Juglone

Juglone is a natural pigment, which has cytotoxicity against various human tumor cells.

Prolylisomerase (Pin1), an isomerase that is overexpressed in various tumors, has become an attractive molecule in cancer research. Pin1 has been reported to regulate proteins involved in essential cellular pathways that mediate cell proliferation, cell cycle progression, differentiation and apoptosis, by altering their stability and function. The results of a study revealed that knockdown of Pin1 in glioblastoma cells using RNA interference or the selective Pin1 inhibitor, juglone, suppressed the tumorigenic features by reducing cell growth, migration and angiogenic potential. Furthermore, knockdown of Pin1 decreased the levels of vascular endothelial growth factor and Matrix metalloproteinase 9, and also triggered apoptosis. Due to the fundamental roles of Pin1 in promoting tumorigenesis, Pin1 inhibitory molecules, including juglone, or alternative synthetic derivatives hold potential for the development of clinical countermeasures against glioblastoma [1].

Tumor stem cells (TSCs) of glioma were enriched from U87 and two primary cells (SHG62, and SHG66) using serum-free medium supplemented with growth factors, including bFGF, EGF and B27. After treatment of juglone with gradient concentrations (0, 10, 20, and 40 μM), the viability and apoptosis of TSCs were evaluated by WST-8 assay and flow cytometry. Reactive oxygen species (ROS) was labeled by the cell-permeable fluorescent probe and detected with flow cytometry. ROS scavenger (NAC) and p38-MAPK inhibitor (SB203580) were applied to resist the cytotoxic effect. Caspase 9 cleavage and p38 phosphorylation (P-p38) were quantified by western blot. Juglone as well as temozolomide (TMZ) were administrated in intracranial xenografts and MR scan was performed every week to evaluate the anti-tumor effect in vivo.

Juglone could obviously inhibit the proliferation of TSCs in glioma by decreasing cell viability ($P < 0.01$) and inducing apoptosis ($P < 0.01$), which was accompanied by increased caspase 9 cleavage in a dose-dependent manner ($P < 0.01$). In the meantime, juglone could generate ROS significantly and increase p38 phosphorylation ($P < 0.01$). In addition, pretreatment with ROS scavenger or p38-MAPK inhibitor could reverse juglone-induced cytotoxicity ($P < 0.01$). More importantly, juglone could also suppress tumor growth in vivo and improve the survival of U87-bearing mice compared with control ($P < 0.05$), although TMZ seemed to have better effect.

Juglone could inhibit the growth of TSCs in gliomas through the activation of ROS-p38-MAPK pathway in vitro, and the anti-glioma effect was validated in vivo, which offers a potential therapeutic agent to gliomas [2].

In a study, Wang et al. determined if juglone exerts antitumor effects in the U251 human glioma cell line and investigated its potential underlying molecular mechanisms. Cell survival, apoptosis, migration, angiogenesis and molecular targets were identified with multiple detection techniques including the MTT cell proliferation assay, dual acridine orange/ethidium bromide staining, electron microscopy, transwell migration assay, chick chorioallantoic membrane assay, quantitative real-time polymerase chain reaction and immunoblotting. The results showed that 5-20 μM juglone markedly suppressed cell proliferation, induced apoptosis, and enhanced caspase-3 activity in U251 cells in a dose- and time-dependent manner. Moreover, juglone inhibited cell migration and the formation of new blood vessels. At the molecular level, juglone markedly suppressed Pin1 levels in a time-

dependent manner. TGF-β1/Smad signaling, a critical upstream regulator of miR-21, was also suppressed by juglone. Moreover, the transient overexpression of Pin1 reversed its antitumor effects in U251 cells and inhibited juglone-mediated changes to the TGF-β1/miR-21 signaling pathway. These findings suggest that juglone inhibits cell growth by causing apoptosis, thereby inhibiting the migration of U251 glioma cells and disrupting angiogenesis; and that Pin1 is a critical target for juglone's antitumor activity. The present study provides evidence that juglone has in vitro efficacy against glioma. Therefore, additional studies are warranted to examine the clinical potential of juglone in human gliomas [3].

1)
Atabay KD, Yildiz MT, Avsar T, Karabay A, Kiliç T. Knockdown of Pin1 leads to reduced angiogenic potential and tumorigenicity in glioblastoma cells. Oncol Lett. 2015 Oct;10(4):2385-2389. Epub 2015 Jul 20. PubMed PMID: 26622856; PubMed Central PMCID: PMC4580010.
2)
Wu J, Zhang H, Xu Y, Zhang J, Zhu W, Zhang Y, Chen L, Hua W, Mao Y. Juglone induces apoptosis of tumor stem-like cells through ROS-p38 pathway in glioblastoma. BMC Neurol. 2017 Apr 7;17(1):70. doi: 10.1186/s12883-017-0843-0. PubMed PMID: 28388894; PubMed Central PMCID: PMC5383964.
3)
Wang J, Liu K, Wang XF, Sun DJ. Juglone reduces growth and migration of U251 glioblastoma cells and disrupts angiogenesis. Oncol Rep. 2017 Aug 3. doi: 10.3892/or.2017.5878. [Epub ahead of print] PubMed PMID: 28791366.