

Gliomas/Cancer

Gliomas (tumors in the brain) are especially aggressive malignant forms of cancer, often resulting in the death of affected patients within one to two years following diagnosis. There is no cure for gliomas and most available treatments provide only minor symptomatic relief.

A review of the modern scientific literature reveals numerous preclinical studies and one pilot clinical study demonstrating cannabinoids' ability to act as antineoplastic agents, particularly on glioma cell lines.

Writing in the September 1998 issue of the journal *FEBS Letters*, investigators at Madrid's Complutense University, School of Biology, first reported that delta-9-THC induced apoptosis (programmed cell death) in glioma cells in culture.[1] Investigators followed up their initial findings in 2000, reporting that the administration of both THC and the synthetic cannabinoid agonist WIN 55,212-2 "induced a considerable regression of malignant gliomas" in animals.[2] Researchers again confirmed cannabinoids' ability to inhibit tumor growth in animals in 2003.[3]

That same year, Italian investigators at the University of Milan, Department of Pharmacology, Chemotherapy and Toxicology, reported that the non-psychoactive cannabinoid, cannabidiol (CBD), inhibited the growth of various human glioma cell lines *in vivo* and *in vitro* in a dose dependent manner. Writing in the November 2003 issue of the *Journal of Pharmacology and Experimental Therapeutics Fast Forward*, researchers concluded, "Non-psychoactive CBD ... produce[s] a significant anti-tumor activity both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as an antineoplastic agent." [4]

In 2004, Guzman and colleagues reported that cannabinoids inhibited glioma tumor growth in animals and in human glioblastoma multiforme (GBM) tumor samples by altering blood vessel morphology (e.g., VEGF pathways). Writing in the August 2004 issue of *Cancer Research*, investigators concluded, "The present laboratory and clinical findings provide a novel pharmacological target for cannabinoid-based therapies." [5]

More recently, investigators at the California Pacific Medical Center Research Institute reported that the administration of THC on human glioblastoma multiforme cell lines decreased the proliferation of malignant cells and induced cell death more rapidly than did the administration of WIN 55,212-2. Researchers also noted that THC selectively targeted

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malignant cells while ignoring healthy ones in a more profound manner than the synthetic alternative.[6]

Most recently, Guzman and colleagues reported that THC administration decreases recurrent glioblastoma multiforme tumor growth in patients diagnosed with recurrent GBM. In the first ever pilot clinical trial assessing the use of cannabinoids and GBM, investigators found that the intratumoral administration of THC was associated with reduced tumor cell proliferation in two of nine subjects. "The fair safety profile of THC, together with its possible anti-proliferative action on tumor cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids," investigators concluded.[7] Several additional investigators have also recently called for further exploration of cannabis-based therapies for the treatment of glioma.[8-10]

In addition to cannabinoids' ability to moderate glioma cells, separate studies demonstrate that cannabinoids and endocannabinoids can also inhibit the proliferation of other cancer cell lines, including breast carcinoma,[11-15] prostate carcinoma,[16-18] colorectal carcinoma,[19] gastric adenocarcinoma,[20] skin carcinoma,[21] leukemia cells,[22-23] neuroblastoma,[24] lung carcinoma,[25-26] uterus carcinoma,[27] thyroid epithelioma,[28] pancreatic adenocarcinoma,[29-30] cervical carcinoma,[31] oral cancer,[32] biliary tract cancer (cholangiocarcinoma)[33] and lymphoma.[34-35]

Studies also indicate that the administration of cannabinoids, in conjunction with conventional anti-cancer therapies, can enhance the effectiveness of standard cancer treatments.[36] Most recently, investigators at the University of California, Pacific Medical Center reported that cannabinoids possess synergistic anti-cancer properties -- finding that the administration of a combination of the plant's constituents is superior to the administration of isolated compounds alone.[37]

Consequently, many experts now believe that cannabinoids "may represent a new class of anticancer drugs that retard cancer growth, inhibit angiogenesis and the metastatic spreading of cancer cells." [38-39]

REFERENCES

[1] Guzman et al. 1998. Delta-9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. *FEBS Letters* 436: 6-10.

[2] Guzman et al. 2000. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nature Medicine* 6: 313-319.

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- [3] Guzman et al. 2003. Inhibition of tumor angiogenesis by cannabinoids. *The FASEB Journal* 17: 529-531.
- [4] Massi et al. 2004. Antitumor effects of cannabidiol, a non-psychotropic cannabinoid, on human glioma cell lines. *Journal of Pharmacology and Experimental Therapeutics Fast Forward* 308: 838-845.
- [5] Guzman et al. 2004. Cannabinoids inhibit the vascular endothelial growth factor pathways in gliomas (PDF). *Cancer Research* 64: 5617-5623.
- [6] Allister et al. 2005. Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells. *Journal of Neurooncology* 74: 31-40.
- [7] Guzman et al. 2006. A pilot clinical study of delta-9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *British Journal of Cancer*.
- [8] Parolaro and Massi. 2008. Cannabinoids as a potential new drug therapy for the treatment of gliomas. *Expert Reviews of Neurotherapeutics* 8: 37-49
- [9] Galanti et al. 2007. Delta9-Tetrahydrocannabinol inhibits cell cycle progression by downregulation of E2F1 in human glioblastoma multiforme cells. *Acta Oncologica* 12: 1-9.
- [10] Calatuzzolo et al. 2007. Expression of cannabinoid receptors and neurotrophins in human gliomas. *Neurological Sciences* 28: 304-310.
- [11] Cafferlati et al. 2006. Delta-9-Tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation. *Cancer Research* 66: 6615-6621.
- [12] Di Marzo et al. 2006. Anti-tumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *Journal of Pharmacology and Experimental Therapeutics Fast Forward* 318: 1375-1387.
- [13] De Petrocellis et al. 1998. The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. *Proceedings of the National Academy of Sciences of the United States of America* 95: 8375-8380.
- [14] McAllister et al. 2007. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. *Molecular Cancer Therapeutics* 6: 2921-2927.
- [15] Cafferlati et al. 2010. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. *Molecular Cancer* 9: 196.
- [16] Sarfaraz et al. 2005. Cannabinoid receptors as a novel target for the treatment of prostate cancer. *Cancer Research* 65: 1635-1641.
- [17] Mimeault et al. 2003. Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines. *Prostate* 56: 1-12.
- [18] Ruiz et al. 1999. Delta-9-tetrahydrocannabinol induces apoptosis in human prostate PC-3 cells via a receptor-independent mechanism. *FEBS Letters* 458: 400-404.

- [19] Pastos et al. 2005. The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase-2. *Gut* 54: 1741-1750.
- [20] Di Marzo et al. 2006. op. cit
- [21] Casanova et al. Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. 2003. *Journal of Clinical Investigation* 111: 43-50.
- [22] Powles et al. 2005. Cannabis-induced cytotoxicity in leukemic cell lines. *Blood* 105: 1214-1221
- [23] Jia et al 2006. Delta-9-tetrahydrocannabinol-induced apoptosis is jurkat leukemic T cells in regulated by translocation of Bad to mitochondria. *Molecular Cancer Research* 4: 549-562.
- [24] Manuel Guzman. 2003. Cannabinoids: potential anticancer agents (PDF). *Nature Reviews Cancer* 3: 745-755.
- [25] Ibid.
- [26] Preet et al. 2008. Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. *Oncogene* 10: 339-346.
- [27] Manuel Guzman. 2003. Cannabinoids: potential anticancer agents (PDF). *Nature Reviews Cancer* 3: 745-755.
- [28] Baek et al. 1998. Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Archives of Pharmacal Research*: 21: 353-356.
- [29] Carracedo et al. 2006. Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes. *Cancer Research* 66: 6748-6755.
- [30] Michalski et al. 2008. Cannabinoids in pancreatic cancer: correlation with survival and pain. *International Journal of Cancer* 122: 742-750.
- [31] Ramer and Hinz. 2008. Inhibition of cancer cell invasion by cannabinoids via increased cell expression of tissue inhibitor of matrix metalloproteinases-1. *Journal of the National Cancer Institute* 100: 59-69.
- [32] Whyte et al. 2010. Cannabinoids inhibit cellular respiration of human oral cancer cells. *Pharmacology* 85: 328-335.
- [33] Leelawat et al. 2010. The dual effects of delta(9)-tetrahydrocannabinol on cholangiocarcinoma cells: anti-invasion activity at low concentration and apoptosis induction at high concentration. *Cancer Investigation* 28: 357-363.
- [34] Gustafsson et al. 2006. Cannabinoid receptor-mediated apoptosis induced by R(+)-methanandamide and Win55,212 is associated with ceramide accumulation and p38 activation in mantle cell lymphoma. *Molecular Pharmacology* 70: 1612-1620.
- [35] Gustafsson et al. 2008. Expression of cannabinoid receptors type 1 and type 2 in non-Hodgkin lymphoma: Growth inhibition by receptor activation. *International Journal of Cancer* 123: 1025-1033.

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[36] Liu et al. 2008. Enhancing the *in vitro* cytotoxic activity of Δ^9 -tetrahydrocannabinol in leukemic cells through a combinatorial approach. *Leukemia and Lymphoma* 49: 1800-1809.

[37] Marcu et al. 2010. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. *Molecular Cancer Therapeutics* 9: 180-189.

[38] Natalya Kogan. 2005. Cannabinoids and cancer. *Mini-Reviews in Medicinal Chemistry* 5: 941-952.

[39] Sarafaraz et al. 2008. Cannabinoids for cancer treatment: progress and promise. *Cancer Research* 68: 339-342.