Burdenko's Journal of Neurosurgery
2024, №6, pp. 97–102
https://doi.org/10.17116/neiro20248806197

Antidepressants as additional drugs for human brain gliomas

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ABSTRACT
Glioblastoma (GB) is the most aggressive malignant brain tumor. To date, there is no optimal treatment approach for this disease. Antidepressants with antitumor effects are one of the new therapeutic directions. A distinctive feature of these drugs is their approval for clinical practice in the treatment of depressive disorders.
Objective. To analyze available literature data on mechanisms of antitumor action and advisability of antidepressants for GB.
Material and methods. We reviewed the databases using the keywords «glioma», «antidepressants», «drug repurposing».
Results. According to numerous preclinical studies, activity of antidepressants at the cellular level is aimed at enhancing apoptosis and autophagy, inhibiting the cell cycle, differentiating and/or maintaining the stem cell status, as well as migrating tumor cells.
Conclusion. Available data can substantiate further experimental and clinical studies, as well as searching for therapeutic combinations using antidepressants for the treatment of human gliomas.

Keywords: *glioma, antidepressants, drug repurposing.*

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TO CITE THIS ARTICLE:
Revishchin AV, Pavlova GV. Antidepressants as additional drugs for human brain gliomas. *Burdenko's Journal of Neurosurgery*. 2024;88(6):97–102. (In Russ.). https://doi.org/10.17116/neiro20248806197

Abbreviations

ERK — extracellular signal-regulated kinase
NF-ϰB — nuclear factor kappa-light-chain-enhancer of activated B cells
MGMT — MGMT gene encoding O6-methylguanine methyltransferase involved in DNA repair
(PI3K)/AKT/mTOR — intracellular signaling pathway with phosphoinositide 3-kinase (PI3K) as a central component
SAM — S-adenosylmethionine
siRNA — small interfering molecules of ribonucleic acid (RNA)
VEGF — vascular endothelial growth factor
VEGFR — vascular endothelial growth factor receptor
GB — glioblastoma
SSRIs — selective serotonin reuptake inhibitors
GSC — glioma stem cell
TMZ — temozolomide
TCAs — tricyclic antidepressants

Introduction

A commercial approach to drug development has improved drug selection technology. However, the number of approved drugs and those reached the second phase of clinical trials is decreasing [1, 2]. In this regard, a special approach to the treatment of various diseases is searching for alternative uses of previously approved drugs with multifunctional properties [3]. This approach accelerates their implementation, since these drugs have been analyzed for pharmacokinetics in humans. Toxicity was estimated in preclinical and clinical studies [4]. To describe this process, Zhang Y. et al. [3] proposed the concept of "repurposing".

Despite various combinations of treatment regimens, there is still no significant progress in life expectancy of these patients [5—7]. In this regard, some researchers emphasized antitumor properties of known and approved antidepressants [7]. Antidepressants are common for additional treatment of depressive disorders in patients with gliomas [8]. They well penetrate the blood-brain barrier and have small number of side effects [7].

The objective of the study was to analyze the studies devoted to antitumor mechanisms of antidepressants in patients with glioblastoma (GB).

Results

Most data on antitumor effect of antidepressants were obtained in experiments in vitro on tumor cell cultures. There is antitumor effect of various antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and other compounds with known antidepressant activity.

Among the TCAs prescribed by oncologists [10], imipramine has the clearest antitumor activity. The last one is due to inhibition of serotonin and norepinephrine reuptake [11]. In vitro, imipramine inhibited phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling activity and activated autophagy-related protein beclin-1. These processes induced U-87MG glioma cell death through autophagy [12]. Knockdown of beclin-1 induced by siRNA abolished imipramine-induced cell death [12]. In vitro, imipramine inhibits extracellular signal-regulated kinase (ERK)/NF-κB reducing expression of tumor progression-associated proteins: matrix metallopeptidases MMP-2 and MMP-9, urokinase-type plasminogen activator (uPA), VEGF and cyclin D1 [13]. According to experiments on athymic mice with implanted U87/NF-κB/luc2 cells, imipramine blocks invasion, angiogenesis and proliferation of glioma cells through inhibition of ERK/NF-κB pathway [13]. In addition, imipramine prevents tumor growth by inhibiting the expression and translocation of yes-associated protein. This protein is essential in development and growth of GB [14]. There is a synergy of imipramine and temozolomide (TMZ) in suppression of glioma cell proliferation and increase of survival of mice with implanted tumors [14].

Available data indicate anti-invasive activity of imipramine. According to experiments on serrated adenocarcinoma cells, imipramine is a blocker of fascin-1. This protein is essential for tumor invasion. Fascin-1 overexpression in various cancers, including glioma, is associated with poor prognosis [15]. Analysis of lamellipodia, migration and invasion of colorectal cancer cells in vitro using 3D structure of human tissue confirmed anti-invasive activity of imipramine [15]. A clinical trial of efficacy of imipramine for targeted therapy of tumors overexpressing fascin-1 is currently underway [16]. High expression of fascin-1 in patients with glioblastoma multiforme is associated with shorter survival [17]. In addition, there is anti-invasive activity of small chimeric molecule, imipramine blue, inhibiting glioma invasion in vitro and in vivo models [18].

Glioma stem cells (GSCs) are of particular importance for invasive GB growth, its recurrence and resistance to therapy. Their reprogramming towards loss of stem phenotype can overcome this resistance [19, 20]. In experiments on T98G GB cells, imipramine and amitriptyline reduced expression of GSC marker proteins (CD44, Sox2 and Nestin). This suppressed GSC profile and reduced malignant phenotype of GB. Unlike TMZ, these TCAs stimulated viability of normal human astrocytes [21]. Combination of imipramine with VEGF/VEGFR pathway inhibitors (e.g., axitinib) reprograms immunosuppressive tumor-associated macrophages into immunostimulatory ones and enhances CD8+ and CD4+ T cell infiltration and activation. This provides therapeutic effect in mouse models of GB [22]. These preclinical data justify testing of imipramine for monotherapy or combination with TMZ in patients with glioma.

Antitumor activity was studied in another TCA (amitriptyline). Amitriptyline can suppress NF-κB activity, potently inhibit p65 NF-κB gene expression and maintain balance between pro- and anti-inflammatory mediators [23]. Amitriptyline reduces GSC levels and induces apoptosis in cells of glioblastoma multiforme [21].

Clomipramine (tricyclic antidepressant close to imipramine) stimulated apoptosis in patient-derived GB cell culture [24]. Combined effects of clomipramine and imatinib on C6 glioblastoma cell culture demonstrated synergy in suppressing proliferation [25, 26].

SSRIs are also of interest. In addition to neurotransmitter functions, serotonin is also a mitogenic factor for normal and tumor cells via 5-HT1 and 5-HT2 receptors [27]. Serotonin stimulates migration of glioma cells in human cell cultures [28]. Therefore, suppression of this function may inhibit tumor activity. Indeed, treatment with sertraline leads to cell death in all tested glioma cell cultures enriched with stem cells [27].

A typical SSRI fluoxetine [29] in experiments on human glioma cell lines (T98G, U138, SF767 and U251) disrupts activation of NF-κB and reduces expression of the MGMT gene encoding O-6-methylguanine-DNA methyltransferase. This enzyme protects the cell from cytotoxic effects of alkylating agents, for example, TMZ [30]. Combined exposure to fluoxetine and TMZ revealed synergistic effect on GB C6 cells [31]. Synergistic effect of fluoxetine and ionizing radiation on glioma was demonstrated in experiments on human U-87 GB cells. At the same time, radioprotective effect of fluoxetine was demonstrated on HFFF2 non-tumor fibroblasts [32]. Bi J. et al. [33] revealed higher dependence of GB cells on sphingomyelin phosphodiesterase 1 (SMPD1) and demonstrated its potential as a therapeutic target. In experiments on human U87/EGFRvIII GB cells, the authors found that fluoxetine inhibits enzymatic activity of SMPD1. Fluoxetine exposure leads to GB cell death by inhibition of signaling through EGFRvIII and activation of lysosomal stress. Combination of fluoxetine with TMZ caused complete regression of GB xenografts in mice [33]. Analysis of electronic medical records from the IBM MarketScan database revealed that combination of fluoxetine with standard treatment could improve survival of patients with brain tumors [33].

In experiments on U87 GB cells, sertraline was able to reduce the number of tumor cells in a dose-dependent manner [34]. Combination of sertraline with TMZ resulted an additive effect [34].

Another SSRI, fluvoxamine [35], was effective in suppression of actin polymerization in human GB cell lines

(A172, U87MG, U251MG) [36]. Daily administration of fluvoxamine to athymic mice implanted with human GB cells blocked tumor cell invasion and prolonged survival [36].

Paroxetine [37] can reduce cell viability and induce DNA fragmentation in GB C6 cell lines [38]. Impaired immunity in GB is associated with reduced number of T cells and their dysfunction [39]. Oral administration of paroxetine to mice with GB increased T cell infiltration into tumors [40].

S-adenosylmethionine (SAM) is a coenzyme involved in methyl transfer reactions. It was first described in 1952 [41]. Molecular weight is 399.447 g/mol. SAM actively penetrates the blood-brain barrier [42]. In Europe, SAM is prescribed for the treatment of arthritis and depression [43]. In Russia, this drug was registered only in 1994 under the name "Geptral". Mosca L. et al. [44] revealed that SAM selectively inhibited viability and proliferation of human GB cell lines U87MG, U343MG, U251MG and in GB cells after intraoperative biopsy. SAM induced apoptosis and cell cycle arrest, as well as suppressed DNA repair promoting GB cell death. Thus, SAM may be a potential adjuvant in therapy for GB.

Hypericin is the main active component of St. John's wort. Its effects are similar to standard antidepressants. Hypericin is widely used in the treatment of depression [45]. Photophysical properties of hypericin are being studied for potential photodynamic therapy [46]. Hypericin was perspective in phase I/II clinical trial against recurrent and progressive GB [47]. In experiments on human GB U87 cells, addition of hypericin causes cell death via apoptosis [48]. Gene expression profile changes in U87 cell line suggest that hypericin can modulate immune cell infiltration [48]. Currently, the studies devoted to hypericin in the treatment of glioma are ongoing [49, 50].

Ketamine is a NMDA antagonist used as an anesthetic agent in human and veterinary medicine. Meta-analysis revealed its effectiveness in the treatment of major depressive disorder [51]. Experiments on C6 GB cells revealed that ketamine suppressed proliferation of these cells. At the same time, ketamine had no effect on non-malignant astrocytes [52]. NMDA receptor blockade is involved in ketamine-induced decrease in C6 cell proliferation [52].

Recent comparisons of clinical outcomes in patients with GB with and without additional antidepressant therapy [53, 54] revealed a negative association between antidepressant intake and survival. However, these authors rightly emphasized advisability of further analysis to clarify the causal relationship of these results.

Conclusion

Studies of effects of antidepressants on high-grade glioma cells revealed their antitumor effect through activation of apoptosis and autophagy, effects on signaling pathways controlling cell cycle, differentiation and/or preservation of stem properties, as well as migration of tumor cells. These data confirm potential advisability of some antidepressants in adjuvant therapy for GB. Further laboratory and clinical studies are needed to find optimal therapeutic combinations with antiproliferative antidepressants. The last ones can slow down growth of human glioma.

Author contribution:
Concept and design of the study — Revishchin A.V., Pavlova G.V.
Collection and analysis of data — Revishchin A.V.
Writing the text — Revishchin A.V., Pavlova G.V.
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The study was carried out with financial support of the Ministry of Education and Science of the Russian Federation, grant No. 075-15-2024-561.

The authors declare no conflicts of interest.

REFERENCES

1. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical r&d efficiency. *Nature Reviews Drug Discovery*. 2012;11:191-200. https://doi.org/10.1038/nrd3681
2. Hodos RA, Kidd BA, Shameer K, Readhead BP, Dudley JT. In silico methods for drug repurposing and pharmacology. *Wiley Interdisciplinary Reviews: Systems Biology and medicine*. 2016;8:186-210. https://doi.org/10.1002/wsbm.1337
3. Zhang Y, Zheng Q, Zhou Y, Liu S. Repurposing clinical drugs as adometdc inhibitors using the scar strategy. *Frontiers in Pharmacology*. 2020;11:248. https://doi.org/10.3389/fphar.2020.00248
4. Baker NC, Ekins S, Williams AJ, Tropsha A. A bibliometric review of drug repurposing. *Drug Discovery Today*. 2018;23:661-672. https://doi.org/10.1016/j.drudis.2018.01.018
5. King JL, Benhabbour SR. Glioblastoma multiforme-a look at the past and a glance at the future. *Pharmaceutics*. 2021;13(7):1053. https://doi.org/10.3390/pharmaceutics13071053
6. Minniti G, Amelio D, Amichetti M, Salvati M, Muni R, Bozzao A, Lanzetta G, Scarpino S, Arcella A, Enrici RM. Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide. *Radiotherapy and Oncology*. 2010;97:377-381. https://doi.org/10.1016/j.radonc.2010.08.020
7. Pinkiewicz M, Pinkiewicz M, Walecki J, Zaczynski A, Zawadzki M. Breaking barriers in neuro-oncology: A scoping literature review on invasive and non-invasive techniques for blood-brain barrier disruption. *Cancers*. 2024;16(1):236. https://doi.org/10.3390/cancers16010236
8. van der Meer PB, Dirven L, Hertler C, Boele FW, Batalla A, Walbert T, Rooney AG, Koekkoek JAF. Depression and anxiety in glioma patients. *Neuro-Oncology Practice*. 2023;10:335-343. https://doi.org/10.1093/nop/npad019
9. Shi C, Lamba N, Zheng LJ, Cote D, Regestein QR, Liu CM, Tran Q, Routh S, Smith TR, Mekary RA, Broekman MLD. Depression and survival of glioma patients: A systematic review and meta-analysis. *Clinical Neurology and Neurosurgery*. 2018;172:8-19. https://doi.org/10.1016/j.clineuro.2018.06.016

10. Tan SK, Jermakowicz A, Mookhtiar AK, Nemeroff CB, Schurer SC, Ayad NG. Drug repositioning in glioblastoma: A pathway perspective. *Frontiers in Pharmacology*. 2018;9:218. https://doi.org/10.3389/fphar.2018.00218
11. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *British Journal of Pharmacology*. 2007;151:737-748. https://doi.org/10.1038/sj.bjp.0707253
12. Jeon SH, Kim SH, Kim Y, Kim YS, Lim Y, Lee YH, Shin SY. The tricyclic antidepressant imipramine induces autophagic cell death in u-87mg glioma cells. *Biochemical and Biophysical Research Communications*. 2011;413:311-317. https://doi.org/10.1016/j.bbrc.2011.08.093
13. Hsu FT, Chiang IT, Wang WS. Induction of apoptosis through extrinsic/intrinsic pathways and suppression of erk/nf-kappab signalling participate in anti-glioblastoma of imipramine. *Journal of Cellular and Molecular Medicine*. 2020;24:3982-4000. https://doi.org/10.1111/jcmm.15022
14. Wang Y, Wang X, Wang X, Wu D, Qi J, Zhang Y, Wang K, Zhou D, Meng QM, Nie E, Wang Q, Yu RT, Zhou XP. Imipramine impedes glioma progression by inhibiting yap as a hippo pathway independent manner and synergizes with temozolomide. *Journal of Cellular and Molecular Medicine*. 2021;25:9350-9363. https://doi.org/10.1111/jcmm.16874
15. Alburquerque-Gonzalez B, Bernabe-Garcia M, Montoro-Garcia S, Bernabe-Garcia A, Rodrigues PC, Ruiz Sanz J, Lopez-Calderon FF, Luque I, Nicolas FJ, Cayuela ML, Salo T, Perez-Sanchez H, Conesa-Zamora P. New role of the antidepressant imipramine as a fascin1 inhibitor in colorectal cancer cells. *Experimental and Molecular Medicine*. 2020;52:281-292. https://doi.org/10.1038/s12276-020-0389-x
16. *Histological and clinical effects of imipramine in the treatment of patients with cancer over-expressing fascin 1*. European Union Clinical Trials Register, 2021. https://www.clinicaltrialsregister.eu/ctr-search/search?query=HITCLIF
17. Zhang H, Cong QX, Zhang SG, Zhai XW, Li HF, Li SQ. High expression levels of fascin-1 protein in human gliomas and its clinical relevance. *Open Medicine (Wars)*. 2018;13:544-550. https://doi.org/10.1515/med-2018-0080
18. Munson JM, Fried L, Rowson SA, Bonner MY, Karumbaiah L, Diaz B, Courtneidge SA, Knaus UG, Brat DJ, Arbiser JL, Bellamkonda RV. Anti-invasive adjuvant therapy with imipramine blue enhances chemotherapeutic efficacy against glioma. *Science Translational Medicine*. 2012;4:127ra136. https://doi.org/10.1126/scitranslmed.3003016
19. Kolesnikova V, Revishchin A, Fab L, Alekseeva A, Ryabova A, Pronin I, Usachev DY, Kopylov A, Pavlova G. Gqicombi application to subdue glioma via differentiation therapy. *Frontiers in Oncology*. 2024;14:1322795. https://doi.org/10.3389/fonc.2024.1322795
20. Pavlova G, Kolesnikova V, Samoylenkova N, Drozd S, Revishchin A, Shamadykova D, Usachev DY, Kopylov A. A combined effect of g-quadruplex and neuro-inducers as an alternative approach to human glioblastoma therapy. *Frontiers in Oncology*. 2022;12:880740. https://doi.org/10.3389/fonc.2022.880740
21. Bielecka-Wajdman AM, Lesiak M, Ludyga T, Sieron A, Obuchowicz E. Reversing glioma malignancy: A new look at the role of antidepressant drugs as adjuvant therapy for glioblastoma multiforme. *Cancer Chemotherapy and Pharmacology*. 2017;79:1249-1256. https://doi.org/10.1007/s00280-017-3329-2
22. Chryplewicz A, Scotton J, Tichet M, Zomer A, Shchors K, Joyce JA, Homicsko K, Hanahan D. Cancer cell autophagy, reprogrammed macrophages, and remodeled vasculature in glioblastoma triggers tumor immunity. *Cancer Cell*. 2022;40(10):1111-1127.e9. https://doi.org/10.1016/j.ccell.2022.08.014
23. Troib A, Azab AN. Effects of psychotropic drugs on nuclear factor kappa b. *European Reviews for Medical and Pharmacological Sciences*. 2015;19:1198-1208.
24. Parker KA, Pilkington GJ. Apoptosis of human malignant glioma-derived cell cultures treated with clomipramine hydrochloride, as detected by annexin-v assay. *Radiology and Oncology*. 2006;40. (2). Retrieved from https://www.radioloncol.com/index.php/ro/article/view/1265
25. Bilir A, Erguven M, Yazihan N, Aktas E, Oktem G, Sabanci A. Enhancement of vinorelbine-induced cytotoxicity and apoptosis by clomipramine and lithium chloride in human neuroblastoma cancer cell line sh-sy5y. *Journal of Neurooncology*. 2010;100:385-395. https://doi.org/10.1007/s11060-010-0209-6
26. Xia Z, Depierre JW, Nassberger L. The tricyclic antidepressants clomipramine and citalopram induce apoptosis in cultured human lymphocytes. *Journal of Pharmacy and Pharmacology*. 1996;48:115-116. https://doi.org/10.1111/j.2042-7158.1996.tb05889.x
27. Pollard SM, Yoshikawa K, Clarke ID, Danovi D, Stricker S, Russell R, Bayani J, Head R, Lee M, Bernstein M, Squire JA, Smith A, Dirks P. Glioma stem cell lines expanded in adherent culture have tumor-specific phenotypes and are suitable for chemical and genetic screens. *Cell Stem Cell*. 2009;4:568-580. https://doi.org/10.1038/bjc.2016.109
28. Sarrouilhe D, Mesnil M. Serotonin and human cancer: A critical view. *Biochimie*. 2019;161:46-50. https://doi.org/10.1016/j.biochi.2018.06.016
29. Cheer SM, Goa KL. Fluoxetine: A review of its therapeutic potential in the treatment of depression associated with physical illness. *Drugs*. 2001;61:81-110. https://doi.org/10.2165/00003495-200161010-00010
30. Song T, Li H, Tian Z, Xu C, Liu J, Guo Y. Disruption of nf-kappab signaling by fluoxetine attenuates mgmt expression in glioma cells. *OncoTargets and Therapy*. 2015;8:2199-2208. https://doi.org/10.2147/OTT.S85948
31. Ma J, Yang YR, Chen W, Chen MH, Wang H, Wang XD, Sun LL, Wang FZ, Wang DC. Fluoxetine synergizes with temozolomide to induce the chop-dependent endoplasmic reticulum stress-related apoptosis pathway in glioma cells. *Oncology Reports*. 2016;36:676-684. https://doi.org/10.3892/or.2016.4860
32. Hosseinimehr SJ, Najafi SH, Shafiee F, Hassanzadeh S, Farzipour S, Ghasemi A, Asgarian-Omran H. Fluoxetine as an antidepressant medicine improves the effects of ionizing radiation for the treatment of glioma. *Journal of Bioenergetics and Biomembranes*. 2020;52:165-174. https://doi.org/10.1007/s10863-020-09833-9
33. Bi J, Khan A, Tang J, Armando AM, Wu S, Zhang W, Gimple RC, Reed A, Jing H, Koga T, Wong IT, Gu Y, Miki S, Yang H, Prager B, Curtis EJ, Wainwright DA, Furnari FB, Rich JN, Cloughesy TF, Kornblum HI, Quehenberger O, Rzhetsky A, Cravatt BF, Mischel PS. Targeting glioblastoma signaling and metabolism with a re-purposed brain-penetrant drug. *Cell Reports*. 2021;37:109957. https://doi.org/10.1016/j.celrep.2021.109957
34. Tzadok S, Beery E, Israeli M, Uziel O, Lahav M, Fenig E, Gil-Ad I, Weizman A, Nordenberg J. In vitro novel combinations of psychotropics and anti-cancer modalities in u87 human glioblastoma cells. *International Journal of Oncology*. 2010;37:1043-1051. https://doi.org/10.3892/ijo_00000756
35. Xu D, Wang C, Zhu X, Zhao W, Jiang B, Cui S, Sun Y, Cui Z. The antidepressant-like effects of fluvoxamine in mice involve the mtor signaling in the hippocampus and prefrontal cortex. *Psychiatry Research*. 2020;285:112708. https://doi.org/10.1016/j.psychres.2019.112708
36. Hayashi K, Michiue H, Yamada H, Takata K, Nakayama H, Wei FY, Fujimura A, Tazawa H, Asai A, Ogo N, Miyachi H, Nishiki T, Tomizawa K, Takei K, Matsui H. Fluvoxamine, an anti-depressant, inhibits human glioblastoma invasion by disrupting actin polymerization. *Scientific Reports*. 2016;6:23372. https://doi.org/10.1038/srep23372
37. Thakerar A, Simadri K, Alexander M, Fullerton S. Paroxetine for the treatment of intractable and persistent cough in patients diagnosed with cancer. *Journal of Oncology Pharmacy Practice*. 2019;26:803-808. https://doi.org/10.1177/1078155219870594
38. Levkovitz Y, Gil-Ad I, Zeldich E, Dayag M, Weizman A. Differential induction of apoptosis by antidepressants in glioma and neuroblastoma cell lines: Evidence for p-c-jun, cytochrome c, and caspase-3 involvement. *Journal of Molecular Neuroscience*. 2005;27:29-42. https://doi.org/10.1385/JMN:27:1:029
39. Woroniecka KI, Rhodin KE, Chongsathidkiet P, Keith KA, Fecci PE. T-cell dysfunction in glioblastoma: Applying a new framework. *Clinical Cancer Research*. 2018;24:3792-3802. https://doi.org/10.1158/1078-0432.CCR-18-0047
40. Wang T, Zhang H, Han Y, Zheng Q, Liu H, Han M, Li Z. Reversing t cell dysfunction to boost glioblastoma immunotherapy by paroxetine-mediated grk2 inhibition and blockade of multiple checkpoints through biomimetic nanoparticles. *Advanced Science*. 2023;10:e2204961. https://doi.org/10.1002/advs.202204961
41. Cantoni GL. The nature of the active methyl donor formed enzymatically from l-methionine and adenosinetriphosphate1,2. *Journal of the American Chemical Society*. 1952;74(11):2942-2943.
42. Bottiglieri T, Laundy M, Martin R, Carney MW, Nissenbaum H, Toone BK, Johnson AL, Reynolds EH. S-adenosylmethionine influences monoamine metabolism. *Lancet*. 1984;2:224. https://doi.org/10.1016/s0140-6736(84)90507-5

43. Janicak PG, Lipinski J, Davis JM, Altman E, Sharma RP. Parenteral s-adenosyl-methionine (same) in depression: Literature review and preliminary data. *Psychopharmacology Bulletin*. 1989;25:238-242.
44. Mosca L, Pagano C, Tranchese RV, Grillo R, Cadoni F, Navarra G, Coppola L, Pagano M, Mele L, Cacciapuoti G, Laezza C, Porcelli M. Antitumoral activity of the universal methyl donor s-adenosylmethionine in glioblastoma cells. *Molecules*. 2024;29(8):1708. https://doi.org/10.3390/molecules29081708
45. Linde K, Berner M, Egger M, Mulrow C. St john's wort for depression: Meta-analysis of randomised controlled trials. *The British Journal of Psychiatry*. 2005;186:99-107. https://doi.org/10.1192/bjp.186.2.99
46. Dong X, Zeng Y, Zhang Z, Fu J, You L, He Y, Hao Y, Gu Z, Yu Z, Qu C, Yin X, Ni J, Cruz LJ. Hypericin-mediated photodynamic therapy for the treatment of cancer: A review. *Journal of Pharmacy and Pharmacology*. 2021;73:425-436. https://doi.org/10.1093/jpp/rgaa018
47. Couldwell WT, Surnock AA, Tobia AJ, Cabana BE, Stillerman CB, Forsyth PA, Appley AJ, Spence AM, Hinton DR, Chen TC. A phase 1/2 study of orally administered synthetic hypericin for treatment of recurrent malignant gliomas. *Cancer*. 2011;117:4905-4915. https://doi.org/10.1002/cncr.26123
48. Ghiasvand S, Javidi MA, Mohammadian A, Mousavi SA, Shahriari F, Alavian F. Transcriptome analysis evinces anti-neoplastic mechanisms of hypericin: A study on u87 glioblastoma cell line. *Life Sciences*. 2021;266:118874. https://doi.org/10.1016/j.lfs.2020.118874
49. Doroshenko A, Tomkova S, Kozar T, Stroffekova K. Hypericin, a potential new bh3 mimetic. *Frontiers in Pharmacology*. 2022;13:991554. https://doi.org/10.3389/fphar.2022.991554
50. Hovan A, Pevna V, Huntosova V, Miskovsky P, Bano G. Singlet oxygen lifetime changes in dying glioblastoma cells. *Photochemistry and Photobiology*. 2024;100:159-171. https://doi.org/10.1111/php.13828
51. Han Y, Chen J, Zou D, Zheng P, Li Q, Wang H, Li P, Zhou X, Zhang Y, Liu Y, Xie P. Efficacy of ketamine in the rapid treatment of major depressive disorder: A meta-analysis of randomized, double-blind, placebo-controlled studies. *Neuropsychiatric Disease and Treatment*. 2016;12:2859-2867. https://doi.org/10.2147/NDT.S117146
52. Niwa H, Furukawa KI, Seya K, Hirota K. Ketamine suppresses the proliferation of rat c6 glioma cells. *Oncology Letters*. 2017;14:4911-4917. https://doi.org/10.3892/ol.2017.6806
53. Edstrom S, Hellquist BN, Sandstrom M, Sadanandan SA, Bjorkblom B, Melin B, Sjoberg RL. Antidepressants and survival in glioma-a registry-based retrospective cohort study. *Neuro-Oncology Practice*. 2024;11:125-131. https://doi.org/10.1093/nop/npad057
54. Seliger C, Oppong FB, Lefranc F, Chinot O, Stupp R, Nabors B, Gorlia T, Weller M. Association of antidepressant drug use with outcome of patients with glioblastoma. *International Journal of Cancer*. 2023;152:1348-1359. https://doi.org/10.1002/ijc.34344

Received 06.09.2024
Accepted 20.09.2024