CANNABIDIOL AS POTENTIAL GLIOBLASTOMA MULTIFORME TREATMENT: *IN VITRO* ASSESSMENT OF ANTI-CANCER PROPERTIES AND *IN VIVO* DELIVERY

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Background: Glioblastoma Multiforme (GBM) is the most aggressive brain cancer, with a very poor prognosis of <5% 5-year survival. Resistance to the standard treatment, chemotherapeutic temozolomide (TMZ), occurs in 50% of cases, commonly involving mechanisms of the over-expression of O^6-methylguanine DNA-methyltransferase (MGMT) or by a deficiency of mismatch repair (MMR). The anti-cancer properties of the main natural non-psychoactive phytocannabinoid cannabidiol (CBD) have been investigated in a number of cancers including lung, colon and gliomas. Whilst CBD is commonly reported to exhibit anti-cancer properties against GBM, and to work in synergy with other antineoplastic compounds, its ability to overcome the common resistance mechanisms associated with TMZ treatment has not yet been comprehensively investigated. This work studies the anti-cancer properties of CBD and the drug's ability to overcome MGMT over-expression and MMR-deficiency, as well as the assessment of the delivery of CBD to the specific anatomical locations within the brain following oral administration.

Methods: *In vitro* anti-cancer assessment of CBD against human GBM lines U373-M (MGMT over-expressing) and U373-V (non-resistant) and human colon cancer cell line HCT116 (MMR-deficient) were conducted by MTT and cell count assays. *In vivo* assessment of the delivery of CBD to the brain after oral administration in sesame oil and a control lipid-free vehicle (propylene glycol/ethanol/water) was studied in Sprague-Dawley rats. The distribution of CBD within the brain was assessed up to 8 hrs post administration by means of a validated HPLC-UV methodology.

Results: The *in vitro* assessment confirmed the two common resistances to TMZ treatment in the U373-M and HCT116 cell lines with GI_{50} values of 331.61 μM and 609.21 μM, respectively (U373-V control GI_{50}: 10.42 μM). CBD was shown to efficiently overcome both resistances, with GI_{50} values of 23.16 μM (U373-M), 13.37 μM (HCT116) and 33.04 μM (U373-V control). *In vivo* assessment in rats demonstrated the ability to deliver CBD efficiently to the brain after oral administration in both sesame oil and the lipid-free vehicle. After administration with sesame oil, the maximum CBD concentration is observed at the same time as the maximum concentration in the plasma (3 hrs post administration). However, a higher concentration is seen in the brain, 295 ng/g, compared to the plasma, 123 ng/mL. Assessment of the distribution within the brain demonstrates that CBD can be efficiently delivered to areas where GBM is most commonly found (frontal and temporal lobes).

Conclusions: The data suggest that phytocannabinoid CBD has high efficacy against GBM *in vitro*, and can overcome the two common resistances to treatment by TMZ (MGMT over-expression and MMR-deficiency). This work also demonstrates that CBD can be delivered to the relevant anatomical locations (frontal and temporal lobes) within the brain as quickly as 2 hrs post oral administration, and at concentrations similar to the required *in vitro* GI_{50} values, even when administered at a relatively low oral dose.