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Pochodne podofilotoksyny i benzotiazolu jako leki przeciwnowotworowe – optymalizacja struktury i badanie mechanizmu działania

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Key words: podophyllotoxin, benzothiazole, anti-cancer drugs, pharmacology, oncology, cancers, HPV, green synthesis, nasopharyngeal cancer.

Abstract

„New derivatives of podophyllotoxin and benzothiazole as anticancer agents - structure optimization and mechanism of action study."

This dissertation presents a series of four publications on the design, synthesis and study of the anticancer activity of new podophyllotoxin and benzothiazole derivatives with an analysis of the mechanism of action of both the parent substance and the new derivatives synthesized by our team.

Podophyllotoxin (PPT) is a plant-derived compound with potent anticancer properties, but its clinical use is limited due to its high toxicity. Since the middle of the last century, PPT has been used experimentally to treat HPV-related cancers of the nose, throat and larynx, among others. Despite its promising efficacy, due to its high toxicity, it has not been recommended in many cases. Currently, it is only used topically to treat anal and genital condylomas.

However, PPT serves as a scaffold for the development of less toxic and more effective substances for systemic anticancer therapy. Examples include anticancer drugs such as etoposide and teniposide, which are derivatives of PPT and have entered everyday use in oncology.

The aim of the study was to obtain new derivatives with a better therapeutic profile and therefore higher anti-cancer efficacy and lower toxicity toward healthy cells, as well as to learn more about the mechanism of action of the new drugs and compare their effects to PPT in a cellular model.

In this work, a series of new compounds KL1, KL2, and KL3 were synthesized and tested *in vitro* on various cell lines, including: non-cancer cell lines HaCaT, NIH 3T3, and cancer cell lines: HeLa, MDA-MB-231, MCF-7, PC-3, DU-145, CFPAC-1. The most promising derivative is KL3, which is a combination of PPT and benzothiazole. In our study, compound KL3 showed antitumor activity equal to or more effective than PPT and was less toxic to non-cancer cells than the parent PPT. The selectivity index for most of the cell lines tested showed that KL3 was more selective than PPT. An experimental analysis of the mechanism of action of KL3 and PPT was carried out, including cell cycle assay, induction of apoptosis process and analysis of cell ultrastructure by transmission electron microscopy.

The results were published in three original articles. After analyzing the available bibliography on the applications of PPT derivatives in non-cancerous diseases, the doctoral student undertook the preparation of a systematic review to fill the gap in knowledge on this subject. To this end, and using the knowledge gained in doctoral school, a systematic review was created in 2025.