SUMMARY

Gliomas are the most common and malignant tumors of the central nervous system. They are characterized by aggressive growth and invasive infiltration of healthy brain tissue. Unfortunately, the prognosis for patients are very poor. The average survival time of patients diagnosed with a tumor at the most malignant stage does not exceed 15 months. The currently proposed therapeutic strategies allow only prolongation and improvement of the patient's quality of life, but not cure. High mortality is associated with the infiltrative nature of the tumor and emerging resistance to chemotherapy. Great attention is paid to plant compounds as a treasury of natural substances of a health-promoting nature. It has been shown that the use of these compounds in combination with chemotherapeutic agents enhances their anticancer properties, while protecting normal cells. In my thesis, I attempted to determine the anticancer effects of quercetin (a natural flavonoid), lensoside Aβ (a derivative of quercetin) and sorafenib (a cytostatic drug), in a single and simultaneous application, as effective inducers of programmed cell death.

Human cell lines of anaplastic astrocytoma (MOGGCCM, LN-229, SW1783) and glioblastoma multiforme (T98G, LN-18, CCF-STTG1) were the research model used in the in vitro studies. Microscopic observations showed that all tested compounds induced programmed death in the tested lines, and the most common type was apoptosis. At the same time. Flavonoids, quercetin and lensoside Aβ, in a single application proved to be ineffective inducers of apoptosis, and the level of cells dying in this way did not exceed 12% in anaplastic astrocytoma and glioblastoma multiforme lines. An exception was the LN229 line (stage III), where lensoside Aβ induced 45.3% of apoptosis. Propapoptotic properties, at a level comparable to flavonoids, were also demonstrated by sorafenib. Only in the LN-18 line the level of apoptotic death was 37%. Interestingly, this compound also showed significant pro-autophagal activity in T98G cells.

Simultaneous application of sorafenib with lensoside Aβ turned out to be much more effective in eliminating glioma and astrocytoma cells by apoptosis, compared to single compounds. Quercetin was weak adjuvant. Both flavonoids reduced the pro-autofagal potential of sorafenib. The pro-apoptotic properties of the tested substances were also confirmed using flow cytometry techniques, showing a decrease in the mitochondrial membrane potential of anaplastic astrocytoma and glioblastoma cells.

Immunoblotting technique shown that at the molecular level, the pro-apoptotic activity of the tested compounds, both in single and combined application, caused an increase in the level of active caspase 3. Autofagy death was correlated with an increased amount of beclin-1. The studies showed that the tested compounds also have the ability to reduce the level of Raf kinase. This protein is a key element of the intracellular Ras/Raf/MEK/ERK survival signaling pathway, the increased activity of which is noted in gliomas. Blocking the expression of the Raf gene with specific siRNAs did not significantly increase the sensitivity of glioma cells to the induction of programmed death under the tested compounds, which may suggest that this pathway is not the main mechanism responsible for the resistance of glioblastoma cells to chemotherapy.

Considering the availability of flavonoids and their proven health-promoting effects, including anticancer potential, the obtained results may be the basis for the development of new therapeutic strategies to eliminate glioblastoma cells by programmed cell death. Learning the function of additional substituents in the structure of flavonoids will allow for the construction and anticipating the effects of their use.

Key words: gliomas, programmed cell death, quercetin, lensoside Aβ, sorafenib

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