Summary

Cancer is a global problem. One of the main characteristics of cancer cells is uncontrolled proliferation, which is why cancers, due to the aberrations occurring in them, are often called "cell cycle diseases." The cell cycle is regulated by several proteins and checkpoints whose task is to monitor the course of individual phases of the cell cycle and determine the conditional transition to its following stages. The leading group of cell cycle regulators includes cyclins and cyclin-dependent kinases (CDKs). Deregulation of the expression of the division cycle proteins is currently becoming the subject of intensive research because their expression and regulation disorders may contribute to carcinogenesis. Cyclin Y has been defined as a protein that can connect the course of the cell cycle with the transcription process but also as a regulator of the Wnt signaling pathway. It was shown that the presence of cyclin Y in the complex with CDK14 affects the promotion of the non-canonical path of the Wnt pathway by enhancing the expression of proteins that are substrates of the described pathway. In addition, the expression of cyclin Y plays an important role in carcinogenesis. NSCLC overexpresses cyclin Y, and cyclin Y expression positively correlates with the histological subtypes of NSCLC (i.e., squamous cell carcinoma and adenocarcinoma) and with tumor size. On the other hand, the decrease in cyclin Y expression in the NSCLC line leads to the inhibition of cancer cell proliferation.

In this doctoral thesis, the research material was the A549 non-small cell lung cancer line with the active p53 protein and the H1299 line devoid of functional p53 protein. Both cell lines were exposed to cisplatin at a concentration of 10 and 30 μM and icaritin at a concentration of 30 and 60 μM. After treatment with the above compounds, the expression of cyclin Y was examined. Furthermore, due to the previously unpredictable results after the treatment of cells with icaritin related to the formation of crystals, their detailed analysis was performed using a polarizing and phase-contrast microscope.

The results of the study showed that the cells of the A549 and H1299 lines were sensitive to cisplatin and icaritin. With the increase in the concentration of compounds and the extension of the incubation time, the number of cells decreased, which may be related to the arrest of the cell cycle and the induction of cell death in both lines. Furthermore, it was shown that cisplatin increased the percentage of cells of both lines in the G2/M phase of the cell cycle. However, the assessment of the types of cell death provided information that

icaritin induced cell death of both lineages by apoptosis. In the case of cisplatin, only the H1299 line showed a statistically significant increase in the percentage of late-apoptotic cells. In addition, the assessment of the migration potential of cells showed that both compounds reduced the number of colonies formed and the migration of cells of both lines. On the other hand, icaritin reduced the migration rate of A549 and H1299 cells. The above studies also showed that the increase in cyclin Y expression depends on the incubation time and the type and dose of the compound used. The increase in cyclin Y expression correlated with a decrease in proliferation, the number of colonies formed, migration, and the migration rate of A549 and H1299 cells after using cytotoxic compounds.

Additional studies have demonstrated the intracellular formation of icaritin crystals. Icaritin is a compound already in the third stage of clinical trials. The presented results showed the potential risk of using this compound in cancer therapy due to the side effect of crystal formation.

In conclusion, the results obtained during the implementation of this doctoral dissertation showed that the expression level of cyclin Y increases after using cell death-inducing agents. The expression of the tested protein increased with increasing doses of cisplatin and icaritin and with longer incubation time with the compounds. The cyclin Y upregulation was correlated with cell cycle arrest, an increase in the percentage of apoptotic cells, and the inhibition of the migration potential of cells of both lines. The results of additional studies that evaluated the formation of crystals suggest that icaritin may be a potential threat in oncological treatment. Based on the presented results, it is considered reasonable that a thorough understanding of the mechanisms of action of cell cycle proteins is important in the prevention, diagnosis, and treatment of cancer.