EFFECT OF THE PLANT ALKALOIDS ON STRUCTURE AND FUNCTION OF G-QUADRUPLEX DNA

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Dedicated to
Ma and Babai

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Overview of the work presented

Under physiological conditions, DNA assumes a double helical structure. However, no less important are the secondary structures such as Holliday junctions, triplexes, i-motifs and G-quadruplexes, which provide important signals for control of gene expression. These structures have gained importance for their association with various human diseases.

This dissertation focuses on one such secondary structure, G-quadruplex. Polyguanine sequences fold into G-quadruplexes in presence of monovalent cations like Na^+/K^+ *in vitro*. The work presented in this thesis reports the association of G-quadruplex DNA with a few putative neoplastic agents from plant sources. The molecular basis of association of three plant alkaloids, ellipticine (ELP), sanguinarine (SGR) and chelerythrine (CHL) with two quadruplex forming sequences: human telomeric DNA sequence (H24-5′-TTAGGGTTAGGGTTAGGGTTAGGG-3′) and NHE III_1 upstream of the promoter region of c-*myc* oncogene (Pu27-5′-TGGGGAGGGTGGGGAGGGTGGGGAAGG-3′) have been studied in depth.

The 1st chapter consists of a brief introduction to the problem addressed in this dissertation. The 2nd chapter consists of the techniques used to address the problem. This is followed by the work done, summarized below chapter wise.

The 3rd chapter addresses the telomerase inhibitory potential of ELP via association with telomeric DNA. Spectroscopic and calorimetric techniques have been used to comprehend the association of ELP with H24 and the ligand induced stability of H24. CD studies have also been done to study the effect of ligand binding on H24 structure, if any.

The 4th and 5th chapters address the quadruplex binding potential of two structurally similar plant alkaloids, SGR and CHL, with H24 and Pu27. The telomerase inhibitory potential of these molecules and their ability to block hybridization of Pu27 with its complementary strand has been reported. Spectroscopic and calorimetric techniques have been used for further characterization of their association with the quadruplexes and the ligand induced stability of both quadruplexes. The conformational changes in quadruplex structures as a sequel to binding have also been examined using CD.

The affinity of all three molecules towards quadruplex DNA, corresponding duplex DNA and a random DNA sequence, ct DNA has also been compared.

The dissertation concludes with the establishment of an additional mechanism by which these plant alkaloids might impart their anticancer activity by targeting and stabilizing quadruplexes apart from their already known mechanisms of action.