

Radioprotective Nature of *Podophyllum hexandrum* (Himalayan Mayapple)

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Introduction

Human beings are at risk of the exposure of radiation or radioactive materials since the World War II. Nuclear proliferation and terrorist activities has further strengthened the threats of the exposure of ionizing radiation (IR) to military, civilian, and emergency responders. IR possesses sufficient energy to strip electrons from atoms or molecules and thereby create highly reactive ions. IR at high enough doses either directly or indirectly induces ionization events that damage DNA, proteins or membrane lipids, through the generation of Reactive Oxygen Species (ROS) and other free radicals intracellularly. Total Body Irradiation (TBI) is particularly dangerous when exposure is of very short period of time [1]. The Chernobyl Catastrophe and Fukushima- Daiichi nuclear plant misfortunes exemplify the need of radiation countermeasures.

Herbs have been extensively used as a medicine to heal various diseases and other upsets. Even today, more than 70% of the world's population still depends on plant-based remedies to meet their health care needs [2]. *Podophyllum hexandrum* Royle (Himalayan Mayapple), also called as Aindri ("a divine drug") in ancient times, has been reported as a cure for several ailments like allergic and inflammatory conditions of the skin; cold; cancer of the brain, bladder and lung; Hodgkin's disease; mental disorders; rheumatism; septic wounds; and plague [3]. It has been reported to have the antioxidant property of *P. hexandrum* [4]. Therefore, it is reasonable to presume that *P. hexandrum* may contain groups of compounds that can protect against radiation-induced reactive oxygen species (ROS) mediated damage. *P. hexandrum* has been extensively evaluated for the radioprotective efficacy in the last decades.

P. hexandrum extract has been shown to render 80% total-body radioprotection in a murine model [5]. The oral administration of *P. hexandrum* has also been shown effective [6]. The radioprotective mechanism of *P. hexandrum* (rhizome extract) has been investigated using both in vitro and in vivo model systems. *P. hexandrum* exhibited potent antioxidant ability and significant free radical scavenging potential. It reduced the radiation induced lipid peroxidation [7]. We first reported that *P. hexandrum* activates heat shock transcription factor-1 (HSF-1) and MAPKAP (mitogen-activated protein kinase-activated protein) kinase-2 leading to activation of Heat shock protein (HSP) -70 in gastrointestinal murine model [8]. Pre-treatment of mice with *P. hexandrum* activated genes responsible for cellular proliferation [Bcl-2 (B-cell chronic lymphocytic lymphoma 2), Ras-GAP (Ras-GTPase-activating protein) and PCNA (proliferating cell nuclear antigen)]. In addition, *P. hexandrum* also inhibited radiation-induced apoptosis by reducing the expression of AIF, p53, and caspase3 [8]. Further, *P. hexandrum* inhibited the radiation induced cleavage of an inhibitor of caspase-activated DNase (ICAD) and thereby prohibited the translocation of CAD (caspase-activated

DNase) from cytoplasm to nucleus and protected DNA from CAD mediated DNA fragmentation [9].

We evaluated the role of *P. hexandrum* in cell cycle regulations and DNA repair. We observed higher expression of p21 along with lower expression of cyclin E and CDK2 in the *P. hexandrum* pretreated and irradiated mice as compared to irradiated mice showing delays in the G1 phase of cell cycle, which provided extra time for DNA repair or related processes [10]. No significant difference in CDK1 expression in *P. hexandrum* treated cell lines suggested that G2 arrest might not be the only responsible factor for *P. hexandrum* mediated radioprotection. Significant induction of PCNA and GADD45 expression suggested that *P. hexandrum* increased the percentage survival of HepG2 cells by increasing the span of time of DNA repair as well as efficacy of DNA repair processes.

We evaluated the effect of p53 inhibitor (pifithrin- α) on the radioprotective potential of *P. hexandrum*. We observed that pifithrin- α debilitated the radioprotective potential of *P. hexandrum*. Pifithrin- α treatment reduced the radioprotective efficacy of *P. hexandrum* by inhibiting the expression of HSF-1 and Hsp70, leading to inhibition of Bcl2 expression required for cell proliferation [11]. Pifithrin- α up-regulated the cell-cycle regulatory proteins and therefore reduced the span of time required for DNA repair. Pifithrin- α induced Bax mediated apoptosis. Pifithrin- α did not show any effect on p53 regulating protein like MDM2 and pro-survival protein like Ras-GAP [11].

In conclusion, *P. hexandrum* has the potential to be developed as a drug for the medical management of nuclear and radiological emergencies [12]. Besides the free radical scavenging activities, its holistic action at various cellular and molecular levels includes enhancement of pro-survival and DNA repair protein, down-regulation of the proteins associated with apoptosis induction, modulation of cell cycle to provide extra time for cellular repairs.

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