FREE RADICAL BIOLOGY SECTION

Preclinical and translational research for development of new drugs and therapeutics for prevention and mitigation of radiation injury, and treatment of inflammatory disorders and cancers

1. Preclinical research for the development of prophylactic and therapeutic radioprotectors

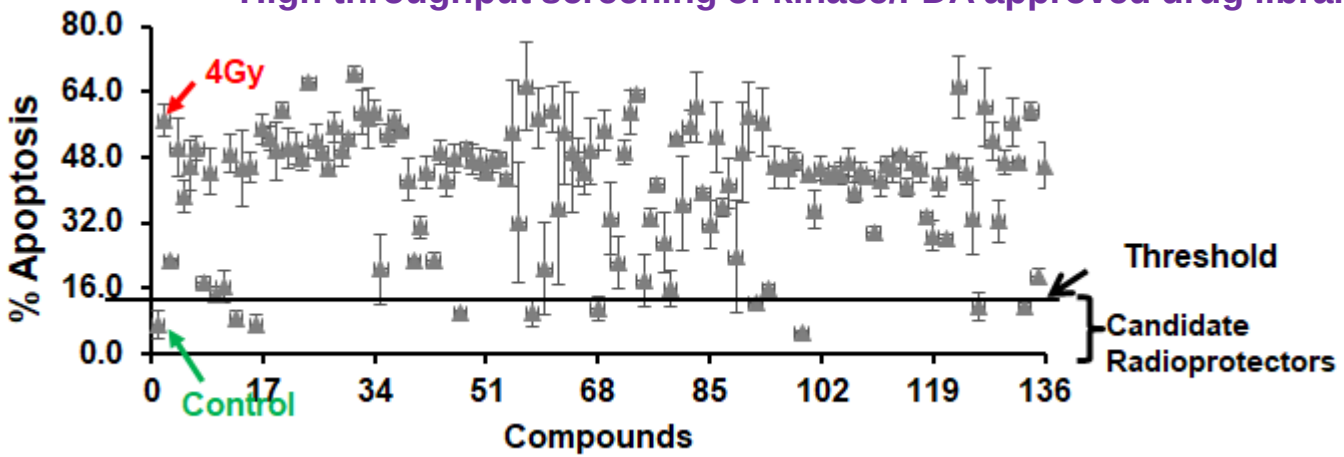
2. Basic research to understand the role of cellular redox balance in regulating inflammation and immunity

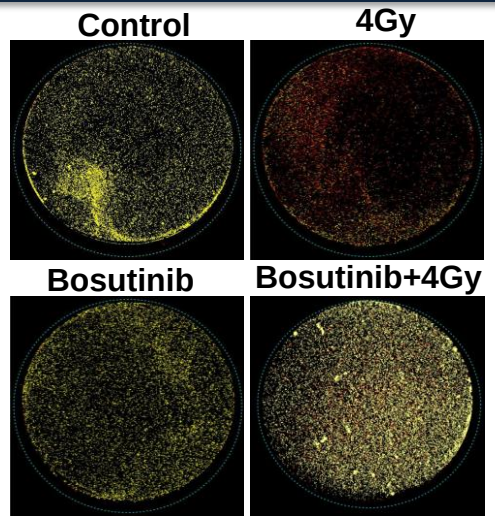
3. Understanding the mechanisms responsible to cancer radio-resistance and to develop novel strategies to overcome

4. Translation of preclinical research from bench to bedside

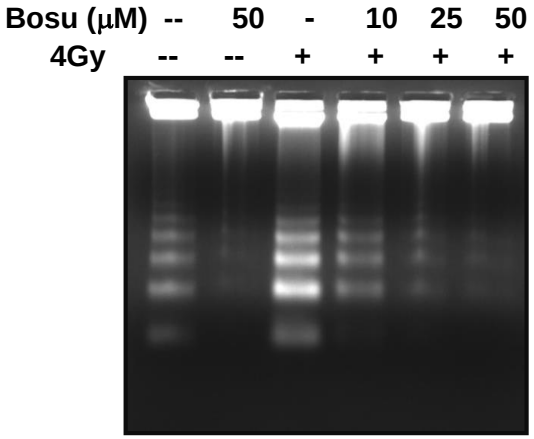
1.1 Screening of FDA-approved drugs and small molecule libraries for the protection of normal cells against ionizing radiation induced toxicity

High throughput screening of kinase/FDA approved drug library

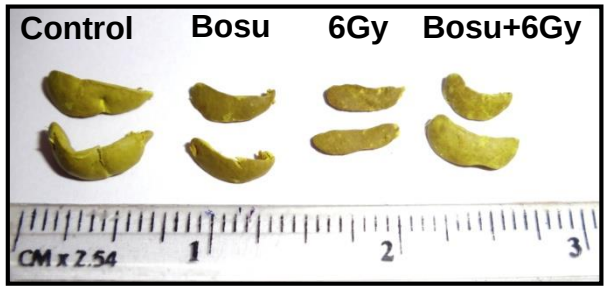




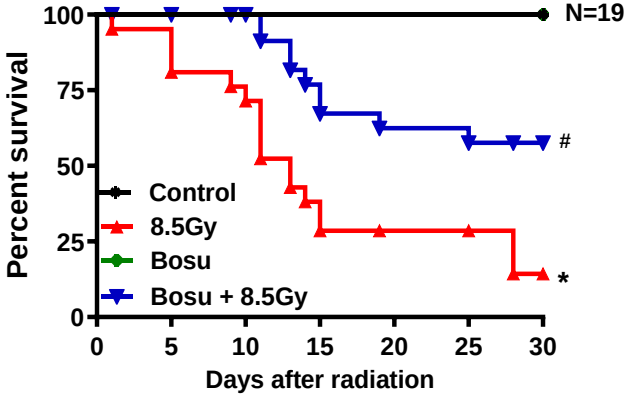
Bosutinib inhibited IR induced apoptosis in lymphocytes



Bosutinib enhanced the endogenous spleen colonies in WBI mice



Bosutinib protected mice from radiation induced mortality

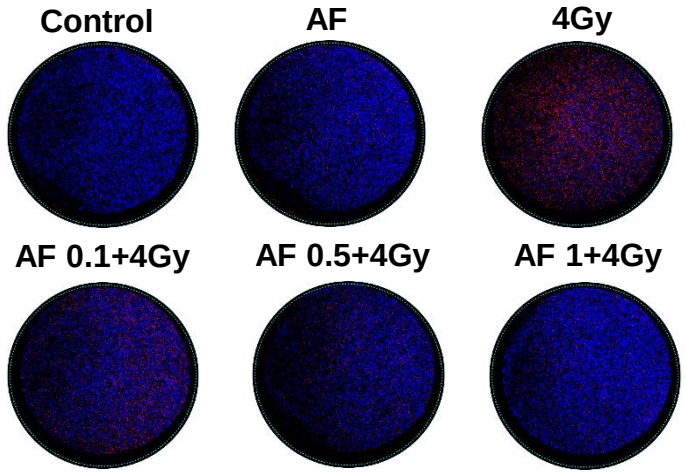


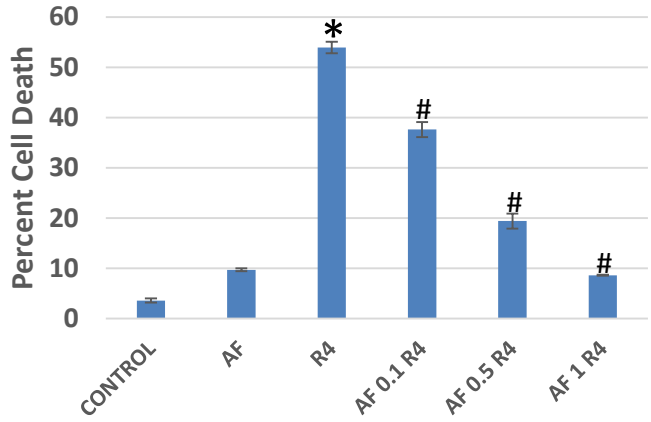
Singh et al, Toxicology and Applied Pharmacology, 2023

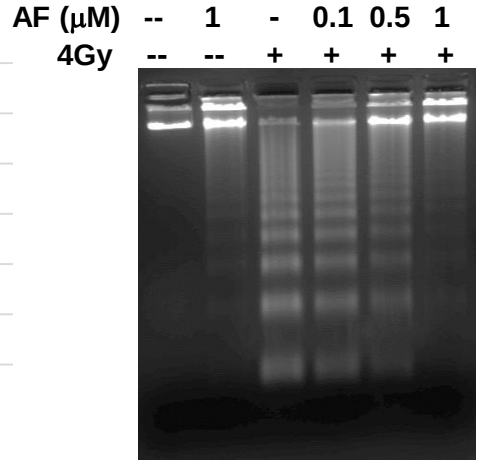
Take home message: Administration of bosutinib (Human equivalent dose) protected animals against 8.5 Gy radiation induced mortality and morbidity by protecting the hematopoietic organs (spleen and bone marrow). Since bosutinib is FDA approved, it has translational potential.

1.2 Repurposing FDA-approved agent for prevention of radiation-induced hematopoietic injury

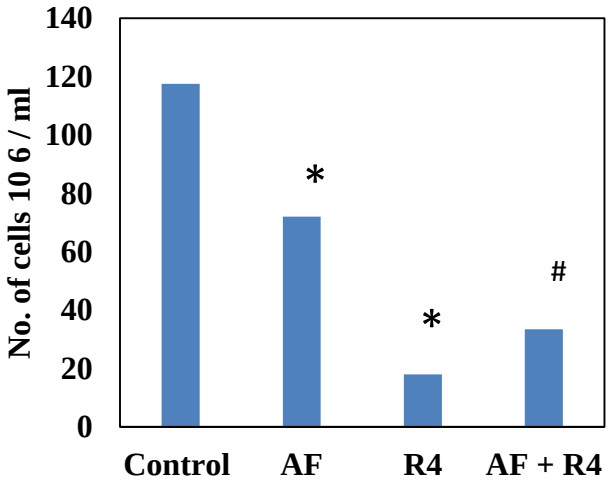
Auranofin (AF) prevented radiation-induced cell death in lymphocytes

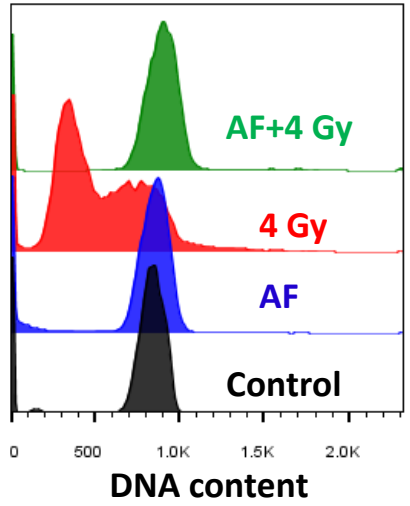


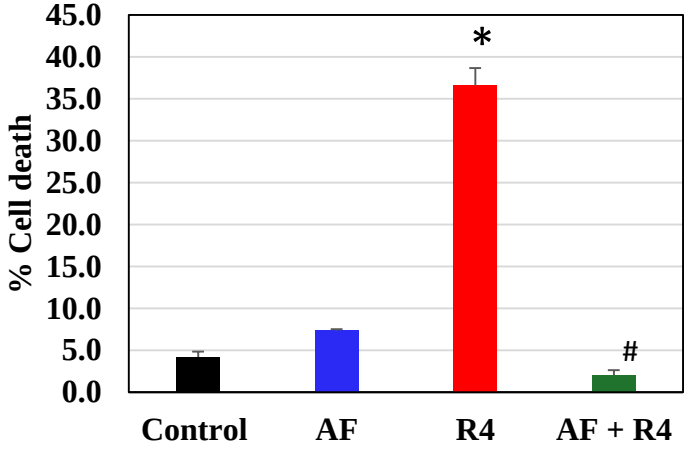




Auranofin protected splenic lymphocytes in vivo against radiation-induced cell death



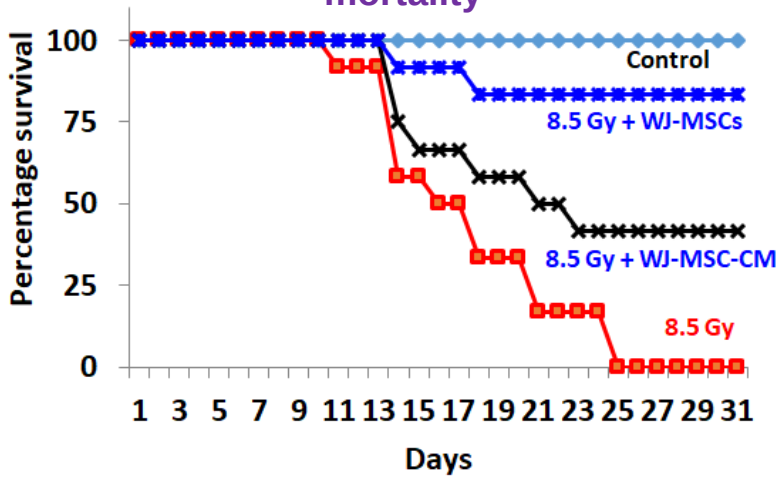




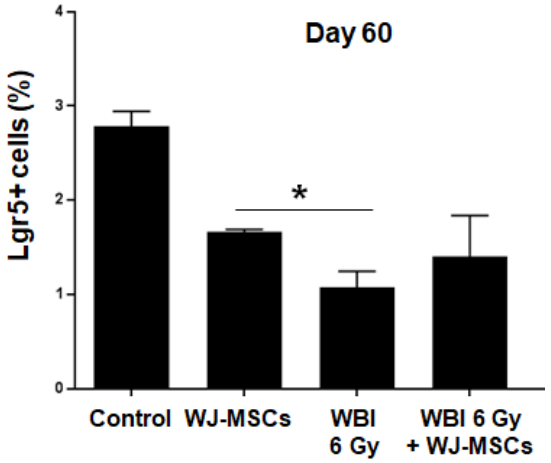
Take home message: Auranofin treatment prevented radiation induced cell death in splenic lymphocytes in vitro and in vivo.

1.3 Stem cells isolated from human umbilical cord has significant therapeutic radioprotective ability

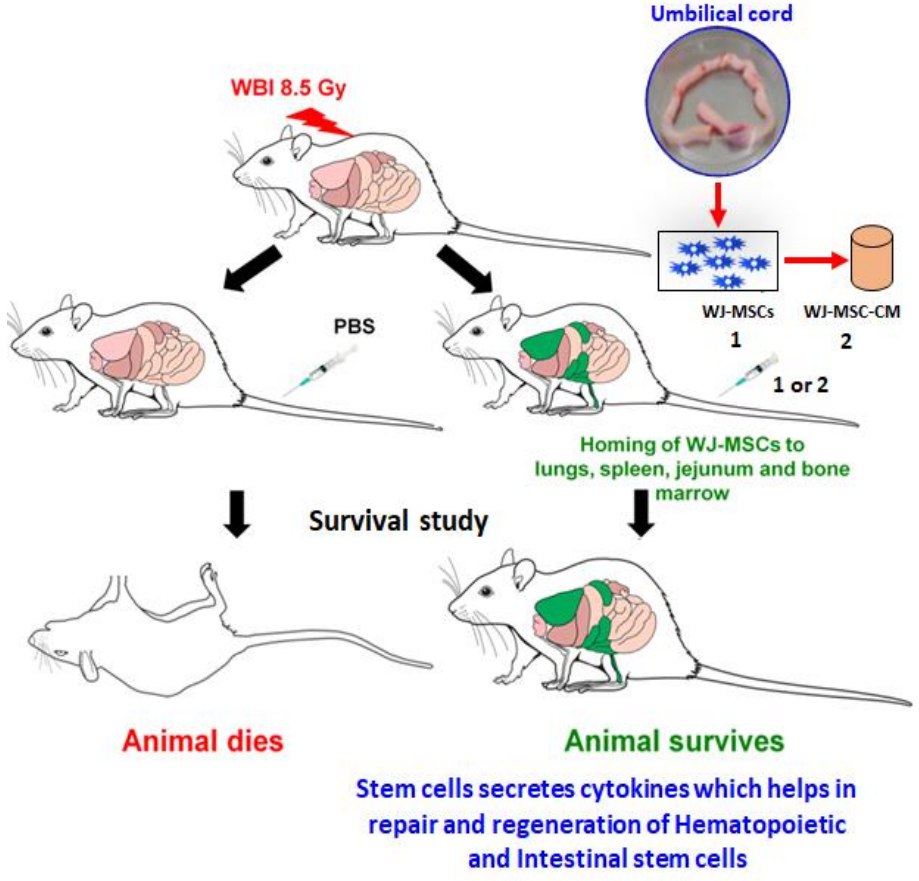
Infusion of WJ-MSC or their conditioned medium rescue mice from WBI induced mortality



WJ-MSC infusion enhanced the frequency of intestinal stem cells in irradiated mice

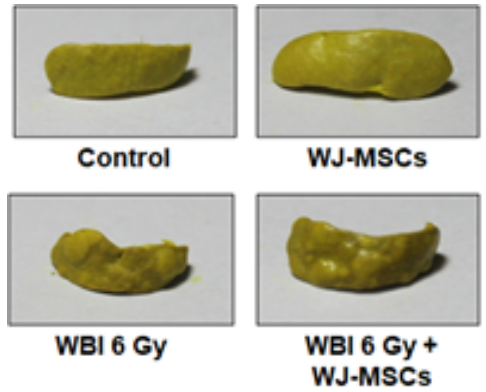


Summary of WJ-MSC mediated therapeutic radioprotection

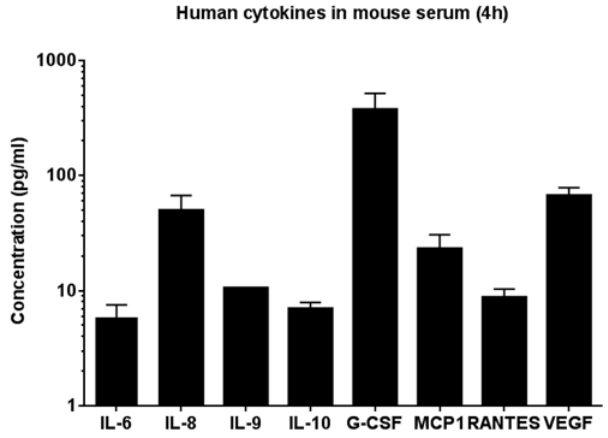


Stem cells secretes cytokines which helps in repair and regeneration of Hematopoietic and Intestinal stem cells

WJ-MSC infusion enhanced the endogenous spleen colonies in WBI mice



Infusion of WJ-MSC elevated the cytoprotective cytokines in mice serum



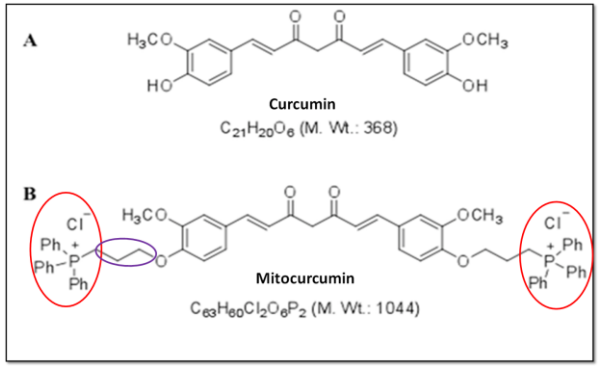
Bandekar et al, American Journal of Transplantation, 2020
Maurya et al, World Journal of Stem cells, 2022

Take home message: Wharton's jelly MSCs and their soluble factors offers significant therapeutic radioprotection in murine model.

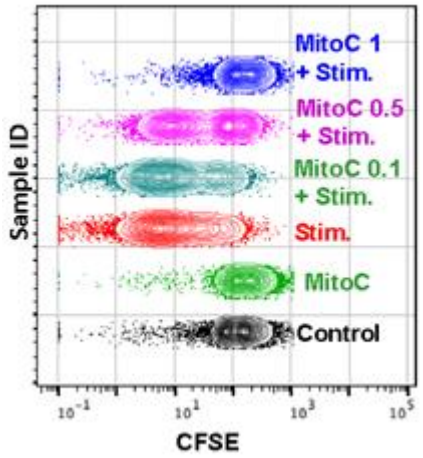
2.1 Mitochondrial targeted curcumin inhibits T cell activation and graft-versus-host disease

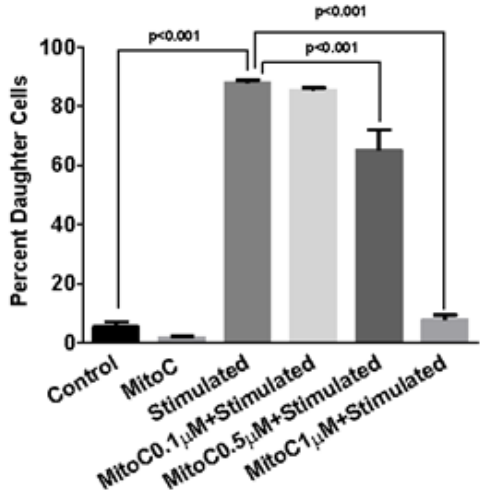
Curcumin is the active ingredient in dietary spice turmeric (Curcuma longa)

Chemical modification of Curcumin to increase uptake and efficacy

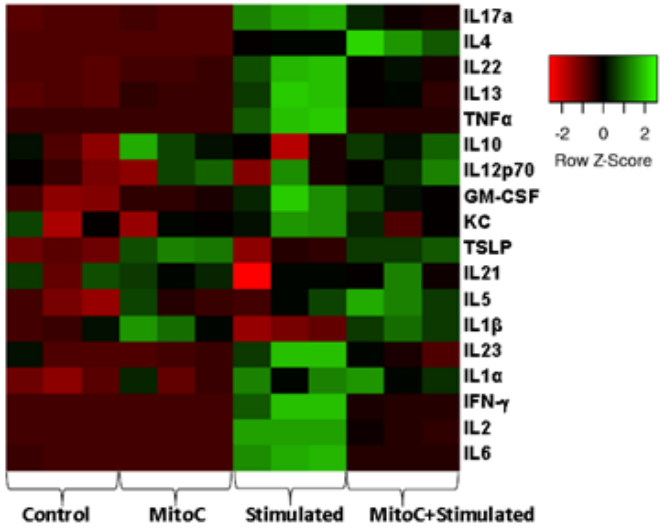


Mitocurcumin suppressed mitogen induced T cell proliferation

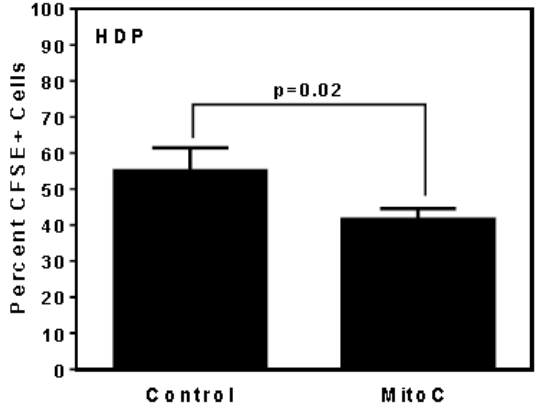


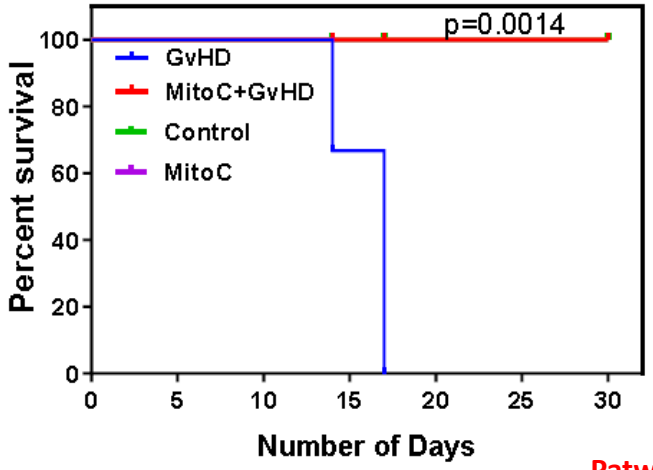


Effect of mitocurcumin cytokines secretion

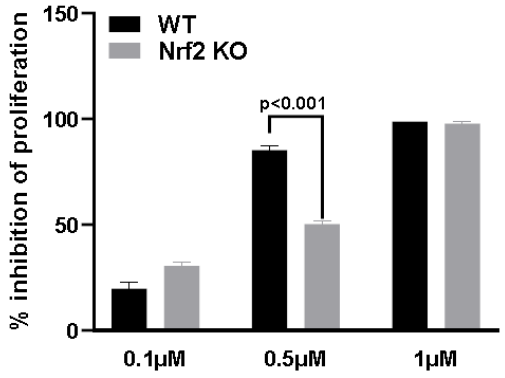


Mitocurcumin suppressed GvHD-associated mortality and morbidity





Mitocurcumin mediated suppression of proliferation is Nrf2 dependent

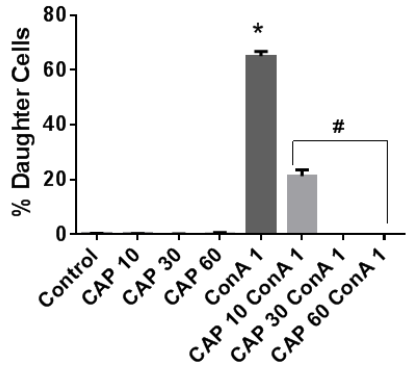


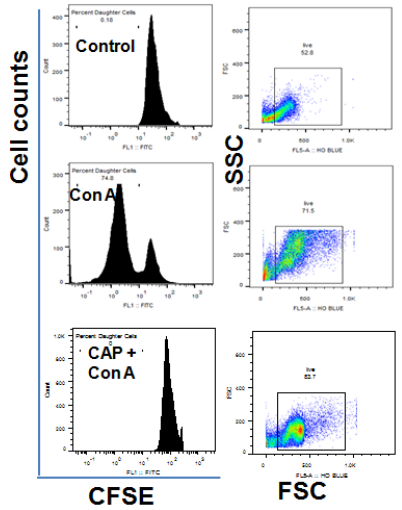
Patwardhan et al, Phytotherapy Research, 2024

Take home message: Mitocurcumin moderates T cell hyperactivation and associated immunological disorder in vivo.

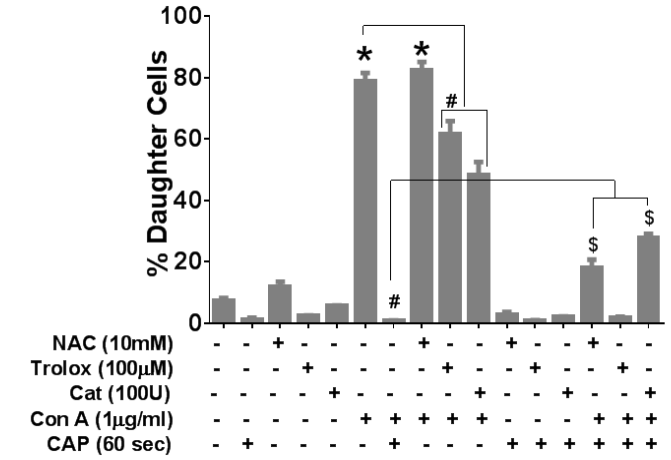
2.2 Cold Atmospheric Plasma (CAP) treatment modulate lymphocytes responsiveness to mitogen

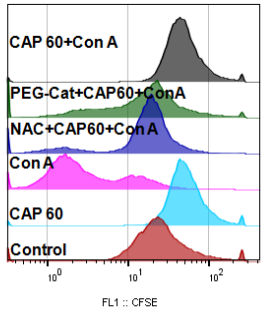
CAP suppressed mitogen induced T cell proliferation



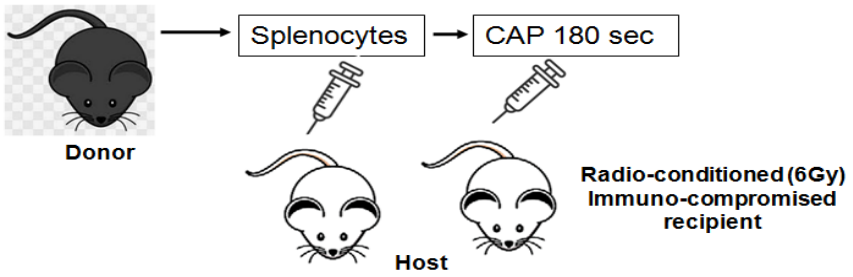


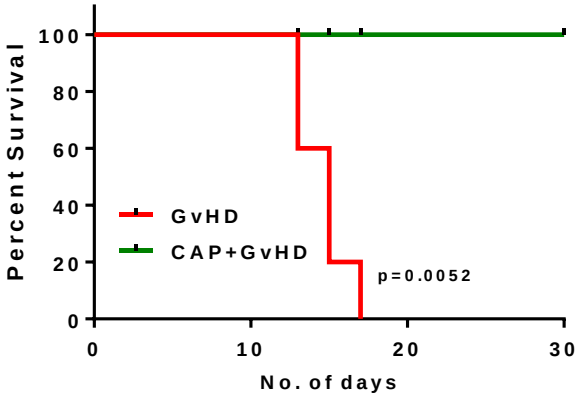
Pre-treatment of antioxidant abrogated CAP mediated inhibition of mitogen induced proliferation

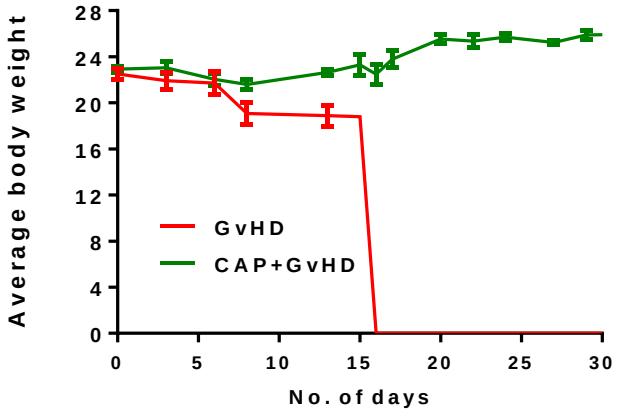




CAP suppressed GvHD-associated mortality and morbidity



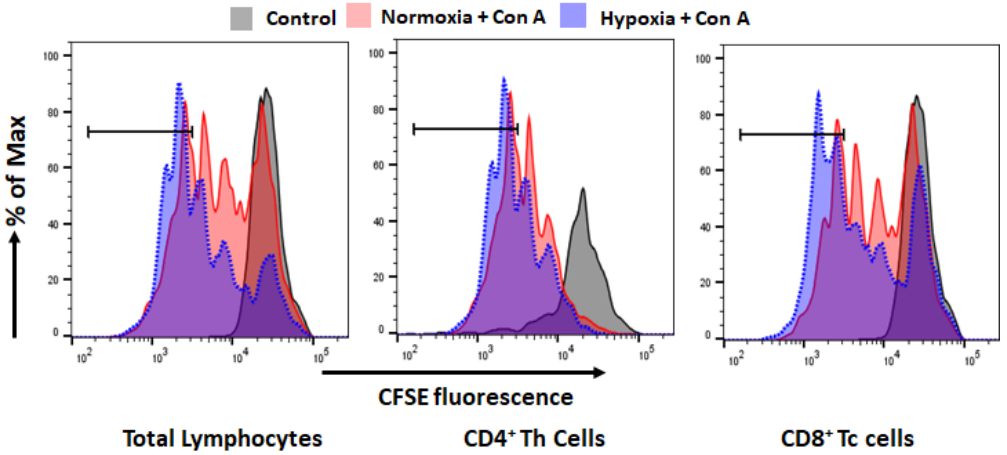




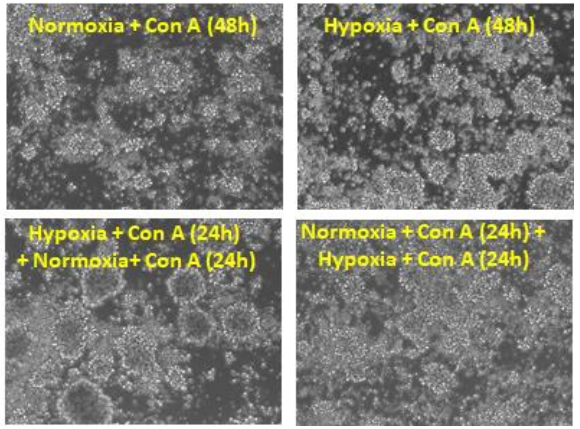
Take home message: CAP treatment can provide research avenues for the development of novel approaches for the treatment of inflammation and transplantation with low cytotoxicity.

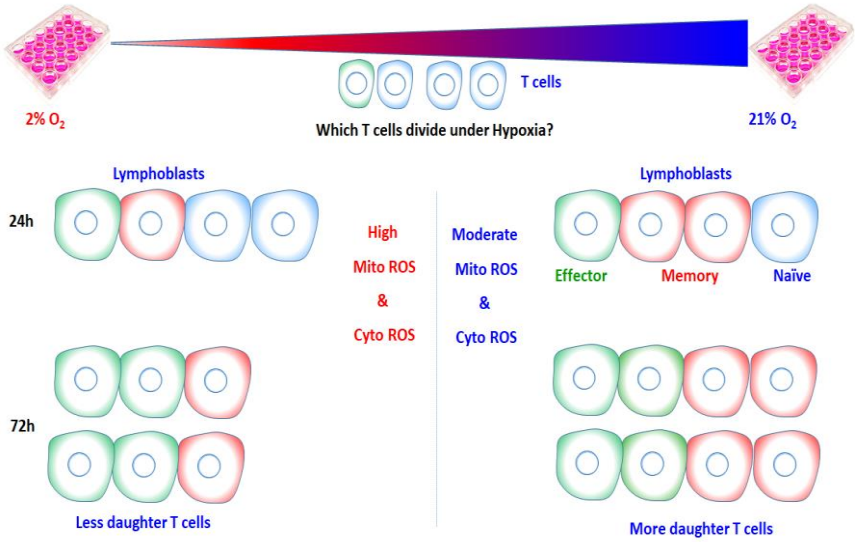
2.3 Hypoxia induces dichotomous and reversible attenuation of T cell responses through ROS dependent phenotype redistribution

Hypoxia delays T-cell proliferation

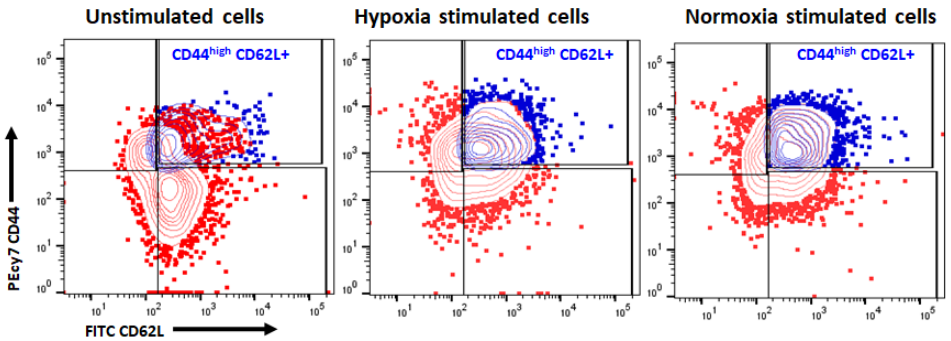


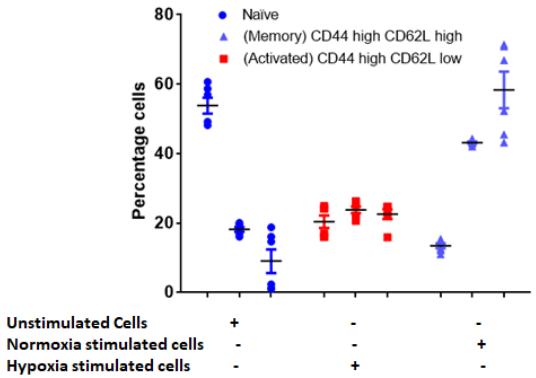
Attenuating effect of hypoxia on of T-cell proliferation is reversible





Hypoxia delays expansion of memory phenotype T cells





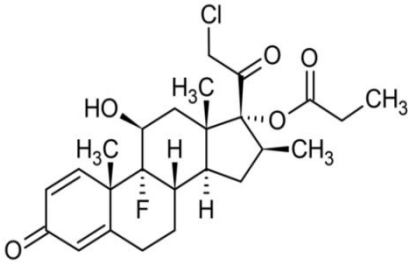
Activated T cells cultured under hypoxic conditions show increased cellular ROS and mitochondrial ROS levels and there is limited expansion of memory phenotype T cells under as compared to activated T cells cultured under normoxia

Maurya et al, Free Radical Research, 2023

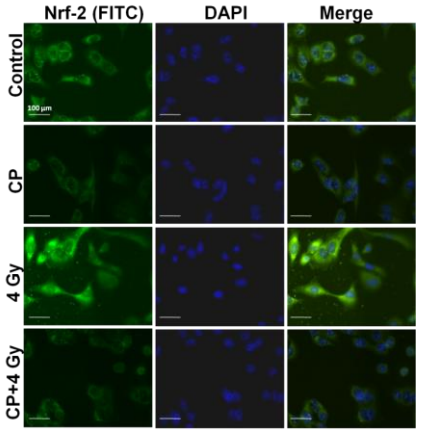
Take home message: Hypoxia induces a reversible delay in proliferation of a subset of T cells which is associated with obliteration of memory phenotype and specific increase in cytosolic / mitochondrial ROS levels in actively dividing subpopulation. Thus, intermittent reoxygenation of hypoxic patients may restore normal T cell responses.

3.1 Repurposing FDA-approved drug clobetasol propionate as a Radio-sensitizing agent

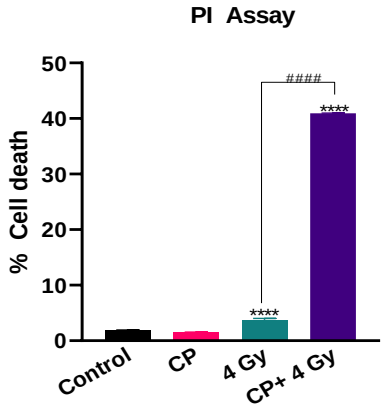
20-25% lung cancers have altered Nrf-2 expression. Overexpression of Nrf-2 confers radio-resistance and survival advantage to cancer cells, thereby interfering with therapeutic efficacy. Inhibition of Nrf-2 is a promising strategy for radio-sensitization of Nrf-2 overexpressing cancer cells.



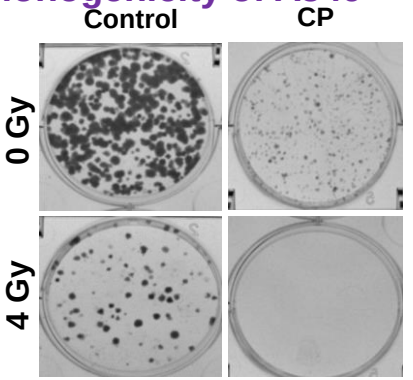
Clobetasol propionate



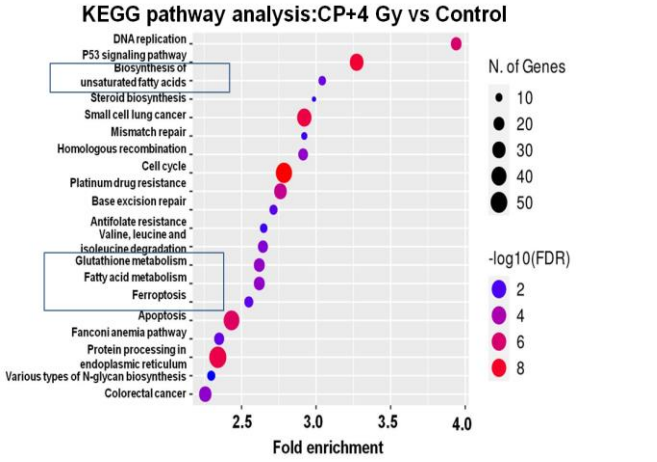
CP+IR led to increased cell death



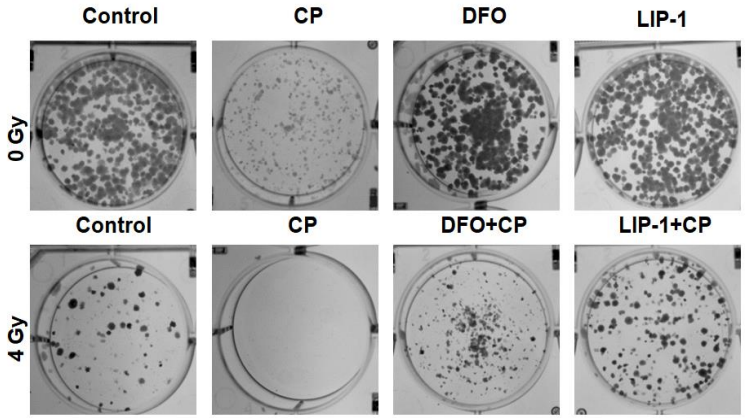
Combination of CP and IR suppressed the clonogenicity of A549



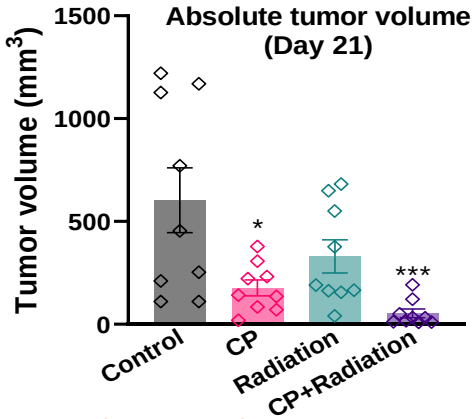
RNA Seq data indicated a potential induction of ferroptosis by CP+IR treatment



CP mediated radiosensitization was abrogated by ferroptosis inhibitors



CP+IR resulted in significant reduction of tumor burden in vivo



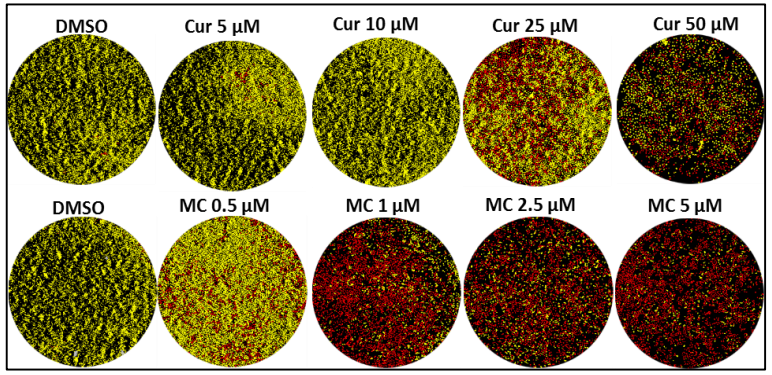
Rai et al, Acta Pharmacologica Sinica, 2024

Take home message: In Nrf-2 overexpressing cancer cells, clobetasol propionate mediated radiosensitization is via ferroptosis.

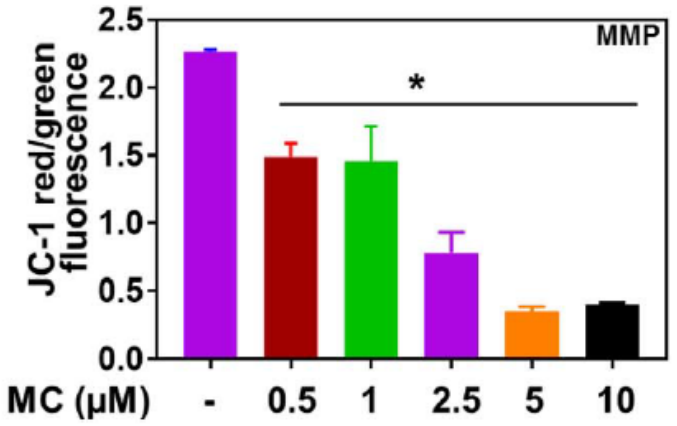
3.2 Development of mitocurcumin as novel anticancer agent

Mitocurcumin is synthetic derivative of curcumin which is design to target mitochondria.

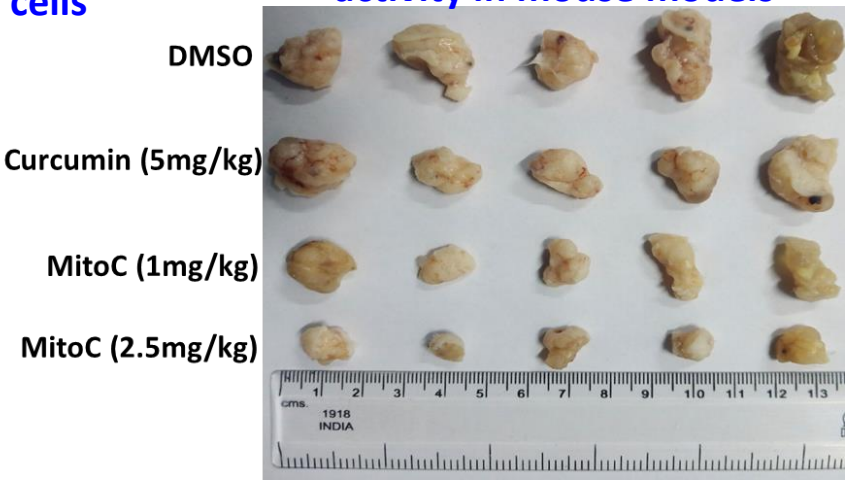
Mitocurcumin is 50 times more effective than curcumin in killing cancer cells and inhibiting cancer cell division



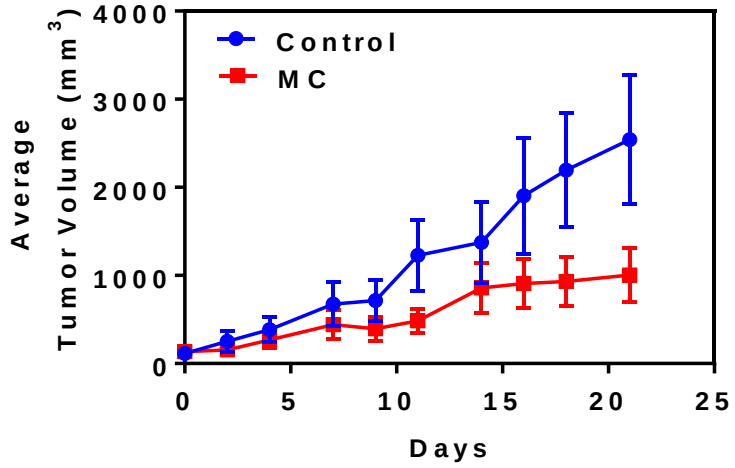
Mitocurcumin treatment lead to mitochondrial dysfunction in cancer cells



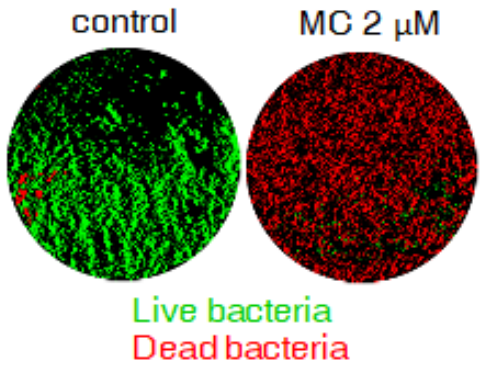
Mitocurcumin shows better anti-tumour activity in mouse models



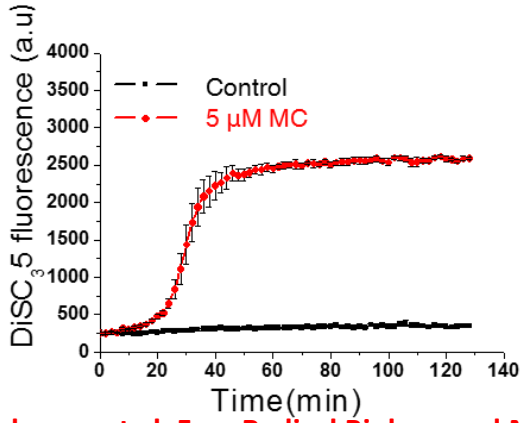
Tumor xenograft in SCID mice



Mitocurcumin exhibits potent antibacterial activity



Mitocurcumin disrupts bacterial membrane potential



Jayakumar et al, Free Radical Biology and Medicine, 2017

Kumari et al, Journal of biosciences, 2020

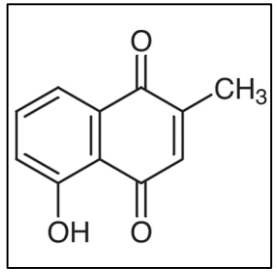
Take home message: Mitocurcumin can be a potent anti-cancer agent and also can be used to control the infection arise during therapy.

3.3 Anti-cancer activity of plumbagin and synthesis of oral plumnbagin nanoparticle formulation

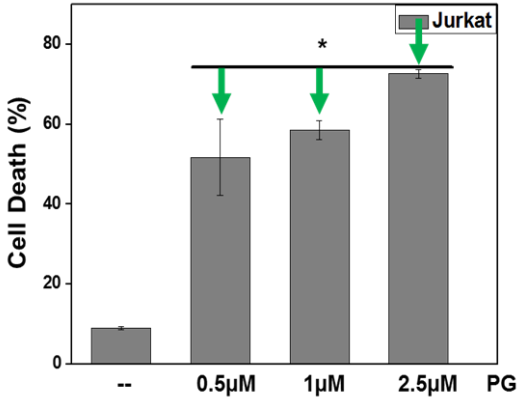
Plumbagin, derived from the root of medicinal plant Plumbago zeylanica (also called Chitrak), is a herb that grows wild in India and has been used for hundreds of years as a traditional medicine.

Chitrak Plant (*Plumbago zeylanica*)

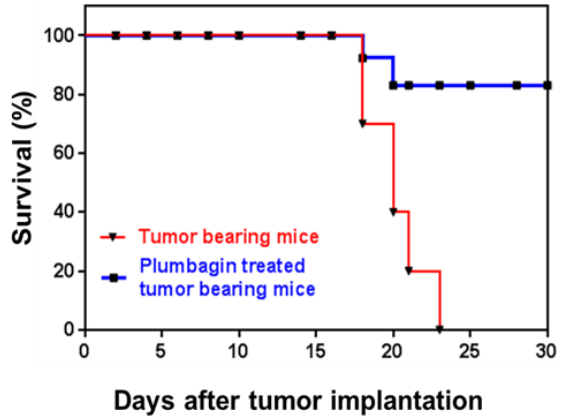
Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone)



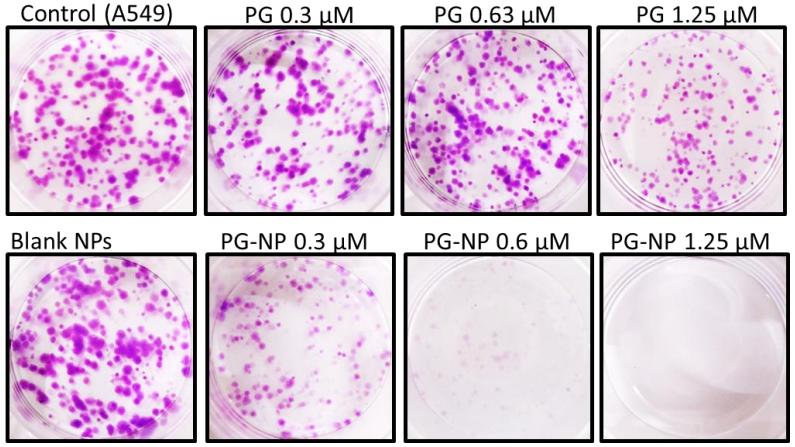
Plumbagin induced cell death in human cancer cells

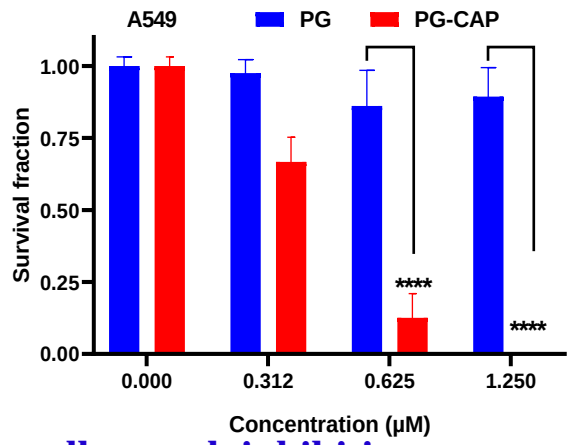


Plumbagin inhibited tumor progression in mice



Plumbagin nanoparticles are also more effective in inhibiting the clonogenic potential of cancer cells

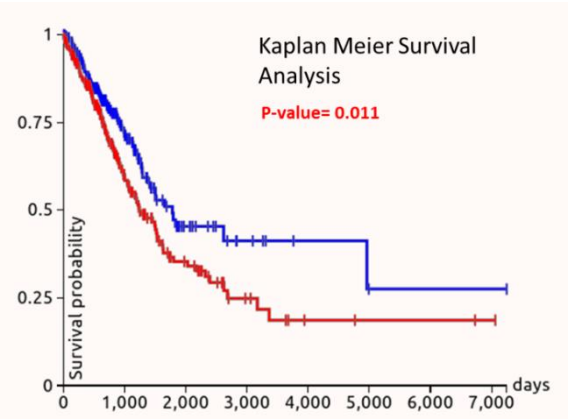




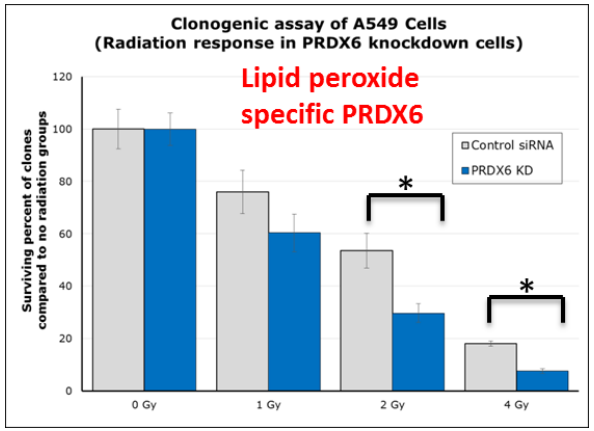
Take home message: Nano formulation of plumbagin is more effective in cancer cell growth inhibition compared to plumbagin alone.

3.4 Understanding the role of Peroxiredoxin 6 (PRDX6) in radiation response of A549 lung cancer cells

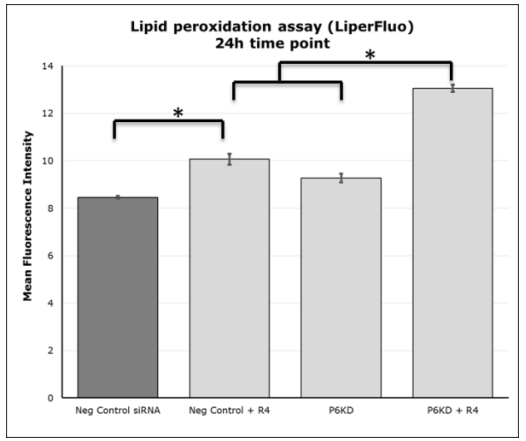
High PRDX6 value correlated with poor survival in lung cancer patients



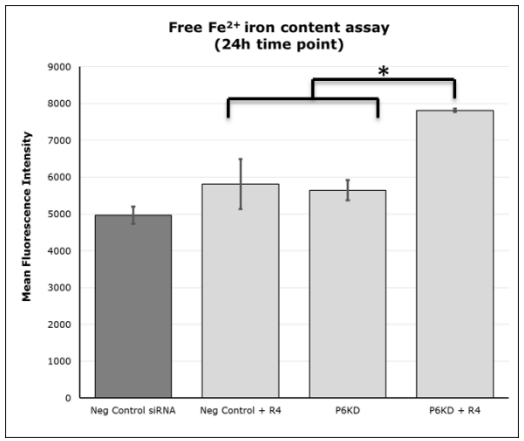
Knockdown of PRDX6 rendered A549 lung cancer cells radio-sensitive

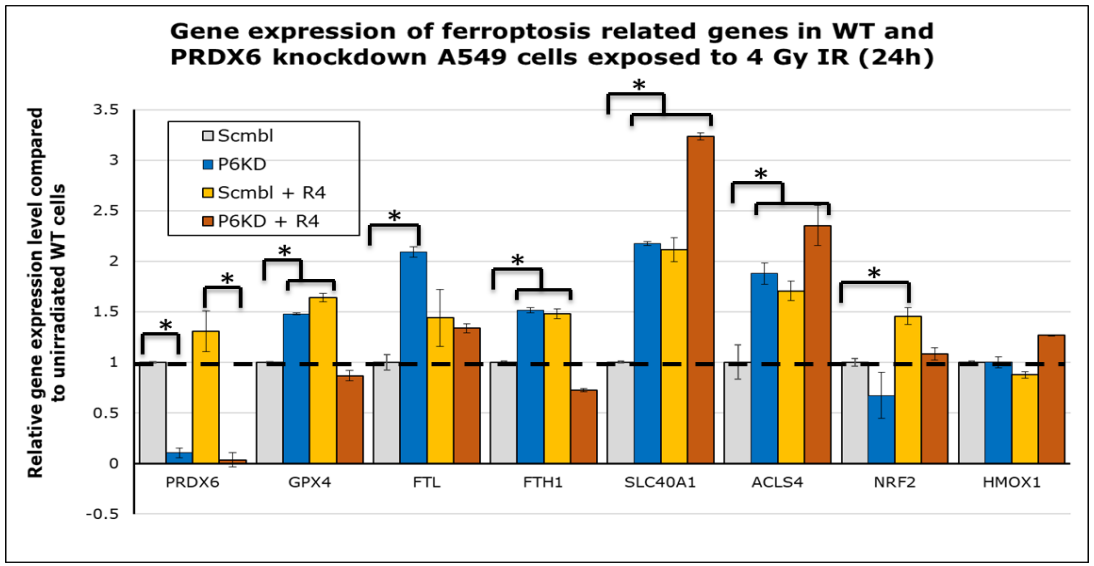


Knockdown of PRDX6 enhanced radiation induced lipid peroxidation



Knockdown of PRDX6 increased free Fe^{2+} pool inside the cell on co-treatment with radiation





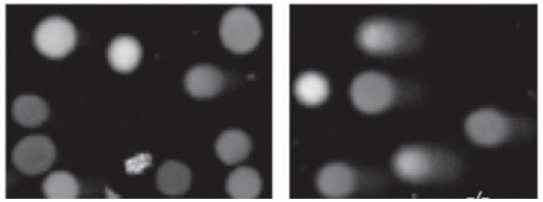
Ferroptosis related genes were highly upregulated on co-treatment of radiation and PRDX6 knockdown.

Take home message: PRDX6 plays pivotal role in preventing ionizing radiation induced ferroptosis, and PRDX6 can be a potential target for radio-sensitization using small mole based approach

3.5 Understanding the role of PSIP1- an epigenetic factor in R-loop homeostasis and maintaining genomic integrity

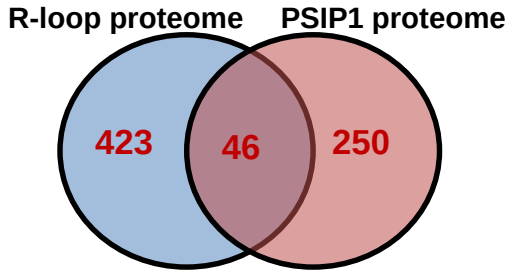
PSIP1 depletion leads to increased DNA damage

comet assay

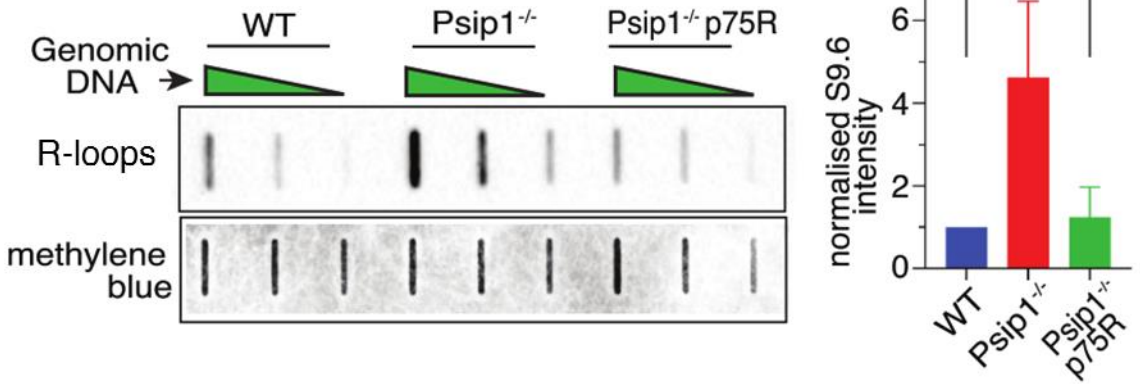


PSIP1 proteome overlaps with R-loop proteome

SILAC-IP-MS

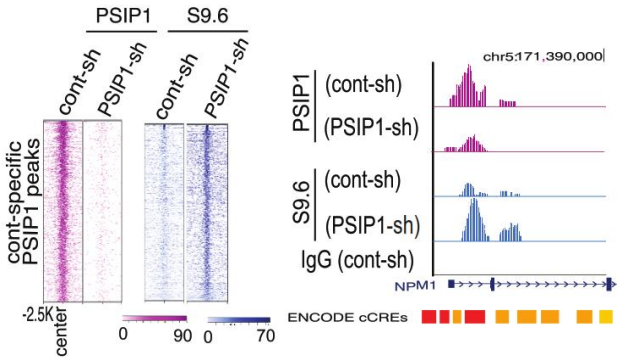


PSIP1 depletion leads to accumulation of R-loops



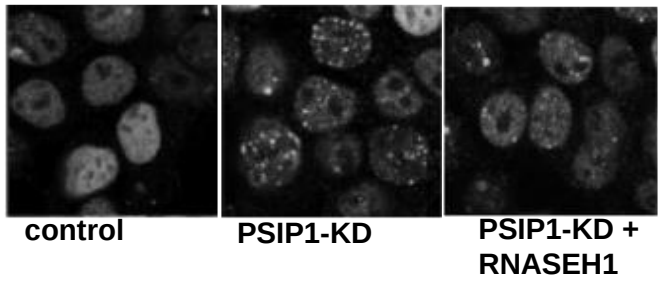
Genome wide accumulation of R-loops linked with PSIP1 binding

CUT&Tag-seq



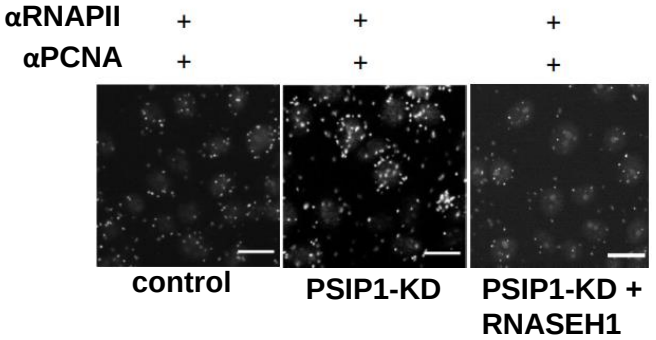
PSIP1 depletion mediated R-loop accumulation causes DNA damage

immunofluorescence



R-loop accumulation causes transcription replication conflicts

Proximity ligation assay



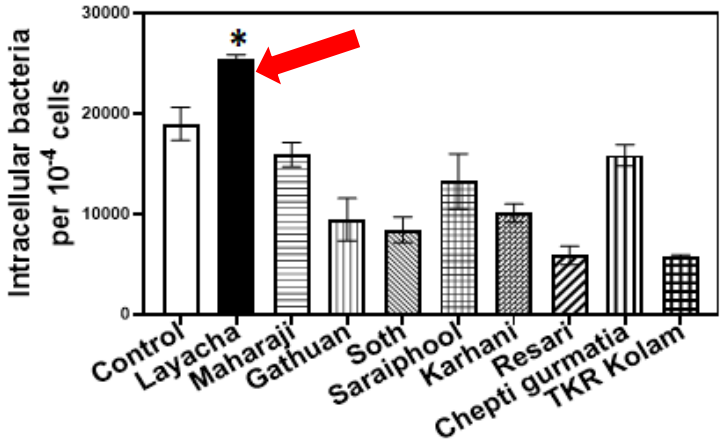
Jayakumar et al. Nature Communications 2024, 15:361

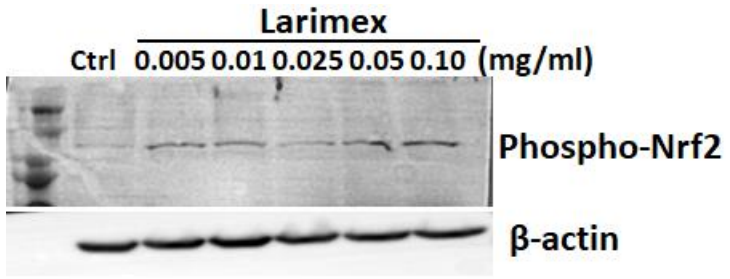
Take home message: PSIP1 binds to unscheduled R-loops formed during transcription and helps in resolving them thereby avoiding transcription replication conflict and DNA damage in the cells.

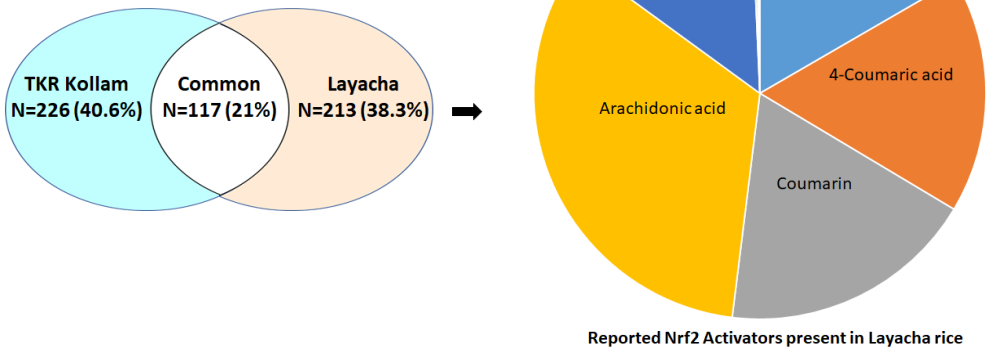
4.1 Translation of medicinal property of rice into immunity booster products

Boosts Immunity Pleasant Aroma Suppresses Inflammation

Layacha Rice Improves Immune Responses via Nrf2 Activation







Reported Nrf2 Activators present in Layacha rice

- Our studies showed that Layacha rice
  - Improves innate and adaptive immunity in healthy mice via activation of Nrf2.
  - Improves recovery from radiation induced immune suppression in mice.
  - Exhibits anti-cancer effects against human lung cancer and breast cancer cell lines in vitro.

Layacha rice Products

Sanjeevani Rice Bar

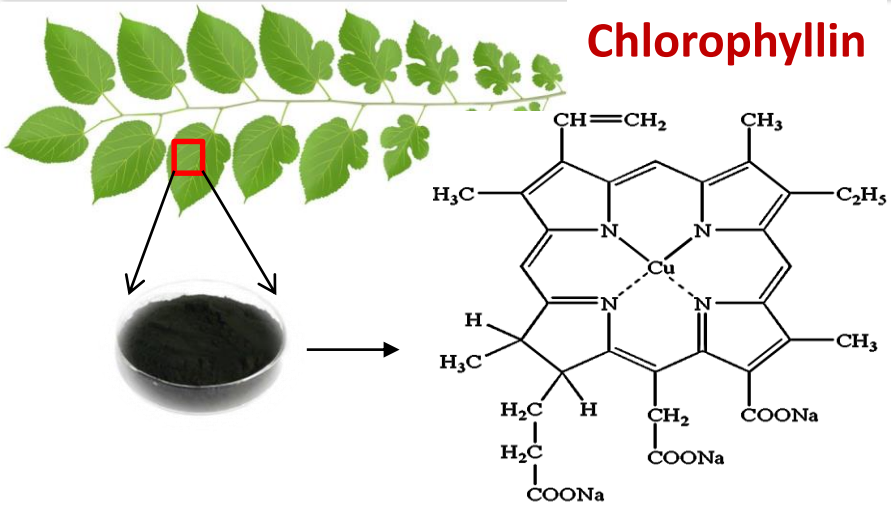
Sanjeevani Instant

Sanjeevani Madhu Kalka

John et al, Food Bioscience, 2023

Take home message: Our medicinal rice (Sanjeevani rice) research translated in to three different products names for boosting immunity.

4.2 AKTOCYTE: Translation of basic research to clinics



- ✓ Water soluble derivative of chlorophyll
- ✓ Color additive in foods, drugs, cosmetics and as a dietary supplement.
- ✓ Antioxidant
- ✓ Protects Radiation induced DNA damage and membrane oxidation
- ✓ Reduces body odor in geriatric patients.
- ✓ Accelerant for wound healing.

https://pib.gov.in/PressReleasePage.aspx?PRID=1985981

Department of Atomic Energy

Azadi Ka Amrit Mahotsav

G20 भारत 2023 INDIA

Breakthrough Nutraceutical 'AKTOCYTE' by the Department of Atomic Energy Set to Transform Cancer Care

Posted On: 13 DEC 2023 6:43PM by PIB Mumbai

Mumbai, 13 December 2023

In a breakthrough towards enhancing the quality of life for cancer patients undergoing radiotherapy, scientists from Department of Atomic Energy and M/s. IDRS Labs Pvt. Ltd. Bengaluru have joined hands to develop AKTOCYTE tablets. Experts from Bhabha Atomic Research Centre, Mumbai; Tata Memorial Hospital, Mumbai; Advanced Centre for Training Research and Education in Cancer, Navi Mumbai collaborated with the IDRS Labs with a primary aim of minimizing the side effects of radiotherapy.

The AKTOCYTE tablets have shown remarkable results, particularly in pelvic cancer patients suffering from radiotherapy-induced Cystitis (Blood in urine). Patients treated with AKTOCYTE tablets demonstrated an extraordinary recovery, eliminating the need for surgical removal of the urinary bladder. The tablets, designed as an adjuvant to cancer radiotherapy, regenerative nutraceutical, immunomodulator, and antioxidant, mark a significant advancement in cancer care.

AKTOCYTE has received approval from the Food Safety and Standards Authority of India (FSSAI), operating under the Ministry of Health & Family Welfare, Government of India
professionals and pati

Remarkable Recovery i
showcasing significan

Versatile Applicatio
nutraceutical, an imm

Regulatory Approv
patient's confidence i

fssai

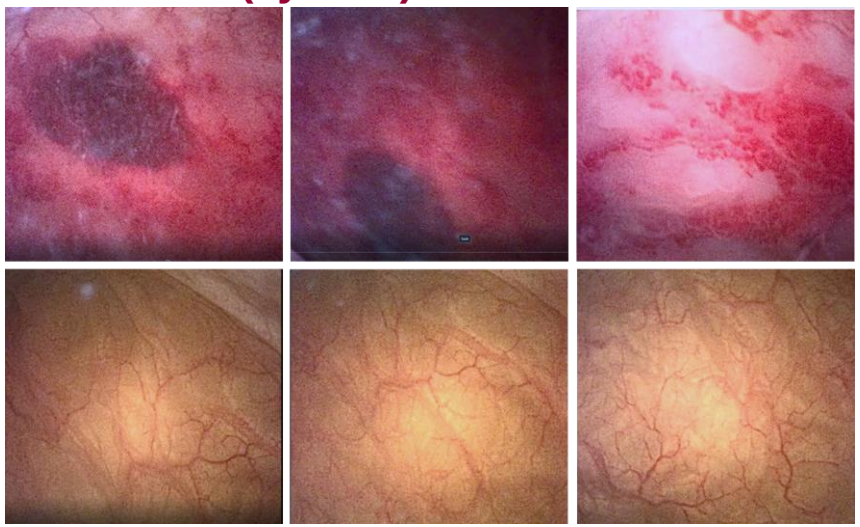
Form C
Government of India
Food Safety and Standards Authority of India
License under FSS Act, 2006

सत्यमेव जयते

अनुज्ञप्ति संख्या / License Number: **11223302000099**

1.	Name & Registered Office address of Licensee / अनुज्ञप्तिधारी के पंजीकृत कार्यालय का नाम और पता:	IDRS Labs Private Limited No.235-H, Phase 3, Bommasandra Industrial Area, Hosur Road,, Bangalore Urban, Karnataka-560099
2.	Address of Authorized Premises / प्राधिकृत परिसरो का पता:	No.235-H, Phase3, Bommasandra Industrial Area, Hosur Road,, Anekal, Bangalore Urban, Karnataka-560099
3.	Kind of Business / कारोबार का प्रकार:	Relabeller - Food or Health Supplements and Nutraceuticals etc. Trade/Retail - Distributor Trade/Retail - Wholesaler

AKTOCYTE Treated Radiotherapy Induced Urinary Bladder Toxicity (cystitis) in Pelvic Cancer Patients



After Radiotherapy Before AKTOCYTE Administration

After AKTOCYTE Administration

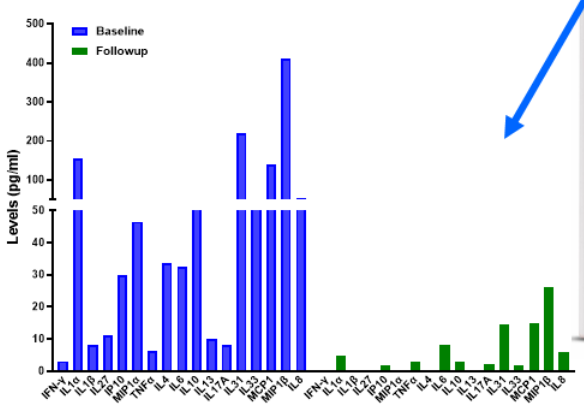
Products

AKTOCYTE 100 mg Tablet

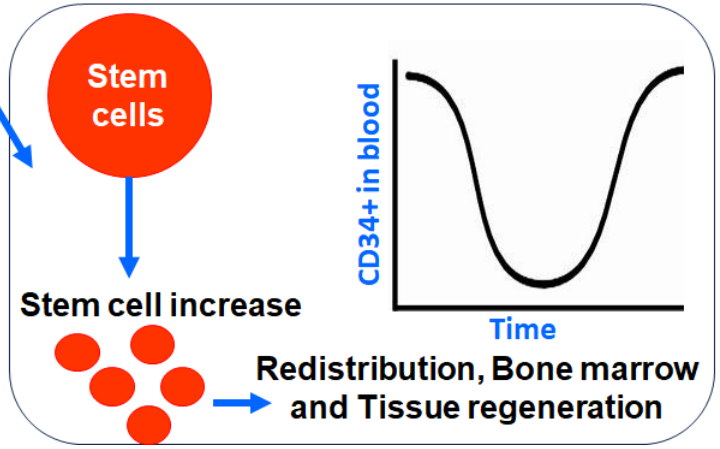
AKTOCYTE 500mg Tablet

AKTOCYTE 750mg Tablet

AKTOCYTE reduces inflammatory cytokines in cancer radiotherapy patients



AKTOCYTE enhances Stem Cell Redistribution and Tissue Regeneration



Take home message: AKTOCYTE lead to Stem cell mediated regeneration, tissue protection, suppression of chronic inflammation, chemoprevention and reduction in cell death.