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Title: **Isolation, Characterization and Applications of Anticancer Compounds from Medicinal Plants.**
Keywords: Natural products and their derivatives, DNA binding, Hemolysis assays, Anticancer and Docking studies.

Abstract

Cancer is a life threatening disease for a long time because of its unpredictable nature and lack of proper treatment. Approximately, more than 200 different cancer types have been recognized so far. The incidences of cancer in the Indian sub-continent are increasing rapidly and steadily. Therefore, cancer stands at second place for causing maximum number of deaths.

Present scenario witnesses the use of different strategies and sophisticated paraphernalia for the effective and safe treatment of cancer. Every cancer treatment methodology is destined to destroy cancer cells and tissues without damaging the normal cells and tissues of body. Among several modalities, chemotherapy rest at top, which consist of synthetic agents as well as natural products (NPs). Nature is a rich and diverse source of medicinally important chemical entities. The NPs include all the compounds derived from plants, animals and microbes. NPs are specific towards their binding receptors making them highly selective for different proteins and nucleic acid domains.

Turmeric (*C. longa*) is a well-known food ingredient used all over the world. Presently, turmeric powder is known for many biological applications including anticancer. Turmeric powder is biological active due to the presence of three active curcuminoids, i.e. curcumin-I, II and III. These molecules have excellent biological safety profiles. Several research groups all over the world are working on these molecules to augment their anticancer properties. In accordance with the literature reports and the continuously growing need of effective anticancer drugs, the selection of these molecules is advantageous for the design and development of new leads.

C. roseus is another medicinally useful plant containing the anticancer drugs (vincristine, vinblastine and their derivatives). This plant has a promising future as it is the source of many other alkaloids. But the drugs obtained from this plant have certain side effects. Thus, it is important to develop derivatives of vinca alkaloids with similar or enhanced activities and less or no side effect.

The main objectives of the thesis are to synthesize different natural product based anticancer agents with no or less toxicity. For this purpose, Knoevenagel condensates of curcuminoids (curcumin-I, II and III) were prepared. The different classes of aldehydes (pyrazolealdehydes and other aromatic aldehydes) were attached to the curcuminoids. Furthermore, Schiff bases of the condensates were also prepared. Besides, new derivatives of anhydrovinblastine have also been synthesized. Briefly, the present thesis describes the syntheses, characterization, DNA binding, hemolysis, anticancer and docking studies of curcuminoids and anhydrovinblastine derivatives.

Chapter 1 deals with the scenario, types and causes of cancer, mechanism of carcinogenesis, cancer treatment modalities, mechanisms of actions of available anticancer drugs and comparison between synthetic and NP based drugs.

Chapter 2 presents the detailed information of the materials and methods used to carry out this research work.

Chapter 3 discusses the process of extraction, separation and characterization of curcuminoids from *C. longa* and vinca alkaloids (catharanthine and vindoline) from *C. roseus*.

Chapter 4 comprises of syntheses and characterization of pyrazolealdehydes, Knoevenagel condensates, Schiff bases and Ru(III) complexes of curcumin-I. The values of DNA binding constant (K_b) ranged from 1.4×10^3 to 8.1×10^5 M^{-1}. The hemolysis assays on rabbit RBCs revealed that most of the compounds had toxicities between 2-20%, whereas a very few of them had more than 40%; indicating low to moderate toxicity of the compounds. The anticancer studies of the compounds were carried out on different cancerous cell lines and moderate activities of the compounds (59-98% viability) were observed. The docking results suggested that the small molecules interacted with DNA via minor grooves while large sized molecules interacted through major grooves.

Chapter 5 presents the syntheses and characterization of Knoevenagel condensates and Schiff bases of curcumin-II. The values of DNA binding constant (K_b) ranged from 6.6×10^3 to 3.3×10^5. These derivatives; unlike to curcumin-I; underwent blue shift with hyper and hypochromic shifting of bands. Additionally, these compounds causes less hemolysis (10-23%) than the derivatives of curcumin-I. These compounds showed moderate anticancer activities on human breast cancer cell line (viability = 80-95%). The docking studies showed that these compounds had high affinity towards the DNA.

Chapter 6 describes the syntheses, characterization, DNA binding, hemolytic, anticancer and docking studies of Knoevenagel condensates and Schiff bases of curcumin-III. DNA binding modes were almost similar to those of curcumin-II. The values of K_b ranged from 1.4×10^3 to 5.0×10^5 M^{-1}, indicating good interactions with DNA. Among the three curcuminoids, the derivatives of curcumin-III were least toxic to mammalian RBCs (hemolysis < 20%). The values of viabilities (%) were found in the range of 80-93%. The docking energy ranged from −5.45 to −7.0 $kcalmol^{-1}$.

Chapter 7 contains the syntheses, anticancer activities and docking studies of anhydrovinblastine derivatives. The synthesized compounds had shown very low hemolysis in comparison to the standard drug. In comparison to standard anhydrovinblastine, these showed good activities against MCF- and HeLa cell lines. The docking studies on tubulin polymer indicated that the reported molecules bound to the same region where AVBL types of compounds did.

The results presented in this thesis indicated that curcuminoids can be separated from turmeric powder by a newly developed HPLC method. The developed method was fast, accurate, economical and reproducible. Vinca alkaloids (catharanthine and vindoline) can also be separated in good yield. The derivatives of curcuminoids and anhydrovinblastine were prepared in good yields. All the synthesized derivatives of curcuminoids had good affinities for DNA. The reported compounds had good anticancer activities. Most of the compounds synthesized had lower toxicities to RBCs than standard drug letrozole and doxorubicin. The docking results well supported the experimental data. Briefly, there is a good future of the reported compounds as anticancer agents.