Melatonin in glioblastoma therapy: clinical promise and mechanistic insights from bench to bedside

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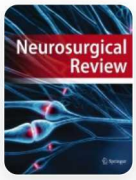

Neurosurgical Review

Aims and scope

Submit manuscript

Omar Alomari, Beyzanur Güney, Rana Al Juhmani, Bassel Alrabadi, Muhammed Edib Mokresh, Hatice Odabas, Tasneem Alomari & Russel J. Reiter

Abstract

Glioblastoma (GBM) is the most common and aggressive primary brain malignancy in adults, characterized by rapid progression, therapeutic resistance, and poor prognosis. Despite multimodal therapy, including maximal resection, radiotherapy, and temozolomide (TMZ), median survival is only 15 months. The recurrence rate exceeds 75%, and five-year survival is < 5%. This critical need for novel adjunctive therapies has drawn attention to melatonin, an indoleamine with multifaceted anti-tumor effects. We systematically reviewed the molecular, cellular, and therapeutic roles of melatonin in GBM to clarify its mechanistic impact and clinical potential. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines, we conducted a systematic search across PubMed, Scopus, and Web of Science. Eligible studies included original preclinical or clinical research on melatonin in GBM models. Risk of bias was assessed using Quality Assessment Tool for In Vitro Studies (QUIN) for in vitro studies, Joanna Briggs Institute (JBI) for

case reports, National Institutes of Health (NIH) for observational studies and Cochrane Risk of Bias 2 (RoB2) for randomized clinical studies. Data were extracted on study design, melatonin formulations, molecular targets, and therapeutic outcomes. The review protocol was registered in PROSPERO (CRD420251113393). Thirty-two studies were included: 28 preclinical, two prospective trials, one retrospective observational study, and one case report. Preclinical data consistently showed that melatonin inhibited GBM proliferation, migration, invasion, stemness, and angiogenesis; disrupted mitochondrial metabolism; induced apoptosis; and modulated key pathways (EZH2–STAT3, HIF-1α, SIRT1, MT1/MT2, miRNAs). Melatonin enhanced the efficacy of TMZ, nimotuzumab, albendazole, and HAD©C inhibitors. Preliminary clinical observations from small-scale studies hint at potential improvements in survival and reduced toxicity, though these findings require validation in larger cohorts. Preclinical models indicate that melatonin exerts pleiotropic anti-tumor effects in GBM and may synergize with standard therapies. However, clinical translation remains in early stages. Current evidence supports its promise as a co-therapeutic agent, though high-quality randomized clinical trials are urgently required to validate its efficacy, optimize dosing, and define delivery strategies.