Molecular Investigation of the Effects of 3′,7-Dihydroxy-3′,4,5-Trimethoxyflavanone and 4,7-Didehydroneophysalin B on Breast Cancer Cell Lines

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Abstract:

Problem statement: Cancer, a significant public health concern worldwide, ranks as the second leading cause of death globally. Breast cancer is the leading cause of cancer-related deaths around the world and holds the highest prevalence among women in Turkey. Despite the availability of developed treatments for breast cancer, the prognosis for patients remains poor due to widespread metastasis and high recurrence rates. The existence of various subtypes of breast cancer, the side effects of existing treatment modalities, drug resistance, and the non-responsiveness of triple-negative breast cancer to hormone therapy have driven researchers to seek more effective treatment strategies with fewer side effects.

Natural compounds are rich sources of bioactive compounds aimed at targeting tumor growth and cell invasion during breast cancer progression, and most therapeutic agents currently used in breast cancer treatment are derived from natural product sources. Products such as alkaloids, steroids, antioxidants, phenolic compounds, and flavonoids obtained from natural products exhibit inhibitory properties against breast cancer by inhibiting angiogenesis, cell migration, and cell proliferation, inducing apoptosis and cell death, and halting the cell cycle.

Results and Conclusion: The IC50 values of the natural extracts 3',7-Dihydroxy-3',4,5-Trimethoxyflavanone and 4,7-Didehydroneophysalin B on MDA-MB-231 breast cancer cells were calculated as 267 µM and 400 µM, respectively. In the migration analysis conducted to examine the effects of the two molecules and their combinations on the migratory abilities of sensitive and cisplatin-resistant MDA-MB-231 cell lines, a time-dependent decrease of approximately 50% was observed in the migration abilities of the sensitive cells treated with 400 µM of 3',7-Dihydroxy-3',4,5-Trimethoxyflavanone and 4,7-Didehydroneophysalin B, and about 60% decrease when administered in combination, alongside an increase in cell deaths compared to the control. In the cisplatin-resistant cells, about a 37% reduction in migratory abilities was observed at the end of 72 hours, and approximately a 50% reduction in cell migration abilities was recorded when administered in combination. It was noted that molecules with potential drug properties were more effective on the motility of sensitive cell lines, but significant efficacy was also demonstrated in the resistant cell lines. When the morphologies of the cells treated with 400 µM of the molecules in sensitive and resistant MDA-MB-231 cell lines were examined compared to the control, positive results indicating apoptosis were observed, such as cell shrinkage, the presence of cytoplasmic shrinkage, and the fragmentation of the nucleus. Unlike the cells in the control groups exhibiting elongated branches at the 48-hour mark, those subjected to the molecules tended to become circular and some detached from the surface, alongside an increase in cell deaths being observed. The findings from the invasion assays in both cell lines showed that the combined application of the molecules increased the reduction in cell numbers, with an approximately 10% higher rate of increase in the sensitive cell lines compared to the resistant ones.

The obtained data serve as preliminary research for new drug candidates to be designed for the treatment of breast cancer, which ranks among the diseases with the highest incidence and mortality rates globally.