMBO Molecular Medicine; 2017, 9 (5): 703-715.
13. Kumar A, Garg T, Sarma GS, Rath G, Goyal AK. Optimization of combinational intranasal drug delivery system for the management of migraine by using statistical design. Eur J Pharm Sci.2015; 70 (4): 140-151.
14. Ivanova NE. Results of application of "Semax" preparation with cognitive impairment in acute period of ischemic stroke and with chronic cerebral ischemia. Neurology and psychiatry. 2012; 2: 8-12 [in Russian].
15. Choi JE, Kim KR, Noh Y, Chung WH, Cho YS, Chung SK, Kim HY. Intranasal distribution and clearance of thermoreversible gel in an animal model Int forum allergy rhinol 2017; 7 (7): 705-711.
16. Filatova EG. Imigran nasal spray - use in clinical practice. Treatment of diseases of the nervous system 2009; 1: 8-13 [in Russian].
17. Rao M, Agrawal DK, Shirsath C. Thermoreversible mucoadhesive in situ nasal gel for treatment of Parkinson's disease. Drug dev ind pharm 2017; 843 (1): 142-150.
18. Katunina EA. Ginkgo biloba: the results of half a century of application experience. Polimodality of the effects of ginkgo biloba: experimental and clinical studies. Neurology and rheumatology 2013; 2: 53-57 [in Russian].
19. van Beek TA, Montoro P. Chemical analysis and quality control of ginkgo biloba leaves, extracts, and phytopharmaceuticals. Journal of Chromatography A 2009; 1216: 2002-2032.
20. Zhou X, Cui G, Tseng HHL, Lee SMY, Leung GPH, Chan SW, Hoi MPM. Vascular contributions to cognitive impairment and treatments with traditional Chinese Medicine. Evidence-Based Complementary and Alternative Medicine 2016; [cited 2019 Mar 6]. Available from: http://dx.doi.org/10.1155/2016/9627258
21. Chan PC, Xia Q, Fu PP. Ginkgo biloba leave extract: biological, medicinal, and toxicological effects. Journal of Environmental Science and Health Part C 2007; 25: 211-244.
22. Korchagina DV, Kurkina AV, Dubishchev AV, Kochneva ON, Gusev DO. The study of the neurotropic activity of medicinal preparations on the basis of Ginkgo biloba L. leaves. Fundamental research 2013; 10 (4): 812-815 [in Russian].
23. Zakharov VV, Bakulin IS. "Bilobyl" is an intensively neuroprotective agent of plant origin: a spectrum of application in neurology. Nervous diseases 2017 (1). [cited 2019 Mar 6]. Available from: http://atm-press.ru [in Russian].
24. Kadykov AS, Shakhparonova NV, Grishina DA. The role of "Bilobyl" preparation in the treatment of patients with cerebrovascular diseases. Russ Medical J2008; 16 (26): 1736-1738 [in Russian].
25. Register of medicines of Russia. [cited 2019 Mar 6]. Available from: https://www.rlsnet.ru/ [in Russian].
26. Burchinsky SG. Ginkgo drugs in the modern strategy of neuroprotection: opportunities and perspectives. Neurology 2011; 360: 29-34 [in Russian].
27. Song Y, Zeng Z, Jin C, Zhang J, Ding B, Zhang F. Protective effect of ginkgolide B against acute spinal cord injury in rats and its correlation with the Jak/STAT signaling pathway. Neurochemical research 2013; 38(3): 610-619.
28. Nash KM, Shah ZA. Current perspectives on the beneficial role of Ginkgo biloba in neurological and cerebrovascular disorders. Integrative medicine insights 2015; 10 IMI-S25054.
29. Qin XF, Lu XJ, Ge JB, Xu HZ, Qin HD, Xu F. Ginkgolide B prevents cathepsin-mediated cell death following cerebral ischemia/reperfusion injury. Neuroreport 2014; 25(4): 267-273.
30. Mohammad Nabavi S, Habtemariam S, Daglia M, Braidy N, Rosa Loizzo M, Tundis R, Fazel Nabavi S. Neuroprotective effects of ginkgolide B against ischemic stroke: a review of current literature. Curr Top Med Chem 2015; 15(21): 2222-2232.
31. Li Y, Wu Y, Yao X, Hao F, Yu C, Bao Y, Wang G. Ginkgolide A Ameliorates LPS-Induced inflammatory responses in vitro and in vivo. Int. J. Mol. Sci 2017; 18(4): 794.
32. Jiang M, Li J, Peng Q, Liu Y, Liu W, Luo C, Mo Z. Neuroprotective effects of bilobalide on cerebral ischemia and reperfusion injury are associated with inhibition of pro-inflammatory mediator production and down-regulation of JNK1/2 and p38 MAPK activation. J Neuroinflammation 2014; 11: 167.
33. Lang D, Kiewert C, Mdzinarishvili A, Schwarzkopf TM, Sumbria R, Hartmann J, Klein J. Neuroprotective effects of bilobalide are accompanied by a reduction of ischemia-induced glutamate release in vivo. Brain Res 2011; 1425: 155-163
34. Zhang C, Wang DF, Zhang Z, Han D, Yang K. EGb 761 protects cardiac microvascular endothelial cells against hypoxia/reoxygenation injury and exerts inhibitory effect on the ATM pathway. J. Microbiol. Biotechnol 2017; 27(3): 584-590.
35. Yin B, Xu Y, Wei R, Luo B. Ginkgo biloba on focal cerebral ischemia: a systematic review and meta-analysis. Am J Chin Med 2014; 42(4): 769-783.

36. Wu C, Zhao X, Zhang X, Liu S, Zhao H, Chen Y. Effect of ginkgo biloba extract on apoptosis of brain tissues in rats with acute cerebral infarction and related gene expression. Genet. Mol. Res. 2015; 14 (2): 6387-6394.
37. Kunelskaya NL, Yanushkina ES, Baybakova EV, Chugunova MA, Tardov MV, Zaoeva ZO, Isotova GN. Influence of Ginkgo biloba leaf extract EGB 761 in monotherapy on subjective ear noise. Medical Council 2017; 8: 76-79 [in Russian].
38. Beck SM, Ruge H, Schindler C, Burkart M, Miller R, Kirschbaum C, Goschke T. Effects of ginkgo biloba extract Egb 761® on cognitive control functions, mental activity of the prefrontal cortex and stress reactivity in elderly adults with subjective memory impairment – a randomized double-blind placebo-controlled trial. Hum. Psychopharmacol Clin Exp. 2016; 31: 227-242
39. Levin OS. The use of Ginkgo biloba extract (EGb 761) for the treatment of cognitive disorders in dyscirculatory encephalopathy. BC. 2009; 17 (20): 1356-1360 [in Russian].
40. Dodge HH, Zitzelberger T, Oken BS, Howieson D, Kaye J. A randomized placebo–controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology 2008; 70: 1809-1817.
41. Demarin V, Kes VB, Trkanjec Z, Budišić M, Pašić MB, Črnac P, Budinčević H. Efficacy and safety of Ginkgo biloba standardized extract in the treatment of vascular cognitive impairment: a randomized, double-blind, placebo-controlled clinical trial. Neuropsychiatric Disease and Treatment 2017; 13: 483-490.
42. Kamchatnov PR. Possibilities of applying the extract of gingko biloba ("Memoplant") in neurological practice. Journal of Neurology and Psychiatry 2010; 5: 51-56 [in Russian].
43. Stefanache F. Monitoring of efficacy and safety of Bilobil intens in patients with moderate and severe cognitive impairment and peripheral circulation impairments. Krka. Data on file, 2011. [cited 2019 Mar 6]. Available from: https://www.krka.biz/hr/lijekovi-i-drugi-proizvodi/bezreceptni-preparati/bilobil-intense-kapsule-120mg/1706/.
44. Al Zedan F, Gladyshev VV, Burlaka BS, Kechin IL. A study of the intensity of amlodipine release from various carriers of nasal ointments. Actual questions of pharmaceutical and medical science and practice 2012; 1(8): 82-85 [in Ukrainian].
45. Yakhkind MI, Tarantseva KR. Nanosystems for intranasal drug delivery. Izvestiya PGPU im. V. G. Belinskogo 2012; 29:284-292 [in Russian].
46. Gladyshev VV, Kuchina GK, Burlaka BS, Biryuk IA, Grigorieva M. Study of the influence of the carrier-base on the biopharmaceutical properties of the diltiazem nasal dosage form. Zaporozhye medical journal 2013; 2 (77): 87-90 [in Russian].
47. Balakrishnan P, Park EK, Song CK, Ko HJ, Hahn TW, Song KW, Cho HJ. Carbopol-incorporated thermoreversible gel for intranasal drug delivery. Molecules 2015; 20(3): 4124-4135.