Summary

Acne vulgaris affects up to 95% of adolescents and often requires the implementation of systemic or local antibiotic therapy. In view of the constantly growing antibiotic resistance of the bacterial acne-trigger (*Cutibacterium acnes*), the search for new active substances with antibacterial properties becomes the priority. The oral treatment of acne is based on the use of antibiotics (limecycline, doxycycline, erythromycin, tetracycline-HCl) and retinoids (isotretinoin), the utilization of which is associated with the occurrence of systemic side effects. Moreover, due to the high degree of skin sensitivity in acne, the topical substances may cause the skin irritation, as in the case of benzoyl peroxide and azelaic acid.

My interest in zinc compounds resulted from the great importance they play in cosmetic products constituting the basis of acne skin care. Some of the zinc compounds have antimicrobial properties. Although zinc complexes show lower toxicity to skin cells than the currently used derivatives, their antimicrobial activity has not been investigated. At present, these substances are used as ingredients in dietary supplements in humans, in animal nutrition or as catalysts for some chemical reactions. Importantly, their antibacterial activity has not been studied so far. In the light of these data, the aim of this doctoral thesis was to search for new active ingredients of dermatological preparations with lower cytotoxicity against skin cells and high antibacterial activity against *C. acnes* bacteria. For my research, I chose to obtain a new group of derivatives from the pool of zinc compounds, which are complex compounds of zinc with amino acids.

A series of zinc complex compounds with a few selected amino acids (L-Glu, Gly, L-His, L-Pro, L-Met and L-Trp) with the general formula $Zn(AA)_2$ was synthesized. The complex compounds did not contain any inorganic anions that could be a potential skin irritant. Depending on the solubility of the reagents in water, two methods of synthesis have been developed: the first for the complexes that are highly soluble in water (ZnGlu, ZnGly, ZnHis, ZnPro) and the second for those that are difficult to dissolve in water (ZnMet, ZnTrp).

All obtained zinc(II) complex compounds were structurally characterized using the proton nuclear magnetic resonance (^{1}H NMR) spectroscopy and elemental analysis for the presence of C, H and N. The structure of the complex particles (ZnGly, ZnHis, ZnPro, ZnMet) was confirmed by X-ray structure analysis of the obtained single crystals.

The antibacterial activity of the obtained zinc complex compounds against the selected strains of aerobic Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Streptococcus pyogenes* ATCC 19615) and anaerobic (*Cutibacterium acnes ATCC 6919*) and Gram-negative (*Escherichia coli* ATCC 25992, *Pseudomonas aeruginosa* ATCC 27853) compared to the reference substance, ZnPCA, used in dermatology as an antimicrobial agent. For all tested bacterial strains, the dependence of their growth on the concentration of the zinc compound used was determined. For some strains, the values of the minimum inhibitory concentration - MIC were additionally determined. The antimicrobial activity of the ZnMet and ZnGly complexes was higher than for the reference compound against Gram-positive aerobic bacterial strains, and against anaerobic strains of *C. acnes*, the ZnGly, ZnHis and ZnMet complexes showed stronger antibacterial activity than ZnPCA.

In the course of further biological analysis, the cytotoxic activity of zinc complexes was assessed against two types of normal human skin cells: fibroblasts (1BR.3.N cell line) and keratinocytes (epidermal cell line) against two reference substances $ZnCl_2$ and ZnPCA. The three complexes (ZnGlu,

ZnGly, ZnPro) showed lower toxicity to keratinocytes than both reference substances. In the case of skin fibroblasts, only the ZnHis complex was shown to be less toxic than the reference substances.

Considering the lowest toxicity towards skin cells and the highest antibacterial activity against anaerobic strains of *C. acnes*, two complexes, namely (ZnGly) and (ZnHis) with optimal properties were selected. With the use of these compounds, the original dermatological preparations were developed, in which the concentrations of active substances were as follow: ZnGly 0.66% for ZnGly and 1.27% for ZnHis. The amount of active substances used - (ZnGly) and (ZnHis) - constituted the same molar equivalent of Zn^{2+} ions as present in 1% ZnPCA. For these two and the placebo preparations, the microbiological purity was confirmed in accordance with the current ISO standards for cosmetic products. The stability of these preparations was tested in turn by measuring a few physicochemical parameters (including pH, density and viscosity) for 6 weeks. In the next stage of the research, the highest effectiveness of the applied preservative system of each preparation was demonstrated, in accordance with the requirements of the European Pharmacopoeia 10.0. There were also no negative interactions of the active substances (ZnGly) and (ZnHis) with the selected preservative system (a mixture of Phenoxyethanol and Ethylhexylglycerin in a weight ratio of 9:1).

Summing up, the conducted research shows that zinc complexes with amino acids, in particular ZnGly and ZnHis compounds, could be used as the new active ingredients of dermatological preparations in the treatment of acne vulgaris.