The olive, known by the botanical name Olea europaea, meaning "European olive", is a species of small tree in the family Oleaceae, found in the Mediterranean Basin from Portugal to the Levant, the Arabian Peninsula, and southern Asia as far east as China, as well as the Canary Islands and Réunion. The species is cultivated in many places and considered naturalized in all the countries of the Mediterranean coast, as well as in Argentina, Saudi Arabia, Java, Norfolk Island, California, and Bermuda.

Tezcan et al. from the Uludag University , Bursa , Turkey, tested the anti-proliferative activity of Olea europaea (OLE) and the effect of the OLE-TMZ combination in the T98G, U138MG and U87 MG GBM cell lines using the cell proliferation reagent WST-1 assay. The mechanism of cell death was analyzed with Annexin A5/fluorescein isothiocyanate (FITC) and TUNEL assays. The effects of OLE on the expression levels of miR-181b, miR-153, miR-145 and miR-137 and potential mRNA targets were analyzed in Glioblastoma stem cell (GSC)s using reverse transcription polymerase chain reaction (RT-qPCR). OLE exhibited anti-proliferative effects via apoptosis and necrosis in the GBM cell lines. In addition, OLE significantly induced the expression of miR-153, miR-145, and miR-137 and decreased the expression of the target genes of these MicroRNAs in GSCs (p < 0.05). OLE causes cell death in GBM cells with different TMZ responses, and this effect is synergistically increased when the cells are treated with a combination of OLE and TMZ. This is the first study to indicate that OLE may interfere with the pluripotency of GSCs by modulating MicroRNA expression. Further studies are required, but we suggest that OLE may have a potential for advanced therapeutic cancer drug studies in GBM  $^{11}$ .

OLE (2mg/mL) caused a significant reduction in tumour weight, vascularisation, invasiveness and migration (p=0.0001, p<0.001, p=0.004; respectively) that was associated with reducing the expression of vascular endothelial growth factor A (VEGFA), MMP-2 and MMP-9. This effect was synergistically increased in combination with bevacizumab<sup>2</sup>.

Exposure to 1 mg/mL OLE caused a significant induction of CpG island methylation in the MGMT gene using Methyl quantitative PCR assay (P < 0.001). In WST-1 analysis, the use of 350  $\mu$ M TMZ plus 1 mg/mL OLE significantly increased the TMZ response of MGMT unmethylated cells (P = 0.003). Using the comet assay, the impact of 1 mg/mL OLE plus 350  $\mu$ M TMZ on the formation of DNA strand breaks was significantly higher than that of 450  $\mu$ M TMZ alone (P < 0.001) and Western blot analysis revealed that, when cells are treated with 1-mg/mL OLE, the total p53 protein levels tended to decrease. The results presented in this study uniquely demonstrated that OLE synergistically increased the TMZ response of GBM tumors by regulating MGMT gene methylation and p53 expression <sup>3)</sup>.

## 1)

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