SUMMARY AND CONCLUSION
Ionizing radiations are responsible for a variety of lesions in biological systems. A significant part of cellular damage that occurs is due to the formation of ROS, which reacts with almost all the biological cellular components to induce oxidative damage (Cerutti, 1985; Repine et al., 1981; Yamaguchi et al., 1994). Free radicals can also initiate a variety of signal transduction pathways that may either aid the cell in coping with the excess oxidative stress or set in motion pathways that lead to the destruction of cells damaged beyond their repair capabilities (Ahmed and Li, 2008; Mikkelsen and Wardman, 2003).

Protective abilities of LA (Bast and Haenen, 1988; Haenen et al., 1990; Kagan et al., 1992; Ramakrishnan et al., 1992); Silver (Bhol and Schechter, 2007; Nadworny et al., 2008; 2010a; 2010b; Wong et al., 2009); Zinc (Bray and Bettger, 1990; Ertekin et al., 2004; Floersheim et al., 1988; Mantena et al., 2008; Richard et al., 1993); TPL (Hahn et al., 1992a; 1997; Li et al., 2006; Mitchell et al., 1991); and POLY-MVA (Antonawich et al., 2004; Sudheesh et al., 2009) against different oxidative stress conditions have been well substantiated. The present study evaluated various protective activities of the following agents viz. i. nanoparticle complexes of Lipoic acid viz. SNLA and ZNLA, ii. Tempol and iii. POLY-MVA.

Nanoparticle complexes of LA viz. SNLA and ZNLA were prepared by ultrasonication in the presence of a nonionic, surfactant Pluronic F-127. SNLA and ZNLA were found to inhibit DPPH free radical formation pointing towards their antioxidant property. To continue with in vivo studies, SNLA and ZNLA had to be screened for any possible toxicity. Extent of membrane peroxidation and endogenous antioxidant levels in various tissues were monitored in mice administered with different concentrations of nanoparticles, SN or ZN for 14 days. To assess the toxicity profile of nanoparticle complexes, the animals were administered with either SNLA or ZNLA for 14 consecutive days and different serum parameters were analyzed. Results showed that none of the parameters differed significantly from the normal levels confirming their non-toxic nature for various in vivo studies.
Radiations produce free radicals in biological systems and cause oxidative conversion of PUFAs to several products including malondialdehyde and lipid peroxides. Radiation also induces an inflammatory response in the target and surrounding normal tissues, and accumulation of leucocytes (Panes and Granger, 1998). In our study, SNLA, ZNLA, TPL or POLY-MVA prevented radiation induced membrane lipid peroxidation in liver tissues under in vitro conditions. SNLA, ZNLA and TPL were found to have anti-inflammatory effects on acute and chronic paw oedema formations suggesting that these agents can have beneficial roles in radioprotection.

Whole body exposure of mice to gamma radiation leads to depletion of tissue antioxidant defense system and damage to hematopoietic and gastrointestinal systems. All the agents under study helped to ameliorate radiation induced membrane lipid peroxidation and lowering of endogenous antioxidants in different tissues of radiation exposed mice. They also had a protective effect on the hematopoietic system against deleterious effects of ionizing radiation as evident from data on bone marrow cellularity, spleen colony formation, spleen weight and different hematological parameters. Gastrointestinal tissues were also found to be protected from radiation induced histological alterations to various extents upon administration with these agents.

Mortality of animals following radiation results from several factors like damages to the hematopoietic system and gastrointestinal system which may ultimately lead to immune suppression (Krishna and Kumar, 2005). Survival studies conducted suggest that all the agents under study bestowed survival advantage to the animals following exposure to the lethal dose of gamma radiation and also delayed the onset of radiation induced body weight alterations. It can be inferred that these agents have the ability to protect various organ systems against gamma radiation induced damages, but understanding the specific mechanisms warrant another study.

Effect of TPL and POLY-MVA on radiation induced plasmid DNA damage demonstrated that they prevented the formation of strand breaks in plasmid DNA as evidenced by the conservation of super coiled form of the DNA. Further, SNLA,
ZNLA, TPL and POLY-MVA were assessed for their protective effects against radiation induced strand breaks in cellular DNA under *ex vivo* and *in vivo* conditions. Comet assay has been utilized as a sensitive, rapid, and simple technique for the evaluation of DNA damage and repair (Singh and Stephens, 1997). Different comet parameters *viz.* Tail DNA %, Tail length, Tail moment and Olive tail moment were seen to be elevated in cells exposed to gamma rays. Treatment with the agents under study helped to lower the extent of DNA damage in a considerable manner.

DNA damage, when un-repaired or mis-repaired, can result in genomic instability, changes in cellular identity and function, cell death, and also neoplastic transformation in multi-cellular organisms. Assays for both micronucleus and chromosomal aberration may be employed as cytogenetic endpoints for measuring chromosomal damage induced in bone marrow cells by different genotoxic agents like radiation. The former assay monitors genotoxic damage in blood reticulocytes while the latter detects the insult in bone marrow cells following metaphase arrest. Whole body gamma radiation exposure induced micronuclei formation in peripheral blood lymphocytes of mice and administration with SNLA, ZNLA or TPL decreased the micronuclei frequency significantly in comparison with the respective irradiated control groups. Similarly, pre-treatment with SNLA, ZNLA or TPL decreased radiation induced chromosomal aberrations under *ex vivo* as well as *in vivo* conditions.

Effect of post-irradiation treatment of SNLA, ZNLA or TPL on repair of damaged cellular DNA was determined by monitoring the comet parameters in radiation exposed cells at different post-irradiation time intervals under *ex vivo* and *in vivo* conditions. Eukaryotic cells have evolved efficient mechanisms to detect and repair DNA lesions induced during each phase of the cell cycle (Bassing and Alt, 2004). The repair system would comprise removal of lesions such as radiation induced base modification through a process of incision and excision at the sites of damages in DNA strand leading to regeneration of strand breaks (Mendiola-Cruz and Morales-Ramirez, 1999). From the ‘Cellular DNA Repair Index’ (CRI) data, it was clear that these test agents enhanced the cellular DNA repair process.
Cancer may be considered the most onerous health problem affecting people worldwide. Though chemotherapy and radiation therapy are commonly used for the treatment modalities, they entail many side effects. An effort was made to understand the adjuvant role of SNLA, ZNLA and TPL as protective agents for normal tissues in tumor therapy. The test agents were found to substantially suppress the DLA solid tumor growth and showed a synergistic effect on antitumor efficacy of radiation. Co-treatment of these agents with either of the chemotherapeutic drugs DOX or CDDP, significantly protected tumor bearing mice from chemotherapy induced bone marrow suppression and micronuclei formation. They also protected the animals from DOX induced cardiotoxicity or CDDP induced nephrotoxicity as assessed from the endogenous antioxidant status, serum marker levels and histopathological analysis. Meanwhile, administration of the agents under study did not interfere with the antitumor efficacy of these chemotherapeutic drugs.

Therapeutic molecules are conventionally delivered via the parenteral route of administration. However, this route of administration has inherent disadvantages in case of a large spectrum of biological molecules when looked at from the standpoint of safety, compliance, convenience, cost and self-administration, whereby making oral delivery of biologically-active agents more preferable. Our results showed that, oral administration of all the test agents, viz. SNLA, ZNLA, TPL and POLY-MVA demonstrated excellent antioxidant and anti-inflammatory properties. All of them effectively protected mice from radiation induced damages when administered prophylactically or therapeutically, signifying their application in planned or unplanned radiation exposure scenarios. Moreover, SNLA, ZNLA and TPL ameliorated the side effects of radiotherapy as well as of commonly used cancer chemotherapeutics (DOX and CDDP) in tumor bearing animals suggesting their use as adjuvants in radiotherapy or chemotherapy.