ABSTRACT

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Thesis Title: Design and synthesis of rutaecarpine analogs as potential cytotoxic agents for cancer chemotherapy treatment

Cancer is a progressive multifactorial collection of diseases that causes disorders and decreases quality of life of patients and in some cases results in death. Cancer can affect people of all ages, sexes and races and can be diagnosed in tissues of whole body. It is the second leading cause of death in the world after cardiovascular disorders. There are many ways how to treat cancer and they variy with each type of cancer.

Nowadays treatment of cancer is based on surgery, chemotherapy, radiotherapy, biological treatment, immunotherapy and hormonal therapy. Chemotherapy represents the basis of cancer cure and is often used in combination with other approaches for tumour treatment and maximal effect of therapy and to prevent and cure metastases. Chemotherapy consists of cytotoxic agents that induce apoptosis by various pathways. These drugs interfere with cell cycle of all body cells but, in general, chemotherapy agents are aimed at fast proliferating cells more than cells with physiological cell cycle. Cytotoxic chemotherapy agents act by various mechanisms that lead to programmed cell death and are divided to five categories; these are alkylating agents, antimetabolites, anti-tumour antibiotics, topoisomerase inhibitors and tubulin binding drugs all aimed at modifications in DNA replication and transcription and cell division.

Rutaecarpine is an alkaloid found in fruits of *Evodia rutaecarpa* called Wu-Chu-Yu that have been widely used in traditional Chinese medicine for a very long time. Rutaecarpine has been proved to possess many pharmacological properties including cytotoxic activity. Its planar structure promises potential cytotoxicity through intercalation into DNA and derivatives of rutaecarpine have been proved to inhibit topoisomerase I and topoisomerase II. Topoisomerase inhibitors are widely used agents in clinical practice either alone or in combination with other antineoplastic agents.

This work is focused on preparation of rutaecarpine derivatives that could show cytotoxic activity equal to rutaecarpine but would possess increased water solubility, because the natural alkaloid is very poorly soluble. Due to the position chosen for substitution also inhibitory activity against topoisomerases could be increased. Cytotoxic activity together with better solubility of prepared derivatives could bring new options for their potential use as anti-cancer treatment.