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Cannabinoids administration enhances the anticancer activity of Bevacizumab in preclinical models of glioma

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Glioblastoma (GB) is one of the most aggressive forms of cancer. It has been proposed that the presence within these tumors of a population of cells with stem-like characteristics, termed glioma stem-like cells or glioma-initiating cells (GICs), which exhibit high resistance to chemo- and radiotherapy, is responsible for the relapses that almost invariably occur in patients with this disease. Another factor that contributes to the aggressive behavior of GB is the tumor microenvironment. Specifically, GB are highly angiogenic and vascularized tumors whose growth is dependent on the formation of new blood vessels. Accordingly, different antiangiogenic agents have been assayed in GB patients, being the most widely used Bevacizumab (BVZ), a humanized monoclonal antibody that prevents the interaction of the Vascular Endothelial Growth Factor (VEGF) with its receptor, VEGFR. Although the initial studies using this agent showed promising results, BVZ treatment has not been able to significantly modify the survival of patients with GB. Thus, the development of novel therapeutic approaches (and specifically those targeting the population of GICs and/or improving the response to anti-angiogenic agents) are urgently needed to improve the survival of the patients suffering this devastating disease.

Previous observations by our group and others had shown that ?^{9}-Tetrahydrocannabinol (THC, the main active ingredient of marijuana) and other cannabinoids including cannabidiol (CBD) exert antitumoral actions in animal models of glioma. This anticancer activity is based at least in part on the ability of these compounds to; (i) induce glioma cell death; and (ii) inhibit tumor angiogenesis via downregulation of the VEGF/VEGFR signaling pathway. We also found that the administration of THC (or of THC+CBD at a 1:1 ratio) in combination with temozolomide (TMZ), the benchmark agent for the treatment of GB, synergistically reduces the growth of glioma xenografts including those derived from GICs. However, the effect of the combined administration of cannabinoids and antiangiogenic agents has not been investigated.

Therefore, in this study we explored the potential efficacy of these combinational treatments in GB models. Our results show that the combined administration of THC (or of THC and CBD at a 1:1 ratio) and BVZ: (i) decreased the proliferation and self-renewal capacity of GICs; (ii) interfered with the vessel-forming capacity of endothelial cells; (iii) reduced the growth of intracranial GICs-derived xenografts; and (iv) enhanced the survival of the animals bearing these tumors, at a higher extent than the treatment with cannabinoids or BVZ alone. We also found that BVZ further enhanced the anticancer activity of the combination of THC:CBD (1:1) and TMZ in the above models. Our findings support the idea that the combined administration of cannabinoids, BVZ and TMZ could be explored as a potential therapeutic strategy for the management of GB.