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| **METFORMIN EFFECTS** | **MOLECULAR PATHWAYS** | **REFERENCE** |
| Metformin specifically acts on neoplastic or glioma stem cells, while not affecting normal cells | Metformin acts by blocking the chloride channel CLIC1. The downstream cascade is yet to be studied | [104] |
| Metformin alters cells metabolism by acting on ETC I and, consequently, by impairing the ATP/AMP ratio and activating AMPK | Metformin decreases oxidative phosphorylation while increasing the amount of ATP produced through anaerobic glycolysis | [99] |
| Metformin decreases the protein synthesis through the inhibition of mTOR while inducing the predominance of catabolic processes | [88] |
| Metformin increases oxidative stress in Glioblastoma cells | Metformin blocks ETC I, generating an impaired mitochondria action and leading to an increase in ROS production | [99] |
| Metformin inhibits mitochondrial superoxide dismutase, increasing ROS production | [86] |
| Metformin inhibits cell proliferation | By activating AMPK, through the phosphorylation of PIKE-A, Metformin inhibits the Akt/mTOR axis | [86] |
| By activating TSC2 and RAPTOR, Metformin inhibits mTOR | [87] |
| Metformin inhibits cell motility and invasiveness | By activating AMPK, through the phosphorylation of PIKE-A, Metformin inhibits the Akt/mTOR axis | [105] |
| Metformin moderately increases apoptosis | Metformin increases the levels of caspase 3 | [86, 106] |
| Metformin increases the levels of caspase 9 | [106] |
| Metformin increases the levels of Bax, while reducing the levels of Bcl-2 | [99,106] |
| Metformin increases sensitivity to chemo- and radiotherapy | Metformin inhibits HIF and its downstream effects | [60,101] |
| Metformin acts on GSCs | Together with TMZ, Metformin inhibits proliferation and promotes apoptosis | [107,108] |
| Metformin induces GSCs differentiation by activating FOXO3 | [109] |
| Metformin induces GSCs differentiation by inhibiting STAT3, through AMPK (phosphorylation site Ser727) or directly (phosphorylation site Y705) | [110] |
| Metformin inhibits GSCs EMT through the inhibition of the axis YAP/Hippo | [111] |

**Table 1.** Overview of in vitro and in vivo studies reporting an anti-GBM effect of Metformin