PREFACE

With the advent of nuclear era, there is an ever increasing use of ionizing radiation or radioisotopes in diverse areas such as, medical diagnosis and therapy, industry, agriculture, sterilization of various food products etc apart from power generation. The diverse use of nuclear radiation also he has caused a scare of human exposure due to accidents. Exposure to ionizing radiation causes a lot of deleterious consequences in living organisms. The vital targets for radiation inactivation are DNA and membrane. In mammalian systems, the exposure to γ-radiation causes a lot of syndromes such as haematopoietic syndrome, GI syndrome, CNS syndrome etc depending on the dose of exposure. The need for developing agents to protect man from radiation was realized very near. Major research in the development of radioprotective chemicals started after Second World War, more than 50 years ago in the U.S, at the inception of the Manhattan Project. The most effective compounds were those with sulfhydryl groups at one end of a 2 or 3 carbon chain and a strong basic amino group at the other end (Livesey & Reed, 1987). A large number (> 4000) of these types of compounds were synthesized at the Walter Reed Army Research Center in the U.S. Most of them were found to be toxic and unsuitable for human use. The synthesis of WR 2721 or amifostine or ethiofos [S-2-(3- aminopropylamino) ethylphosphorothioic acid] was a major breakthrough in the development of radioprotective drugs (Glowe et al., 1984; Weiss, 1997). Among the various sulfhydryl radioprotectors, amifostine is the only radioprotector that has been clinically approved by the Food and Drug Administration (FDA) for mitigating side effects (xerostomia) in patients undergoing radiotherapy [Brown et al,1982, Cassatt et al, 2002]. The synthesis of aminoethyl isothiourea (AET) was an important development, and research on its radioprotective mechanisms helped us to better understand the structural features of sulfhydryl compounds which are cardinal for radioprotection. The selective
radioprotection of normal cells by this drug has been related to its differential absorption by normal and malignant tissues and its conversion into an active sulfhydryl compound (WR 1065) in normal tissues by alkaline phosphatase action (Wasserman, 1994; Tannehil & Mehta, 1996; Valles et al., 1995; Travis, 1984). The prior treatment of patients undergoing radiation and chemotherapy with this drug significantly reduced haematologic, mucosal and renal toxicity as well as the frequency of neuropathy. It remains one of the most promising compounds at present in clinical radiation therapy for protecting normal tissues, because it is safe and practical to administer in a clinical setting. Although this drug offers good protection, but is relatively toxic (nausea, vomiting and hypotension being some of the most common adverse effects (Koukourakis, 2000). The search for less toxic, more effective radioprotectors is still continuing. In recent years, radioprotective agents with a novel mode of action have been investigated; in particular, compounds that can affect haematopoietic stem cell regeneration have attracted significant interest. The aim of this strategy is to increase survival rate by stimulating the function and regeneration of the stem cell population that is decreased, due to radiation induced damage (Whitnall et al., 2000; Landauer, et al., 2003). Immunomodulators and cytokines represent the bulk of agents in this category. Naturally occurring compounds that function as antioxidants is one strategy for the development of radioprotective agents with low toxicity. Therapeutic agents that can be administered following irradiation are another strategy for reducing side effects induced by ionizing radiation; cytokines and immunomodulators, through induction of bone marrow recovery and extra haematological tissue regeneration can represent such a class of agent. Growing clinical, toxicological and biochemical evidence supports the use of different natural products as adjunct treatment for patients exposed to radiation as well as in chemopreventive strategies. Plants and isolated compounds possess
several biological properties which include antioxidant, anti-inflammatory, immunomodulatory, anti-hormone effects, with modification of drug-metabolizing enzymes, influence on the cell cycle progression and differentiation of cells, induction of apoptosis and suppression of proliferation, metastasis and angiogenesis. The combined biological effects make the plants to play a role as efficient radioprotective agents.

In the present study we have tested three herbal extracts (Centella asiatica, Rubia cordifolia Linn and Holarrhena antidysenterica Wall) and one phytoceutical asiaticoside, a major component present in the extract of Centella asiatica, for their radioprotective activities. All these compounds possess significant radioprotecting activity and hence we decided to evaluate DNA repair enhancing ability of the extract of Centella asiatica and asiaticoside in animal models.