Tipo	Periódico
Título	Dipotassium Glycyrrhizinate on Melanoma Cell Line: Inhibition of Cerebral Metastases Formation by Targeting NF-kB Genes-Mediating MicroRNA-4443 and MicroRNA-3620-Dipotassium Glycyrrhizinate Effect on Melanoma
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Programa/Curso (s)	Programa de Pós-Graduação Stricto Sensu em Ciências da Saúde
DOI	10.3390/ijms23137251.
Assunto (palavras chaves)	CD209; Dipotassium Glycyrrhizinate; NF-kB pathway inhibition; TCN genes modulation; anti-migratory effect; melanoma cell line SK-MEL-28; miR-4443 and miR-3620.
Idioma	Inglês
Fonte	Título do periódico: Int J Mol Sci Volume/Número/Paginação/Ano: 23(13):7251, 2022
Data da publicação	2022 Jun 29
Formato da produção	Impressa ou digital
Resumo	Glycyrrhizic acid (GA), a natural compound isolated from licorice (Glycyrrhiza glabra), has exhibited anti-inflammatory and anti-tumor effects in vitro. Dipotassium glycyrrhizinate (DPG), a dipotassium salt of GA, also has shown an anti-tumor effect on glioblastoma cell lines, U87MG and T98G. The study investigated the DPG effects in the melanoma cell line (SK-MEL-28). MTT assay demonstrated that the viability of the cells was significantly decreased in a time- and dose-dependent manner after DPG (IC50 = 36 mM; 24 h). DNA fragmentation suggested that DPG (IC50) induced cellular apoptosis, which was confirmed by a significant number of TUNEL-positive cells (p-value = 0.048) and by PARP-1 [0.55 vs. 1.02 arbitrary units (AUs), p-value = 0.001], BAX (1.91 vs. 1.05 AUs, p-value = 0.09), and BCL-2 (0.51 vs. 1.07 AUs, p-value = 0.0018) mRNA compared to control cells. The proliferation and wound-healing assays showed an anti-proliferative effect on DPG-IC50-treated cells, also indicating an inhibitory effect on cell migration (p-values < 0.001). Moreover, it was observed that DPG promoted a 100% reduction in melanospheres formation (p-value = 0.008). Our previous microRNAs (miRs) global analysis has revealed that DPG might increase miR-4443 and miR-3620 expression levels. Thus, qPCR showed that after DPG treatment, SK-MEL-28 cells presented significantly high miR-4443 (1.77 vs. 1.04 AUs, p-value = 0.02) and miR-3620 (2.30 vs. 1.00 AUs, p-value = 0.01) expression compared to control cells,

	which are predicted to target the NF-kB, CD209 and TNC genes, respectively. Both genes are responsible for cell attachment and migration, and qPCR revealed significantly decreased CD209 (1.01 vs. 0.54 AUs, p-value = 0.018) and TNC (1.00 vs. 0.31 AUs, p-value = 2.38 × 10-6) mRNA expression levels after DPG compared to untreated cells. Furthermore, the migration of SK-MEL-28 cells stimulated by 12-O-tetradecanoylphorbol-13-acetate (TPA) was attenuated by adding DPG by wound-healing assay (48 h: p-value = 0.004; 72 h: p-value = 7.0 × 10-4). In addition, the MMP-9 expression level was inhibited by DPG in melanoma cells stimulated by TPA and compared to TPA-treated cells (3.56 vs. 0.99 AUs, p-value = 0.0016) after 24 h of treatment. Our results suggested that DPG has an apoptotic, anti-proliferative, and anti-migratory effect on SK-MEL-28 cells. DPG was also able to inhibit cancer stem-like cells that may cause cerebral tumor formation.
Fomento	