Tipo	Periódico
Título	Kaempferol and Biomodified Kaempferol from Sophora japonica Extract as Potential Sources of Anti-Cancer Polyphenolics against High Grade Glioma Cell Lines
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Programa/Curso (s)	Programa de Pós-Graduação Stricto Sensu em Ciências da Saúde
DOI	10.3390/ijms241310716
Assunto (palavras chaves)	NF-kB pathway; Sophora japonica extract; biomodified kaempferol; cell lines; high-degree gliomas; kaempferol
Idioma	Inglês
Fonte	Título do periódico: International Journal of Molecular Sciences ISSN: 1422-0067 Volume/Número/Paginação/Ano: 24(13):10716, 2023.
Data da publicação	27/06/2023
Formato da produção	Impressa ou digital
Resumo	The enzymatic hydrolysis of the extract of Sophora japonica by two glycosyl hydrolases (hesperidinase and galactosidase) was performed in order to obtain kaempferol (KPF)-enriched extract with an enhanced anticancer activity. The current study examined the effectiveness of both Sophora japonica extracts (before (KPF-BBR) and after (KPF-ABR) bioconversion reactions) in reducing cell viability and inducing apoptosis in human high-degree gliomas in vitro. Cytotoxicity was determined using an MTT assay. The effects of both compounds on the proliferation of glioma cell lines were measured using trypan blue exclusion, flow cytometry for cell cycle, wound healing (WH), and neurosphere formation assays. Cellular apoptosis was detected by DNA fragmentation and phosphatidylserine exposure. qPCR and luciferase assays evaluated NF-kB pathway inhibition. The survival rate of NG-97 and U-251 cells significantly decreased in a time- and dose-dependent manner after the addition of KPF-BBR or KPF-ABR. Thus, a 50% reduction was observed in NG-97 cells at 800 µM (KPF-BBR) and 600 µM (KPF-ABR) after 72 h. Both compounds presented an IC50 of 1800 µM for U251 after 72 h. The above IC50 values were used in all of the following analyses. Neither of the KPF presented significant inhibitory effects on the non-tumoral cells (HDFa). However, after 24 h, both extracts (KPF-BBR and KPF-ABR) significantly inhibited the migration and proliferation of NG-97 and U-251 cells. In addition, MMP-9 was downregulated in glioma cells stimulated by 12-O-tetradecanoylphorbol-13-acetate (TPA) plus KPF-BBR and TPA+KPF-ABR compared with the TPA-treated cells. Both KPF-BBR and KPF-ABR significantly inhibited the proliferation of glioma stem cells

	(neurospheres) after 24 h. DNA fragmentation assays demonstrated that the apoptotic ratio of KPF-ABR-treated cell lines was significantly higher than in the control groups, especially NG-97, which is not TMZ resistant. In fact, the flow cytometric analysis indicated that KPF-BBR and KPF-ABR induced significant apoptosis in both glioma cells. In addition, both KPF induced S and G2/M cell cycle arrest in the U251 cells. The qPCR and luciferase assays showed that both KPFs downregulated TRAF6, IRAK2, IL-1β, and TNF-α, indicating an inhibitory effect on the NF-kB pathway. Our findings suggest that both KPF-BBR and KPF-ABR can confer anti-tumoral effects on human cell glioma cells by inhibiting proliferation and inducing apoptosis, which is related to the NF-κB-mediated pathway. The KPF-enriched extract (KPF-ABR) showed an increased inhibitory effect on the cell migration and invasion, characterizing it as the best antitumor candidate.
Fomento	88887464813/2019-00/Coordenação de Aperfeiçoamento de Pessoal de Nível Superior 88887.706776/2022-00/Coordenação de Aperfeiçoamento de Pessoal de Nível Superior