

## Gliomas/Cancer

Gliomas (tumors in the brain) are especially aggressive malignant forms of cancer, often resulting in the deaths of affected patients within the 12 to 18 months 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, as well as a limited number of case reports and human studies, 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, were the first to report that delta-9-THC-induced apoptosis (programmed cell death) in glioma cells in culture.<sup>1</sup> 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.<sup>2</sup> Researchers again confirmed cannabinoids' ability to inhibit glioma tumor growth in animals in 2003.<sup>3</sup>

Italian investigators that same year similarly 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 antitumor activity both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as an antineoplastic agent."<sup>4</sup>

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."<sup>5</sup>

Investigators at the California Pacific Medical Center Research Institute reported that the administration of THC to human glioblastoma multiforme cell lines decreased the proliferation of malignant cells and induced cell death more rapidly than the administration of the synthetic cannabinoid agonist WIN 55,212-2. Researchers also noted that THC selectively targeted malignant cells while ignoring healthy ones in a more profound manner than the synthetic alternative.<sup>6</sup> A separate preclinical trial reported that the combined administration of THC and the pharmaceutical agent temozolomide (TMZ) "enhanced autophagy" (programmed cell death) in brain tumors resistant to conventional anticancer treatments.<sup>7</sup>

A limited number of human studies demonstrate similar results. In 2006, Guzman and colleagues conducted the first ever pilot clinical trial assessing the intracranial 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.<sup>8</sup> Several additional investigators have also called for further exploration of cannabis-based therapies for the treatment of glioma.<sup>9-11</sup>

In 2017, researchers affiliated with the British biotechnology firm, GW Pharmaceuticals, announced that the adjunctive use of plant-derived cannabis extracts was associated with increased survival times in patients with glioma. Trial participants taking medical cannabis lived a median of 550 days while those who did not lived a median of 369 days.<sup>12</sup>

A handful of case reports also provide promising evidence. One report, published in 2011 in the *Journal of the International Society for Pediatric Neurosurgery*, documents the spontaneous regression of residual brain tumors in two children coinciding with the subjects' use of cannabis.<sup>13</sup>

Another case report, published in 2018, notes of the reduction of a brain tumor in a five-year-old patient following the use of synthetic CBD. Researchers acknowledged: "A scan carried out in December 2016 showed that tumor volume had decreased by ~60 percent. Further scans, carried out since December 2016, continued to show stable disease. CBD was the only treatment."<sup>14</sup>

The following year, Brazilian investigators described the use of CBD in two 38-year-old patients with brain cancer. Authors reported that patients' use of CBD in addition to traditional anticancer treatment was associated with a "significant improvement" in clinical outcomes and a lack of disease progression for two years. Researchers concluded, "These observations are of particular interest because the pharmacology of cannabinoids appears to be distinct from existing oncology medications and may offer a unique and possibly synergistic option for future glioma treatment."<sup>15</sup>

A case series published that same year also reported on the use of plant-derived CBD in patients with brain cancer. Investigators reported that the concomitant administration of 400 mg of CBD with standard anticancer therapy was associated with longer than expected survival times in eight of nine select patients.<sup>16</sup>

Most recently, a team of Australian researchers assessed the daily administration of cannabis extracts containing either a one to one ratio or a four to one ratio of THC and CBD in 83 patients with glioma. Subjects in the trial consumed the extracts for a period of at least four weeks. Investigators concluded: "This study provides robust evidence that medicinal cannabis administered to this patient population is safe, well tolerated, and can provide symptomatic relief to these patients. ... [It] suggests that cannabis, especially a 1:1 CBD/THC mixture, can be helpful for many of the symptoms impacting QoL [quality of life] in this patient population, especially sleep disturbance. As such, MC [medical cannabis] may be a valuable potential therapy for maintaining the best QoL and daily function for this poor prognosis population, whilst also assisting patients during anticancer and potential life extending therapies."<sup>17</sup>

In addition to cannabinoids' ability to moderate glioma cells in laboratory models, separate preclinical studies demonstrate that cannabinoids and endocannabinoids can also inhibit the proliferation of other cancer cell lines,<sup>18-19</sup> including breast carcinoma,<sup>20-24</sup> prostate carcinoma,<sup>25-29</sup> colorectal carcinoma,<sup>30-31</sup> gastric adenocarcinoma,<sup>32</sup> skin carcinoma,<sup>33</sup> leukemia cells,<sup>34-38</sup> neuroblastoma,<sup>39-40</sup> lung carcinoma,<sup>41-42</sup> uterus carcinoma,<sup>43</sup> thyroid epithelioma,<sup>44</sup> pancreatic adenocarcinoma,<sup>45-46</sup> cervical carcinoma,<sup>47-48</sup> oral cancer,<sup>49</sup> biliary tract cancer (cholangiocarcinoma)<sup>50</sup> urological cancers,<sup>51</sup> and lymphoma,<sup>52-53</sup> among others. In some instances, improved anticancer activity has been reported when cannabinoids are administered in concert with one another, rather than in isolation.<sup>54-55</sup> A 2013 case report published in the journal *Case Reports in Oncology* also reports successful treatment with cannabis extracts in a 14-year-old patient diagnosed with an aggressive form of acute lymphoblastic leukemia.<sup>56</sup> Population studies also

report an inverse relationship between cannabis use and the prevalence of various types of cancer, including lung cancer,<sup>57</sup> head and neck cancer,<sup>58</sup> and bladder cancer.<sup>59</sup>

Experts acknowledge that there exists “solid scientific evidences supporting that cannabinoids exhibit a remarkable anticancer activity in preclinical models of cancer,”<sup>60</sup> and that cannabinoids may one day “represent a new class of anticancer drugs that retard cancer growth, inhibit angiogenesis and the metastatic spreading of cancer cells.”<sup>61-62</sup> Presently, medical cannabis use is prevalent among patients with various types of cancer, though many say that they “desire but are not receiving information about cannabis use during their treatment from oncology providers.”<sup>63</sup> Despite an absence of large-scale clinical trials, “abundant anecdotal reports describe patients having remarkable responses to cannabis as an anticancer agent, especially when taken as a high-potency orally ingested concentrate. ... [Further] human studies should be conducted to address critical questions related to the foregoing effects.”<sup>64</sup>

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