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AN INNOVATIVE APPROACH FOR THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER USING A TARGETED DELIVERY SYSTEM: FOLATE-TARGETED LIPOSOMAL SN38 AND FLAVONOID COMBINATION

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KEY WORDS *(at least 5 words)*

- ✓ TRİPLE NEGATİVE BREAST CANCER
- ✓ LIPOSOME
- ✓ FOLATE RECEPTOR
- ✓ SN38
- ✓ FLAVONOID

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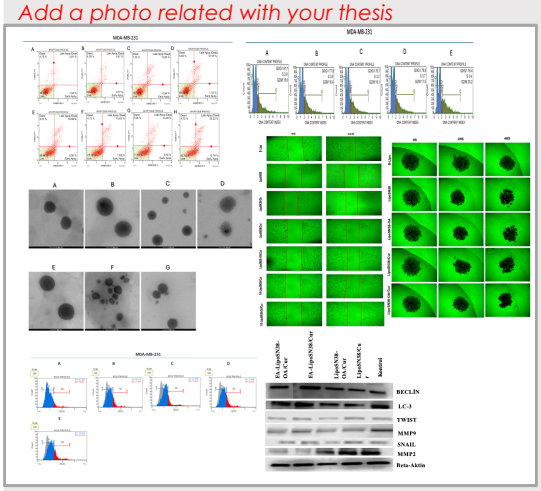

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THESIS ABSTRACT

Triple-negative breast cancer is a heterogeneous tumor group with high recurrence and metastasis. Since the clinic has limited treatment options, new drug discoveries and treatment approaches are needed. Irinotecan is an effective anticancer agent used in the clinic. Although irinotekan shows anticancer effect through the active metabolite SN38, the short half-life and side effects of SN38 limit its use. In the present thesis, SN38-OA modification was performed to overcome the limitations of SN38. The combination of SN38-OA with kurkumin phenolic was evaluated to enhance the anticancer effect of SN38-OA and to reduce its cytotoxicity in healthy cells. The combination was encapsulated in liposomes to provide long circulation time, increased stability and targeted activity, and the liposomes were conjugated with folic acid targeting folate receptors. This is the first study to report the synergistic effect of SN38-OA lipophilic prodrug synthesis with kurkumin in the MDA-MB-231 cell line, as well as the antitumour and antimetastatic effects of folic acid-conjugated liposomal encapsulated SN38-OA/Cur combination. Within the project's scope, FA-LipoSN38-OA/Cur nanoformulation was extensively analyzed in terms of its impact on proliferation, apoptosis induction, oxidative stress levels, cell cycle regulation, cell migration inhibition, and tumorsphere formation in MDA-MB-231 cells. In addition, expression changes of genes related to the EMT pathway were analyzed. As a result, with the FA-LipoSN38-OA/Cur nanoformulation obtained, a long-circulating, stable, three-dimensional tumor structure-acting, tumor-targeted drug delivery with highly reduced toxicity in healthy cells was obtained by avoiding the limitations of SN38 (IC50:25nM/25uM; CI<1.0, *$p<0,001$). FA-LipoSN38-OA/Cur nanoformulation inhibited cell migration by suppressing the EMT pathway and induced autophagy with apoptosis by increasing the levels of reactive oxygen species. The findings suggest that FA-LipoSN38-OA/Cur nanoformulation may be a potential therapeutic agent alternative to the treatment options used in triple negative breast cancer, tumour targeted and with minimal toxicity in healthy cells.

APPLICATION AREAS OF THE THESIS RESULTS

Medıcıne, Health, Medical Biology, Cancer Biology, Drug Development

ACADEMIC ACTIVITIES

Balaban R, Cecener G, PATIR İ, Sahin S, Poslu A, Koz G (2023, 14-16 November), Evaluation of Potential Anticarcinogenic Characteristics of Liposomal SN38-OA on MDA-MB-231 Cells, Cellular Bases for Patient Response to Cancer Therapies, European Associated Cancer Research Congress abstract proceedings book, Lyon, France (poster presentation)

Balaban R, Cecener G, Poslu H. A, Koz G, Egeli Ü (2023, 26-29 October), Synergistic Effects of SN38-OA/Cur Combination on Triple Negative Breast Cancer Cell Line, 18th . Medical Biology and Genetic Congress abstract proceedings book, Ankara, Türkiye (oral presentation)