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Lutein is a major xanthophyll carotenoid present in green leafy vegetables. It is known to selectively accumulate in the macula of the human retina where it functions as an antioxidant and filters blue light and protect the eyes which will reduce age related macular degeneration (AMD) and cataract. But the possibility of lutein as a cancer preventive agent has not been explored previously. In the present study, lutein was checked for its antioxidant, antimitogenic, anticarcinogenic and antitumour activity as well as its possible mechanism to prevent cancer incidence and progression. It was also evaluated for its hepatoprotective, chemoprotective, radioprotective, gastroprotective as well as anti-inflammatory activity.

Lutein was found to scavenge superoxide radicals, hydroxyl radicals and inhibited in vitro lipid peroxidation. Ferric reducing power of lutein was found to be high when compared to other known antioxidant compounds. Lutein was found to inhibit superoxide generation in macrophages in vivo. Oral administration of lutein for 1 month in mice significantly increased the activity of catalase, superoxide dismutase, glutathione reductase and glutathione in blood and liver while the activity of glutathione peroxidase and glutathione-S-transferase were also found to be increased in the liver tissue.

Lutein was investigated for its antimutagenic activity in vitro by Ames test using Salmonella typhimurium strains TA 98, TA 100, TA 102 and TA 1535. Mutagens used were direct acting mutagens such as sodium azide, nitro-o-phenylenediamine, N-methyl-N’-nitro-N-nitrosoguanidine, tobacco extract and acetamidofluorene which needed microsomal activation. Lutein could significantly inhibit the mutagenicity produced by direct acting mutagens as well as mutagens needing activation by cytochrome P450 enzymes at very low concentration (IC₅₀ <50 µg/plate).

Lutein was checked for its anti carcinogenic activity using different models in experimental animals. Models included hepatocellular carcinoma, sarcoma as well as papilloma. Lutein could significantly inhibit the hepatocellular carcinoma (HCC) induced by nitrosodiethyl amine (NDEA) as seen from the tumor development as well as serum marker enzymes, alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP). Similarly lutein could significantly inhibit the activity of γ-glutamyl transpeptidase (GGT) in the liver which is markedly elevated in response
to the cellular proliferation produced by NDEA. Oral administrations of lutein inhibited the sarcoma development in mice as seen from the delay the onset of sarcoma and increase the survival rate. Lutein also inhibited carcinogenesis at two stages produced by the application of 7, 12 dimethyl benz[a] anthracene (DMBA) followed by croton oil application. Papilloma formation was found to be significantly inhibited by the simultaneous application of lutein on the skin. Cytotoxicity and antitumor potential of lutein was evaluated and 14 µg/ml lutein gives 50% cytotoxicity against DLA cells. Lutein was found to reduce the solid tumor volume in mice compared to the untreated group. Lutein significantly elevated the survival rate of ascites tumor bearing animals.

Initial studies on the mechanism of action of lutein indicated that it could significantly inhibit cytochrome P450 enzymes in vitro and in vivo in rats. Moreover lutein could enhance the detoxifying enzymes glutathione-S-transferase and UDP glucuronyl transferase in vivo. These studies indicated that inhibition of carcinogenesis produced by lutein could be due to a combined action of its antioxidant activity along with inhibition of cytochrome P450 enzymes and increased levels of detoxifying enzymes.

In the present study we have also evaluated the nephroprotective activity of lutein to reduce the cisplatin induced renal damage in mice. Serum urea and creatinine levels in the cisplatin induced mice were significantly elevated compared to normal group and it was reduced by the lutein treatment. The antioxidant enzymes in the kidney such as superoxide dismutase, catalase activities and the level of reduced glutathione were reduced and the level of malondialdehyde was elevated in the control as well as in vehicle treated groups. These enzymes were significantly increased by lutein treatment and the level of malondialdehyde declined significantly in treated groups. WBC count and bone marrow cellularity which were significantly lowered in control groups were also significantly elevated in all lutein treated groups. This study concludes that lutein could effectively protect the kidney of mice treated with cisplatin which was also supported by histopathology of kidney.

Lutein pre-treatment significantly reduced myelosuppression during radiation as evident from increased WBC count, bone marrow cellularity and number of matured monocytes in lutein treated animals when compared to radiation control animals. Activities of superoxide dismutase, catalase, glutathione peroxidase and glutathione in both liver and intestinal mucosa were found to be decreased after irradiation. But these were markedly elevated by lutein administration. Lutein showed significant anticlastogenic activity as seen from decreased number of micronuclei formation and
chromosomal aberrations in lutein pre-treated animals when compared to radiation control. Irradiation also resulted in damage to cellular DNA as evidenced by comet formation where the comet parameters like percentage of DNA in tail, tail length, and tail moment of cells of radiation control animals were found to be increased. But these damages were decreased by lutein pre-treatment.

Other pharmacological activities of lutein were also studied. Lutein exhibited significant anti-inflammatory activity against carrageenan and dextran induced acute paw edema and formalin induced chronic paw edema. Carotenoid lutein was evaluated for antiulcerogenic activity in rats. Ulcer was induced by ethanol and the ulcer index was found to be reduced in lutein-treated groups. Morphological and histopathological examination supported the protection of lutein during alcohol-induced damage in rat stomach. Antioxidant enzymes, such as catalase, super oxide dismutase, glutathione peroxidase as well as glutathione levels, which were found to be reduced in the gastric mucosa of alcohol-treated groups, were found to be elevated after lutein treatment. The mechanism of antiulcer activity may be due to the inhibition of oxidative stress produced by alcohol by lutein administration. These findings suggest the potential therapeutic use of lutein as an effective antiulcer agent. Lutein was also evaluated for its hepatoprotective activity during paracetamol ethanol and carbobon tetrachloride induced liver toxicity. Levels of ALT, AST and ALP which were increased in the serum were found to be significantly reduced by the treatment of lutein in a dose dependent manner indicating that lutein could reduce hepatotoxicity induced by these agents. Serum bilirubin was also significantly low in lutein treated groups compared with control. Increased lipid peroxidation, conjugated diene and hydroperoxides in the liver tissue produced by the administration of paracetamol were found to be reduced in lutein treated groups. The antioxidant enzymes and glutathione levels in liver tissue were found to be increased in lutein treated groups compared with control group during alcohol and CCl₄ induced liver toxicity. Hydroxyproline which is an indicator of fibrosis in liver tissue was high in ethanol treated control group. Hydroxyproline level was decreased by simultaneous lutein administration. Histopathological evidences confirmed the protection offered by lutein from the tissue damage caused by hepatotoxins. Hepatoprotective action of lutein may be due to its ability to scavenge reactive oxygen radicals.

Present study demonstrated that lutein could inhibit chemical carcinogenesis by the inhibition of cytochrome P 450 enzymes as well as it activates Phase 2 enzymes.
Lutein also showed profound chemoprotective, nephroprotective as well as radioprotective activity. This study also looked into other pharmacological actions of lutein such as anti-inflammatory, antiulcer as well as hepatoprotective activities in experimental animals. Results presented in this thesis indicate that lutein which is non-toxic compound can stand as one of the prime compounds in the chemoprevention trials of the future. Its role as an adjuvant in the chemotherapy and radiation therapy needed for future evaluation.

**Key words:** Anticancer, Lutein, Carcinogenesis, Antioxidant, Anti-inflammatory, Nephroprotection, Radioprotection, Chemoprotection, Cytochrome P 450 enzymes, Phase 1 enzymes, Phase 2 enzymes.