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# Anthelmintic drug ivermectin inhibits angiogenesis, growth and survival of glioblastoma through inducing mitochondrial dysfunction and oxidative stress

## Abstract

Glioblastoma is one of the most vascular brain tumour and highly resistant to current therapy. Targeting both glioblastoma cells and angiogenesis may present an effective therapeutic strategy for glioblastoma. In our work, we show that an anthelmintic drug, ivermectin, is active against glioblastoma cells in vitro and in vivo, and also targets angiogenesis. Ivermectin significantly inhibits growth and anchorage-independent colony formation in U87 and T98G glioblastoma cells. It induces apoptosis in these cells through a caspase-dependent manner. Ivermectin significantly suppresses the growth of two independent glioblastoma xenograft mouse models. In addition, ivermectin effectively targets angiogenesis through inhibiting capillary network formation, proliferation and survival in human brain microvascular endothelial cell (HBMEC). Mechanistically, ivermectin decreases mitochondrial respiration, membrane potential, ATP levels and increases mitochondrial superoxide in U87, T98G and HBMEC cells exposed to ivermectin. The inhibitory effects of ivermectin are significantly reversed in mitochondria-deficient cells or cells treated with antioxidants, further confirming that ivermectin acts through mitochondrial respiration inhibition and induction of oxidative stress. Importantly, we show that ivermectin suppresses phosphorylation of Akt, mTOR and ribosomal S6 in glioblastoma and HBMEC cells, suggesting its inhibitory role in deactivating Akt/mTOR pathway. Altogether, our work demonstrates that ivermectin is a useful addition to the treatment armamentarium for glioblastoma. Our work also highlights the therapeutic value of targeting mitochondrial metabolism in glioblastoma. - Highlights: • Ivermectin is effective in glioblastoma cells in vitro and in vivo. • Ivermectin inhibits angiogenesis. • Ivermectin induces mitochondrial dysfunction and oxidative stress. • Ivermectin deactivates Akt/mTOR signaling pathway. [« less](#)

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