

Antiglioma Potential of Flavonoides

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The malignant gliomas are primary brain tumors and represents about 78% of all malignant tumors of the central nervous system [1]. The majority of these tumors are considered as high-grade tumors according to the current classification of the World Health Organization (grades III and IV) when diagnosed. Glioblastoma (GB) is the most aggressive form of gliomas, and is highly infiltrative and is morphologically very heterogeneous. Currently, the protocol adopted for the treatment of glioblastoma is based on surgery followed by radiation therapy and chemotherapy. Despite recent advances in the therapy of malignant gliomas with the introduction of new therapeutic agents as temozolomide [2] and antibody antiangiogenic therapy against the vascular endothelial growth factor (VEGF) [3] the median survival time for glioblastoma patients is still around 14 months [2]. Therefore, compounds that show antitumor activity may be key allies to improve the conventional treatment applied to tumors of the CNS. The search for alternative drugs for therapeutic interventions against brain tumors has shed light on phytochemical drugs.

A group of molecules that have raised interest in the scientific community are flavonoids present in different genera of plants, taking into account the diversity of biological effects, including antitumor activity [4]. Flavonoids are secondary metabolites of a large number of plants adopted in popular medicine, and protect them against the damaging effects caused by UV-radiation and microbial infections. The basic flavonoid structure is the flavan nucleus, which consists of 15 carbon atoms arranged in three rings (C6-C3-C6), labeled A, B, and C, which consist of two aromatic carbon rings, benzopyran (A and C rings) and benzene (B ring), and can be divided into six subgroups based on the degree of the oxidation of the C-ring, the hydroxylation pattern of the ring structure, and the substitution of the 3-position: flavonols, flavones, flavanones, flavanols, anthocyanidins. *In vitro* and *in situ* blood brain barrier (BBB) studies have been reported that flavonoides can cross the BBB with considerable variation in permeability for different flavonoides depending on its structure [5,6]. However the sensitive of cerebral tissue to naturally occurring flavonoides and synthetic derivatives have been poorly considered and little is known about their pharmacological potential for therapy of malignant gliomas.

In vitro and *in vivo* have been investigated the anti glioma effect of extracts containing flavonoides and purified molecules obtained from different plant species around the world (Table 1). The inhibition of growth and induction of apoptosis of glioma cell lines were demonstrated by Scheck and collaborator (2006) after treatment of human malignant brain tumor cells with extracts derived from the mature roots of *Scutellaria baicalensis*. Flavonoides present in *Vaccinia macrocarpa* (blackberry) induced inhibition of cell proliferation, growth arrest, and apoptosis in the human glioblastoma cell line U87 [7]. The anticancer activity of extracts derived from the mature roots of *Scutellaria baicalensis* on human malignant brain tumor cells was observed by Scheck and collaborators (2006). An antiproliferative effect of quercetin in the human U138MG glioma cell line was also demonstrated by Braganhol et al. [8]. Purified flavonoid Kaempferol induced apoptosis in glioblastoma cells through oxidative stress [9]

and purified silibinin sensitized human glioma cells to TRAIL-mediated apoptosis via DR5 Up-regulation and down-regulation of c-FLIP and surviving [10]. The ability of four flavonoides (5-hydroxy-7,4-dimethoxyflavone, casticin, apigenin, and penduletin) isolated from *Croton betulaster* to inhibit growth of GL-15 human glioblastoma cells and down regulate proangiogenic cytokine transforming growth factor- β 1 (TGF- β 1) was also demonstrated [11]. The flavonoid rutin, extracted from *Dimorphanda mollis*, a Brazilian shrub adopted in popular medicine, and its derivatives have been adopted for the treatment of senile cerebral defects, to relieve micro trauma on tissue and also have pharmacological application to strengthen veins, thus preventing bleeding [6,12,13]. The potential of rutin to induce growth inhibition and apoptosis of GL-15 cells glioblastoma cells was also evidenced [14] as well as down regulation of angiogenic cytokine VEGF and TGF- β 1 [11]. The magnitude of anti-tumoral effect of flavonoides tested against glioblastoma has been related to flavonoides structure, especially to the degree of hydroxylation and methylation. In a study conducted by the group of Costa SL (2012, data not published) comparing the effects of polyhydroxylated flavonoides it was observed that amongst the flavonoides studied, 3',4'-dihydroxyflavone and 3,4',5,7-tetrahydroxyflavone (kaempferol) showed an expressive reduction in filopodia, structures essential for migration, on the cellular surface, suggesting a possible association between the hydroxylated groups in carbons C3' and C4' and the antitumor effect of polyhydroxylated flavonoides. Moreover, in a screening comparing the antitumor potential of nine hydroxylated and four methoxylated flavonoides the same group also observed that U251 glioblastoma cell line and TG-1 neuroglial stem cell enriched line [15] were more sensitive to the polyhydroxylated flavonoid Hinokiflavone and to the polymethylated and polyhydroxylated flavonoid 8-methyl-crisiliol (8-methyl-3',4',5-trihydroxy-6,7-dimethoxyflavone) indicating that both chemical functions are related to anti glioma activity.

Moreover a morphogenic effect has been also demonstrated after exposure of human glioblastoma cells to flavonoides (Figure 1). Exposure of GL-15 cell to rutin and penduletin also induced changes on pattern of expression of cytoskeletal proteins with reduction on expression of nestin and vimentin, and increase on expression of GFAP, a marker of astrocytes, suggesting induction of astroglial differentiation [14,16]. Nestin is Vimentin is the major cytoskeletal

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Flavonoid or Extract	Origin	Human cell Lines	Biological Effects	Reference
Flavonoid rich extract	Scutellaria baicalensis	Glioma cell lines	Growth inhibition and apoptosis	Scheck et al., 2006
Flavonoid rich extract	Vaccinia macrocarpa	U87	Growth inhibition	Ferguson et al., 2006
3,3',4',5,6-Pentahydroxyflavone (quercetin); rutin aglycone)	Many plants (i.e. caparrispinosa, Anethum graveolens, Allium cepa) commercialized	LN229, U87MG, T98G, GL-15	Apoptosis through oxidative stress	Sharma et al., 2007
3',4',5,7-tetrahydroxyflavone (kaempferol)	Many plants (i.e. Allium, Delphinium, Camellia) commercialized			
Silibinin	Sylibum marianum	U251MG	Sensitized human glioma cells to TRAIL-mediated apoptosis	Son et al., 2007
5-hydroxy-7,4-dimethoxyflavone, casticin, apigenin, and penduletin	Croton betulaster	GL-15	Growth inhibition Down regulation of TGF-β	Freitas et al, 2011
Penduletin		GL-15	Astroglial differentiation	Noneste et al., 2011
Rutin	Dimorphandamollis	GL-15	Growth inhibition and apoptosis, Astroglial differentiation Down regulation of TGF-β1 and VEGF	Santos et al., 2011, Noneste et al., 2011, Freitas et al, 2011
Hinokiflavone-8methyl-crisilliol		U251MG; TG-1	Growth inhibition	Costa et al., not published

(*Human cell lines derived from primary and recurrent brain tumors)

Table 1: Effect of flavonoids obtained from different plants in glioma cells.

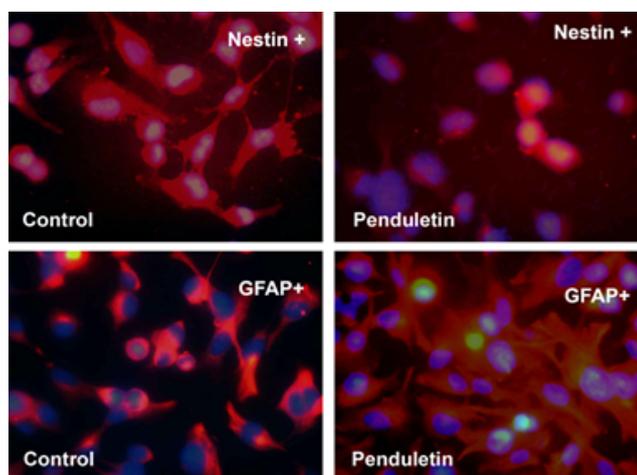


Figure 1: Nestin and GFAP immunocytochemistry in GL-15 human glioblastoma cells cultures in control conditions (vehicle 0.5 % DMSO) or exposed to flavonoid penduletin.

component of immature astrocytes and GFAP is a major protein of astrocytes intermediate filaments and a specific marker for these cells. Moreover, studies have reported that increase in GFAP content is related to differentiation in malignant gliomas [17,18] also investigated the differentiation potential of many flavonoids and found that the rutin aglycone quercetin induced differentiation of rat neural PC12 cells but not rutin, suggesting that structural determinants were needed for differentiation activity induced by flavonoids. Finally the recent findings that astrocytes and microglia are targets for the flavonoid rutin, inducing activation and even the release of trophic factors such as TNF-alpha and nitric oxide [19,20] may lead to the development of new therapy protocols based on stimulation of glial cells response against glioblastomas.

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