„Substrate reduction therapy with flavonoids as a treatment for mucopolysaccharidosis type I in murine model”

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Mucopolysaccharidoses (MPS) are a group of rare, congenital metabolic disorders, which lead to a lack or limited activity of one of the lysosomal hydrolases involved in glycosaminoglycans (GAG) degradation. The imbalance in the metabolism of these macromolecules results in progressive lysosomal accumulation, which usually leads to multiple organ failure and premature death. A broad spectrum of clinical symptoms is observed in the course of MPS I. The most severe phenotype, Hurler syndrome, is characterized by neurocognitive impairment, hepatosplenomegaly, and cardiovascular and respiratory dysfunctions. Available therapeutic methods include hematopoietic stem cell transplantation and enzyme replacement therapy. These therapies reduce somatic manifestations, but the treatment of neurological disorders is ineffective. Alternative methods are based on the use of small molecules, which can cross the blood-brain barrier. The group of these compounds includes genistein and other flavonoids used in the substrate reduction therapy (SRT). In this thesis, I characterized two-component mixtures of genistein, kaempferol, and biochanin A in terms of their cytotoxicity, impact on mice’s fibroblast metabolic activity, antiproliferative properties, efficiency in the inhibition of GAG synthesis, and type of interactions among compounds in the mixtures. In the next research stage, I used the mouse model of MPS I. I assessed the therapeutic potential of selected mixtures of genistein and kaempferol in SRT as well as the safety and effectiveness of biochanin A as an active agent. I showed that applying a two-component mixture of flavonoids does not always lead to increased biological activity, as observed with a single compound. I demonstrated that synergy between genistein and kaempferol enhances the therapeutic effect, enabling the reduction of active agent doses while side effects are minimized. I discovered that the application of mixtures of these flavonoids increases the chances of obtaining therapeutic effects in tissues insensitive to single flavonoid therapy. However, the effect of mixtures on biological processes depends on the active agent’s proportion and may cause side effects. Results presented in this dissertation serve as a base for future studies that allow adjustment of the composition and formulation of flavonoid mixtures to develop an effective drug for glycosaminoglycan reduction therapy.