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Abstract

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Glioblastoma is the most common cerebral tumor in adults. The median survival of glioblastoma patients is 12 months. Metformin is a biguanide used as a standard clinical drug for the treatment of type 2 diabetes. Recently, several studies revealed that the risk of cancer development was significantly reduced for diabetic patients treated with metformin compared to those treated with insulin or sulfonylureas [1]. Even if metformin acts as an antitumoral agent, it is a nontoxic molecule with IC_{50} around 10 mM in cancer cells. In cancer research, naturally occurring phenolic acids are well known to be useful antioxidant agents and allow the inhibition of the migration and adhesion of cancer cells [2]. Moreover, a recent study [3] on nitrones combined with phenolic acids has shown that phenolic acids keep their antioxidant properties even if they are coupled with another molecule. The purpose of this study is to design new molecules combining metformin and a phenolic acid to improve the cytotoxicity on cancer cells.

A series of hybrid molecules was then synthesized. For each molecule, IC_{50} on glioblastoma cell lines (U87 and U251) and on human dermal fibroblasts was tested. After this first screening, the mechanisms through which the best hybrid molecules act on cancer cells were studied and compared with those of metformin. Finally, the study of cytotoxicity on cancer stems cells of glioblastoma, GBM6, and GBM9 revealed that metformin-derived molecules may also restrict the growth of stem cells. As cancer stem cells are one of the causes of tumor resistance [4], metformin hybrid molecules may become a novel therapeutic option to treat glioblastoma.

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