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We previously reported on the use of quantitative trait locus (QTL) mapping in differentially susceptible rat strains to identify *Fry*, the rat ortholog of the *furry* gene in *Drosophila melanogaster*, as a mammary carcinoma susceptibility gene. In lower eukaryotes FRY orthologs regulate epithelial cell differentiation and growth. Consistent with a similar function in mammalian cells, loss of FRY in mammary epithelial and tumor cell lines was associated with reduced expression of gene networks that control differentiation, morphology, polarity and adhesion. Ectopic expression of the wild-type gene in breast cancer cells restored a more normal gene expression profile, induced epithelial differentiation and suppressed epithelial-mesenchymal transition (EMT). Ectopic *FRY* suppressed tumorigenicity of triple negative MB-MBA-321 breast cancer cells *in vitro* and *in vivo*. *in silico* analysis of clinically annotated cancer cohorts, available in the Oncomine 3.0 gene expression database, indicated that *FRY* mRNA expression was significantly decreased in breast cancers. Immunohistochemical analysis of tissue microarrays comprising normal breast tissue and carcinomas confirmed that nuclear FRY protein levels were correlated with hormone receptor status, histopathology, progression, Elston tumor grade, and poor clinical outcomes in a subset of human breast cancers. These findings suggested that loss of nuclear FRY function plays a role in pathogenesis and progression of breast cancer.

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ANTIPROLIFERATIVE AND DIFFERENTIATION-PROMOTING EFFECTS OF ETHANOL-WATER EXTRACTS OF KAZAKHSTAN MEDICINAL PLANTS ON HUMAN ACUTE MYELOID LEUKEMIA CELLS

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Acute myeloid leukemia (AML) is a highly aggressive hematopoietic malignancy characterized by the disruption of differentiation programs and the development of apoptosis resistance in early myeloid progenitors. AML therapy has not changed appreciably for the last several decades and is based on conventional cytotoxic chemotherapy. This approach has limited success in achieving long-term survival in most patients with AML while causing serious side effects, particularly, in the elderly. Therefore, the development of more effective and less toxic therapies is of utmost urgency and a major issue of public health. In this study we determined the *in vitro* antileukemic activities of dried 50% ethanolic leaf extracts of sea buckthorn (*Hippophae rhamnoides;* HR), dog rose (Rosa canina; RC), garden sage (Salvia officinalis; SO) and oregano (*Origanum officinalis;* OO) grown in Kazakhstan. All the extracts tested had high total polyphenol content and induced a dose-dependent inhibition of cell proliferation and cytotoxicity in human HL60 and U937 AML cell lines. Interestingly, cell treatment with combinations of HR extract and RC, SO or OO extracts at minimally effective concentrations of each preparation resulted in enhanced inhibition of cell growth, mostly in a synergistic manner. Similar effects were obtained using RC+SO, RC+OO or SO+OO combinations. These synergistic effects were primarily antiproliferative, without overt cytotoxicity and were associated with a partial cell cycle arrest in the S-phase. Furthermore, extracts of RC, SO and OO leaves, administered alone or in combination at non-cytotoxic concentrations, markedly potentiated differentiation of AML cells induced by near physiologic doses of 1,25-dihydroxyvitamin D_3. Of note, the differentiation-enhancing effect of the HR extract was significantly less pronounced. We suggest that the enhanced cooperative antileukemic effects of low doses of the tested medicinal plant extracts may be employed for the development of novel preventive and therapeutic approaches for the management of AML.

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ANTICANCER DRUG DISCOVERY BASED ON PLANT BIODIVERSITY