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PROTECTION OF MOUSE LIVER FROM GAMMA RAY EXPOSURE: A REVIEW

JAIMALA SHARMA*, RADHA SHARMA AND AARTI MATHUR

Radiation Biology Laboratory, Department of Zoology,
University of Rajasthan, Jaipur-302055, INDIA

ABSTRACT

Gamma radiation induces pathological changes in the mouse liver which are dose dependent. Ionizing radiation at lower doses causes hematopoietic syndrome, at higher dose causes gastrointestinal syndrome and central nervous syndrome. Radiation causes inactivation of certain enzymes, denaturation of proteins, interruption of mitosis, chromosomal aberration etc. The severity of symptoms increased with radiation dose. The liver is the largest gland in the body, it occupies an important place among vital organs. It was considered earlier relatively resistant to gamma radiations. The use of synthetic and chemical agents has limited use due to their toxic nature at therapeutically effective concentration. Phytoextract are reported to contain a large number of bioactive molecules which render protection to most of the vital organs. This article reviews some of the findings in the development of radioprotector with emphasis on prospective medicinal plants and their phytochemical tested in the liver of gamma irradiated mice.

KEYWORDS: Gamma radiation, radioprotector, phytochemical, liver.

JAIMALA SHARMA
Radiation Biology Laboratory, Department of Zoology,
University of Rajasthan, Jaipur-302055, INDIA

INTRODUCTION

Major symptoms of radiation sickness are reduced food and water intake, weight loss, diarrhoea, lethargy, hair loss, disorientation, epilation and necrosis in the tail. Ionizing radiation at lower doses causes hematopoietic syndrome, at higher dose causes gastrointestinal syndrome and central nervous syndrome. Ionizing radiation also causes inactivation of certain enzymes, denaturation of proteins, interruption of mitosis, chromosomal aberration etc in the mouse. The severity of symptoms increases with radiation dose. Liver is the largest gland in the liver and body and it occupies an important place among vital organs. It was considered earlier relatively resistant to gamma radiations but John *et al.*[1] found it moderately sensitive to radiations and to lower doses also. Liver is an organ which suffers from direct and indirect both the types of damage. It mainly contains hepatocytes, blood vessels, bile ducts and reticulo endothelial system. It is a capsular organ. It is responsible for detoxification of toxins produced in the body. Molecular damage in cell is ultimately expanded in the damage of their organelle and membrane function. Irradiation induces necrosis in the liver. All the tissues including reticulo endothelial tissue, hepatic parenchyma, arteries and capsule are affected in the liver after irradiation to high doses of gamma radiation. High doses of irradiation induce histopathological changes in the liver. These include distorted arrangement of hepatic cords, wider and thinner sinusoidal spaces between hepatic cords, degranulation and vacuolation of cytoplasm, crenated and pyknotic nuclei. Activation of lysosomal enzymes, phagocytic activities of Kupffer cells, activities of membrane bound alkaline phosphatases and Lactate dehydrogenases also increase. The basic effect of irradiation on cellular membranes is peroxidation of membrane lipids. Radiolytic products of water including hydroxyl and hydroperoxide radicals can initiate lipid peroxidation in liver[2]. Lipid content of the liver also changes after irradiation. Increase in cholesterol levels was observed after irradiation in liver, plasma and adrenal gland[3]. during the last four decades a large number of chemicals, vitamins and other neutraceuticals, amino acids, minerals and plant products were tested to protect the liver from gamma radiation induced injury. It is well known that liver is responsible for removal of toxic material produced in the body after irradiation, it is essential to protect liver to achieve faster recovery. Significant protection of liver by intake of any of these agents which are without side effects will be a boon to the persons which anyhow suffer from whole body or abdominal exposure to gamma radiations.

RADIOPROTECTION OF LIVER

Cellular and organ physiology of the liver is disturbed after exposure to gamma rays. Some cells degenerate. Mitotic activity is disturbed. Some cells appear giant and many appear with more than one nuclei. According to Montgomery *et al.*[4] low doses of irradiation induces reversible swelling of nuclei in a variety of cells, including Chang liver cells. Necrosis in the liver is the result of hypoxia caused due to hepatic veins partial luminal occlusion in irradiated mouse[5]. Total DNA, RNA and protein contents also decrease after irradiation. Feurgard *et al.*[6] observed that whole body irradiation by 4 Gy caused an increase in the plasma cholesterol and phospholipid levels upto 62% and 37% at day 4 which returned to control values 12 days after irradiation. Nair *et al.*[7] classified different radioprotectors according to their mechanism of action in ten major groups. These are sulphydryl compounds, antioxidants, Angiotensin converting enzyme inhibitors, cytoprotective agents, metalloelements, immunomodulators, lipopolysaccharides and prostaglandins, plant extract and isolated compounds, DNA binding ligands and other compounds (Melatonin, carnosin, tempace and tempol).

Radioprotection by chemicals

Ever since the discovery of radiation protection through several synthetic compounds such as Cysteine[8], 2-Mercapto propionyl glycine[9], WR-2721[10,11], Lipoic acid[12] Deoxyspergulanin[13] etc. were tested to discover their protective action on biological systems. Many of them are sulphur compounds with at least one sulfhydryl group. These are cysteamine, MEA, AET, Glutathione, Serotonin etc.[14,15]. Thiol group (-SH) is generally present in most of the radioprotectors or it becomes active after metabolism. Blocked forms of these compounds like thiosulphate, phosphorothiates and disulphides form free thiols after getting metabolized. The first evidence that sulphur containing chemical compounds have ability to protect against radiation damage was given by Dale[16]. He found that colloidal sulphur and thiourea protect some of the enzymes against inactivation by X-rays. A number of thiol and disulphide compounds are known for their ability to inhibit radiation induced pathology in the liver. Cysteamine protects liver cells against radiation injury[17]. Cellular oedema, enucleated cells, pycnotic nuclei, binucleated and multinucleated cells, degranulated and vacuolated cytoplasm, increased number of Kupffer cells and their hypertrophy, hypereamia and lymphocytic infiltration are also known. Mononuclear phagocytes are attracted to the sites of tissue injury. Flemming and Miller[18] found a decrease in reticulo-endothelial cells. Liver metabolism and enzymatic activities are also damaged by radiations.

Bonfils *et al.*[19] studied action of two radioprotectors Cysteamine and Cystamine on the liver microsomal multi-enzyme hydroxylating system, a key system in drug and biological compounds metabolism. Both the compounds are inactive on NADPH and NADH cytochrome C reductase activities, but slightly denature the cytochrome P_{450} into cytochrome P_{420}. They also inhibit to some extent codeine hydroxylation and totally suppress NADPH-induced lipid peroxidation which occurs during enzymatic functioning. Chirkov *et al.*[20] studied that radioprotectors like Serotonin and Aminoethylisothiouronium (AET) stimulate cyclic AMP-dependent phosphorylation of mouse liver cytosol and nuclear proteins *in vivo*. The activation of cyclic AMP dependent phosphorylation is due to an increase in the intracellular cyclic AMP concentration under the influence of the radioprotectors. Mitznegg[21] assumed that administration of 150mg/kg Cysteamine lead to a transient inhibition of ^{3}H- thymidine incorporation into DNA of liver cells in mice. Cysteamine induced radioprotective effects are mediated by cyclic 3,5-AMP as an intracellular second messenger. They suggested that Cysteamine administration leads to the formation of cyclic 3,5-AMP, which might induce a transient functional suspension of DNA synthesis. At that stage the DNA would be more resistant to ionizing radiation.

The polyhydroxylated fullerene derivative C60(OH)24 protects against ionizingradiation-induced mortality, possibly by enhancing immune function, decreasing oxidative damage and improving mitochondrial function[22]. WR-2721 which is commercially available is a thiophosphate and was reported for the first time by Yuhas and Storer[10] and is the most potent agent at present that is available for clinical use. Symon *et al.*[23] observed that administration of Amifostine (WR-2721) at the rate of 200mg/kg over 15 min before irradiation via the femoral or portal vein effectively protects hepatocytes. A synthetic thiol compound 2-Mercaptopropionylglycine (MPG) is also reported to reduce radiation induce cellular abnormality and accelerated the recovery process in liver of mice after 250-500 and 1000 R of gamma ray exposure. Saini *et al.*[24] observed that MPG given at the dose level of 20mg/kg body weight 15-30 minute before exposure to 1000 R gamma rays imparts protection to mouse liver. Radioprotective action of aminothiols is mediated through their capacity to release reduced Glutathione[25]. Administration of GSH appears to be a useful approach to reduce radiation injury by reducing MDA levels and increasing CAT activities[26].

Maisin[27] summarized chemical radioprotectors tested till then and found that they have high toxicity at the optimum protective doses. Their toxicity limits their clinical use. Hishida *et al.*,[28] observed that glutathione provided protection to rat liver against radiation injury. Glutathione is a tripeptide thiol compound which is synthesized directly from precursor amino acids. It is involved in detoxification mechanism through conjugation reaction. Other functions of GSH may include thiol transfer, destruction of free radicals and metabolism of various exogenous and endogenous compounds. It becomes mandatory for a cell to manage high concentration of intracellular GSH to protect itself from chemical or drug abuse. Disulfiram when given to the mice prior to whole body radiation exposure (4Gy) resulted in a reduction of peroxidation of membrane lipids in mouse liver as well as a decrease in radiation induced damage to cellular DNA[29]. Disulfiram increases the glutathione content and detoxifys phase II enzymes, like glutathione-s-transferase and UDP-glucuronyl transfrease[30]. Caffine is also protective to liver mitochondrial membrane against the toxic component of damage in gamma irradiated cells[31]. Melatonin, N-acetyl-S-methoxytryptamine, is a well known antioxidant that protects DNA, lipids and proteins from free radical damage. Radioprotective potential of Melatonin is assigned to its free radical scavenging activity, stimulation of antioxidant enzymes, inhibition of pro antioxidant enzymes, easy distribution throughout the body and low toxicity levels[32]. Melatonin decreases in TBARS and protein carbonyl contents paralleled with significant elevations of GSH content in the liver[33].

Gencel *et al*.[34] observed that Selenium and Vitamin E supplementation and housing by concrete colemanite was found to offer protection against gamma radiation induced liver damage and oxidative stress in rats. Yanardag *et al* [35] found that intraperitoneal administration of DL-Alpha-tocopherol acetate and Sodium selenate exerted protective effects against radiation induced damage in the liver of rats irradiated with a single dose of 1000cGy Co^{60} gamma radiation. Activity of glutathione reductase, glutathione peroxidase, catalase and NADP-dependent malate (decarboxylating) dehydrogenase (malic enzyme) in liver were decreased one hour after irradiation (0.7Gy) but after pretreatment of β-carotene(15mg/kg b.mass) before irradiation little or no decrease was observed[36]. It is also observed that several micronutrients are known to modify free radical reactions occurring within the cells. Ascorbic acid and α-tocopherol are also known to protect against radiation induced injury in the liver. Mathew *et al*.,[37] examined the antioxidant and radioprotective abilities of Ascorbic acid Monoglucoside (AsAG), a glucoside derivative of ascorbic acid. Ascorbic acid has been reported to have protective effect against radiation induced mortality and cytogenetic damage[38]. The radioprotective effect of ascorbic acid has been ascribed to its interaction with radiation induced free radicals[7]. Administration of 6-Palmitoyl ascorbic acid-2-glucoside (PAsAG) a palmitoyl derivative of ascorbic acid 2- glucoside (80mg/kg b.wt.) one hour prior to whole body gamma radiation (2,4,8 Gy) decreased the MDA levels and helped to maintain the GSH levels in the irradiated animals[39]. According to Ueda *et al*.[40] Ca^{2+} inhibited radiation induced lipid peroxidation in a concentration dependent manner in mouse liver microsomes. Dipyridamole (a vasodilator, is a pyrimido-pyrimidinic derivative) increased survival period of mouse after Co^{60} gamma irradiation and inhibited lipid peroxidation which plays a part in the radiation injury in mouse liver and spleen.

Maurya *et al.*[41] observed that administration of troxerutin (175mg/kg body wt.) 1 hour prior to irradiation decreased lipid peroxidation in the liver. Gandhi and Nair [42] reported that Diethyldithiocarbamate (DDTC) administration before radiation resulted in the inhibition of increase in radiation induced comet parameters, indicating the protection of cellular DNA. Increased level of lipid peroxidation in irradiated animals (7.5Gy) was considerably less in Diltiazem (a calcium channel blocker, DTZ) pretreated animals and pretreatment of DTZ caused a significant increase in glutathione levels in liver in comparison to irradiated animals[43]. Positive effects of Silimarin (100mg/kg P.O. once a day) were manifested at the dose rates of 0.2, 0.6 and 6Gy with increased in mitotic activity and mitigation of chromosomal aberration frequency in the regenerating liver in comparison to non protected irradiated animals[44]. Folic acid administration prevented the radiation induced increase in the hepatic cholesterol and triglycerides in the liver[45]. Administration of Anserine and/or Zinc prior to or after radiation exposure was found to offer protection against gamma radiation induced hepatocellular damage and oxidative stress in rats, probably by exerting a protective effect against hepatocellular necrosis via its free radical scavenging and membrane stabilizing ability[46]. Chemicals have high toxicity and many of them are not absorbed and distributed as per the need. This limits their clinical utility as radioprotectors. The plant and natural products are better options, as they have been used as medicines and food. Therefore, screening of plants and natural products was done for their radioprotective capability.

Radioprotection by herbal formulation

Medicinal plants and polyherbal formulations could prove to be valuable sources of useful radioprotectors as their ratio of effective dose to toxic dose is very high. Liv-52 (a non toxic herbal preparation) found to reduce hepato-toxicity[47,48]. Liv 52 pretreatment elevated the levels of reduced glutathione (GSH), increased the activities of glutathione transferase, GSH peroxidase, GSH reductase, superoxide dismutase, and catalase, and lowered lipid peroxidation (LPx) and the activities of alanine amino transferase and aspartate aminotransferase 30 min after exposure to 7 Gy of γ-radiation. Liv 52 pretreatment also reduced radiation-induced lipid peroxidation and increased GSH concentration 31 days following the exposure[49]. Kumar *et al*[50] observed that the oral administration of Rasayans (tonics) protected mice from radiation induced leucopenia and reduced the formulation of lipid peroxidase in liver as compared to controls. Treatment of mice with Abana, a polyherbal drug, before irradiation caused a significant depletion in lipid peroxidation and significant elevation in GSH concentration in the liver[51].

Radioprotection by isolated active ingredients from medicinal plants

Uma devi *et al*.[52] worked on two flavonoids, Orientin and Vicenin, isolated from the leaves of *Ocimum sanctum* for their radioprotective activity. When injected intraperitoneally before whole body exposure to 11 Gy gamma radiation they provided protection against death from gastrointestinal syndrome. Orientin and Vicenin provided almost equal protection against radiation induced lipid peroxidation in mouse liver[53]. Both the compounds showed a significantly greater free radical inhibiting activity. Inhibition of free radical formulation and free radical scavenging appears to be a likely mechanism of radiation protection by these flavonoids. Tiku *et al*.[54] concluded that Eugenol (4-allyl-1-hydroxy-2-methoxy benzene) is the main constituent of the essential oil obtained from commonly consumed spices such as clove, cinnamon, basil and nutmeg and has ability to provide protection against radiation induced chromosomal damage in *Swiss albino mouse.*

Bhatia *et al*.[55] studied the effect of Gymnemic acid (isolated from the leaves of *Gymnema sylvestre*) against Co^{60} gamma irradiation. It was observed that radiation induced deficit in hepatic GSH and protein levels was significantly cured whereas radiation induced elevation of lipid peroxidation level was markedly averted by Gymnemic acid. The intraperitoneal administration of Genistein (a Soya isoflavone, found naturally in legumes) at 200mg/kg body weight before 24 hrs and 15 min of irradiation (8Gy) increase the acid phosphatase and decreased the alkaline phosphatase in liver of *Swiss albino mice*[56]. Begum *et al*.[57] reported that Apigenin (a common dietary flavone present abundantly in common fruits and vegetables) administration prior irradiation inhibited the decline in the intracellular antioxidant enzymes activities Viz. SOD, CAT, GPx and GSH. The administration of gamma linolenic acid (isolated from the seeds of *Borago officialis*) in the form of commercial drug Neoglandin (daily dose, 150mg/kg P.O.) over 1,3 or 7 days after irradiation reduced the level of lipid peroxidation, normalized the activity of NADPH-oxidase and NADPH reductase and increased the content of cytochromes P-450 and b5 as compared to both irradiated and control animals[58]. Song *et al*.[59] investigated the radioprotective effects of Soybean Isoflavone in irradiated mouse liver. They observed protection at molecular and cellular levels as evidenced by enhanced antioxidant enzyme activities and m-RNA levels and decreased liver peroxidase levels.

Radioprotection by Plant Products

Bhatia and Jain[60] reported that radiation induced changes in lipid peroxidation and glutathione levels in *Swiss albino mouse* were prevented by 15 days consecutive feeding of *S. oleracea*. Soyal *et al* [61] studied that aqueous extract of *Rosemarinus officinalis* leaves at the dose level of 1000mg/kg body weight offered significant protection against radiation induced biochemical alterations in liver. Garlic (*Allium sativum*) prevented rapid increase in hepatic lipids, triglycerides and phospholipids and decrease in free fatty acids induced by radio calcium and the values reached normal values earlier in gallic treated animals[62,63]. *Podophyllum hexandrum* extract has been reported to protect radiation induced oxidative damage in mouse liver mitochondria[64,65]. Gupta *et al*[66] investigated that *Podophyllum hexandrum* protects mitochondria from radiation-induced oxidative stress in a multifaceted manner. *Rubia cordifolia* found to prevent cumene hydroxide induced malondialdehyde formation in the dose and time dependent manner. The effect is accompanied by the maintained reduced glutathione level in the presence of above toxin[67]. Alcoholic extract of *Rubia cordifolia* root possesses significant radioprotective potential and its mechanism of action could be through more than one pathway as it contains several phytomolecules in the extract[68]. Amla (*Phyllanthus emblica*) extract inhibits radiation-induced lipid peroxidation in microsomes and SOD in liver mitochondria[69]. *Hemidesmus indicus* (HI) root extract was found to protect liver microsomal membranes as evident from a reduction in lipid peroxidation values. The extract could also protect DNA from radiation induced strand breaks[70].

Animals irradiated with 6 and 8Gy, total protein content of the liver increased 6hrs after irradiation and it continued to increase up till day 4 and then decreased on day7. This increase was significantly prevented in the animals pretreated with *Centella asitica* extract. Aqueous and Ethanolic both types of extracts of *Centella asiatica* prevented radiation induced histopathological and biochemical changes including damage to the biological macromolecules[71,72,73,74]. Arya and Sharma[75] have also studied the radioprotective effect of a potent ayurvedic medicine (*Tinospora cordifolia*) in lethally irradiated mouse. It was observed that a very small dose (5mg/kg body weight) of *Tinospora cordifolia* aqueous extract protects mouse liver against radiation induced changes in the nucleic acids of mouse liver *in vivo.* Londhe *et al.*[76] isolated flavonoids and ellagitannins from *Phyllanthus amarus* and studied their radioprotective activity using rat liver mitochondria. Both ellagitannins and flavonoids effectively prevented lipid peroxidation and protein oxidation in mitochondria which is due to their effective superoxide scavenging ability.

Aegle marmelos protected against radiation induced lipid peroxidation and elevated GSH concentration in the mouse liver [77]. Pretreatment with *Aegle marmelos* extract (100 mg/kg b.wt.) before irradiation (8Gy) decreased radiation induced changes in Lactate dehydrogenase activity (LDH) and increased acid and alkaline phosphatase activity in liver of mouse[78]. Sunila and Kuttan[79] observed that ethanolic extract of *Piper longum* (Pippali) fruits reduced the elevated levels of glutathione pyruvate transaminase, alkaline phosphatase and lipid peroxidation in the liver and serum of irradiated animals.Treatment with *Adhatoda vasica* (L) Nees leaf ethanolic extract (800mg/kg body weight) before gamma radiation (8Gy) decreased lipid peroxidation and increased GSH levels in liver[80]. Administration of aqueous extract of the fruit of *Terminalia chebula* (80mg/kg body weight) prior to whole body irradiation of mice (4Gy) resulted in a reduction of peroxidation of membrane lipids in the mice liver as well as a decrease in radiation induced damage to DNA[81].

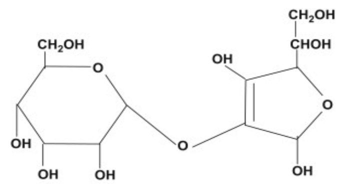
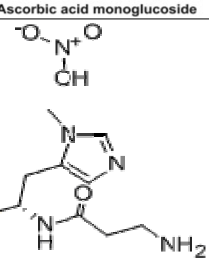
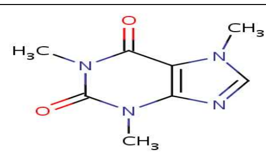
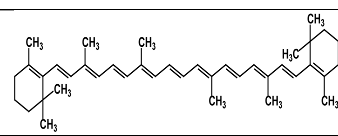
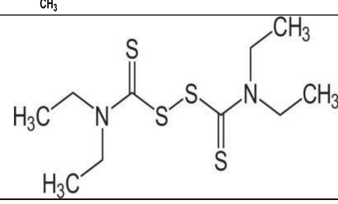
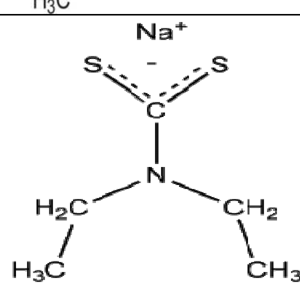
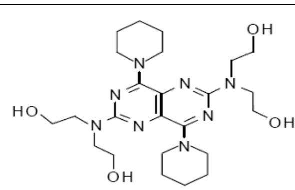
Maharwal *et al.*,[82] detected the radioprotective effects of *Rajgira* extract (800mg/kg body wt.) in the liver of *Swiss albino mice*. Meena[83] studied radioprotective effects of *Acorus calamus* rhizome crude extract, *Moringa olifera* leaf and seed extracts separately against a lethal dose of gamma radiation. She observed that in all the three plant extracts treated groups, most of the pathological changes were reduced by oral treatment of crude extract. According to this report biochemical changes in DNA, RNA, total proteins, ACP, ALP and LDH activity were prevented by plant extract treatment. Krishna and Kumar [84] fed *Amaranthus paniculatus* extract 800mg/kg body wt./day for 15 consecutive days to mice before whole body exposure to radiation. They found that radiation induced changes in the rat liver GSH and lipid peroxidation were significantly prevented.

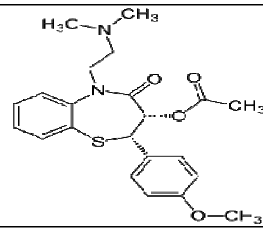
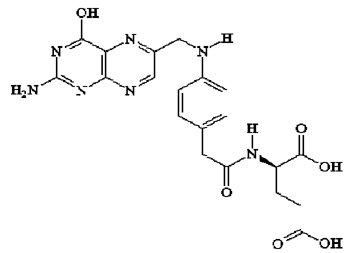
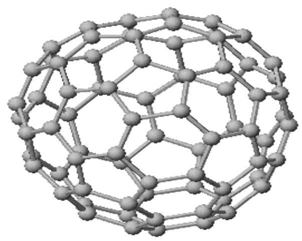
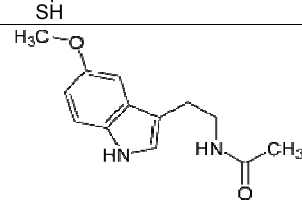
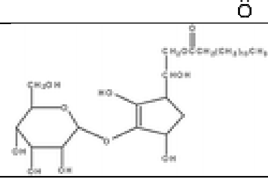
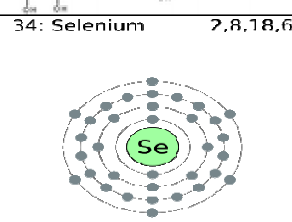
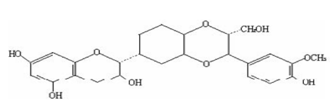
Tripathi and Kamat[85] examined *Andrographis paniculata* for its antioxidant activity using rat liver subcellular organelles as model systems. The oxidative damage was studied against inhibition of membrane peroxidation, protein oxidation and restoration in decrease in Superoxide dismutase (SOD) and Catalase activity and found it very effective. They attributed the antioxidant effect of *Andrographis paniculata* to its high scavenging ability for free radicals. This effect is confirmed *ex vivo* following inhibition in peroxidation, restoration in SOD enzyme, SOD band intensity and protein degradation in *Andrographis paniculata* added liver homogenate.

Pareek[86] observed that histopathological and biochemical lesions produced by irradiation to 8Gy of Co^{60} gamma radiations were prevented by plant extract pretreatment. She observed radioprotective effects of *Picrorhiza kurroa* (rhizome extract), *Acorus calamus* (rhizome extract) and *Ocimum canum* (leaf extract) in the liver of *Swiss albino mouse* at the dose rate of 100mg/kg, 10mg/kg and 100mg/kg body weight respectively. *Asparagus recemosus* is also reported to protect rat liver mitochondria against damage induced by gamma radiation[87]. According to Manu *et al* [88] pretreatment with *Boerhavia diffusa* at the dose rate 20mg/kg body weight reduced the elevated levels of ALP and GPT both in the serum and liver. Maize silk (*Maydis stigma*) ethanol extract (MSE) against gamma radiation (5Gy) has a protective effect in the liver and the up regulation of NF-E2- related factor 2 (Nrf2) could contribute to a defense mechanism. MSE treatment induced the protein expression of Nrf2 and related antioxidase in different degrees[89]. According to Sharma and Kumar [90] deleterious effects of radiation may be reduced by *Myristica fragrans* (MF) seed extract, which significantly reduced LPO level and ACP activity in gamma irradiated mice.

Adaramoye *et al*[91] tested vitamin C and dried fruit extract of *Xylopia aethiopica* against γ-radiation induced liver damage in rat. He found that levels of LPO, GSH, GST, CAT and SOD in the liver were well protected by it. Kaushik *et al*[92] reported that 50% ethanolic extract of *Mentha piperita* (ALM) is effective against radiation induced morbidity and mortality. Jagetia [93] summerised various modes of action and mechanisms of protection of plants and natural products. Most of the plants contain polyphenols which may help in free radical scavenging and elevation of cellular antioxidants. They may upregulate mRNAs of antioxidants enzymes such as catalase, glutathione transferase, glutathione peroxidase, superoxide dismutase and may counteract the radiation induced oxidative stress. Upregulation of DNA repair genes, reduction in lipid peroxidation and elevation in NPSH groups might also contribute. According to Jagetia[93] plant products may also inhibit activation of protein kinase C, Mitogen activated protein kinase, cytochrome P-450, nitric oxide and several other genes responsible for inducing damage after irradiation.

Table 1
Some Chemical Compounds with Radioprotective activity on liver

S No.	Compound	Structure	Dose	Type of Radiation and Dose rate	Reference No.
1.	Amifostine (WR-2721)	NH_2-CH_2-CH_2-CH_2-NH | SPO_3H_2-CH_2-CH_2	200mg/kg	Gamma Radiation; 6Gy	23,10
2.	Ascorbic acid monoglucoside (AsAG)	 Ascorbic acid monoglucoside	100mg/kg	Gamma Radiation; 4Gy	7,37,38
3.	Anserine nitrate with Zinc		0.4mg/kg b.wt. (anserine nitrate) and 10 mg/kg (Zinc)	Gamma Radiation; 5.7Gy	46
4.	Caffine		5µM-4mM	Gamma Radiation; 45-600Gy	31
5.	Cystamine	NH_2-CH_2-Ch_2-S | NH_2-CH_2-CH_2-S	5mg/100g Body weight	Gamma Radiation; 1200R	19
6.	Cysteamine	SH-CH_2-CH_2-NH_2	150mg/kg B.Wt.	Gamma Radiation; 500rads	17,21,19
7.	β-Carotene		15mg/kg b.mass	Gamma Radiation; 0.75Gy	36
8.	Disulfiram		50mg/kg	Gamma Radiation; 4Gy	29,30
9.	Diethyldithiocarbamate		80mg/kg	Gamma Radiation; 4Gy	42
10.	Dipyridamole		2mg/ mouse	Gamma Radiation; 9Gy	40

11.	Diltiazem		100mg/kg	Gamma Radiation; 7.5Gy	43
12.	Folic acid		1.6mg/kg b.wt./day	Gamma Radiation; 7Gy	45
13	Polyhydroxylated fullerene derivative C(60)(OH)(n)		40mg/kg i.p.	Gamma Radiation; 8Gy	22
14.	Glutathione	CONH NH_2-CH-$(CH_2)_2$-CONH-CH COOH CH_2SH CH_2OH		Gamma Radiation; 2,4,6,8Gy	26,28
15.	2-Mercaptopropionyl glycine (MPG)	CH_3-CH-CONH-CH_2-COOH SH	20mg/kg	Gamma Radiation; 250-500 and 1000R	24
16.	Melatonin (N-acetyl-S-Methoxytryplamine)		10mg/kg b.wt.	Gamma Radiation; 4Gy	32,33
17.	6-Palmitoyl ascorbic acid-2-glucoside (PAsAG)		80mg/kg	Gamma Radiation; 2,4,8Gy	39
18.	Selenium		1.5mg/kg	Gamma Radiation; 7Gy	35
19.	Silimarin		70mg/kg b.wt.	Gamma Radiation; 3Gy/6Gy	44

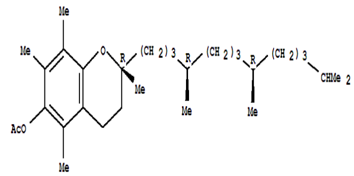
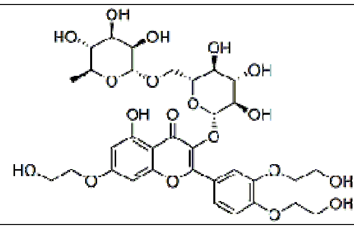
20.	DL-alpha tocopherol acetate		30mg	Gamma Radiation; 1000cGy	35
21.	Troxerutin		175mg/kg b.wt.	Gamma Radiation; 4Gy	41

Table 2
Herbal formulations with radioprotective activity on liver

S.No.	Biological Name	Traditional/Medicinal use	Dose administration	Radiation source and Dose	Reference No.
1.	Abana	Cardioprotective	20mg/kg	Co^{60} Gamma radiation 10Gy	51
2.	Liv-52	Hepatoprotective	500mg/kg b.wt.	Co^{60} Gamma radiation 7 Gy	47,48,49
3.	Rasayans (indigenous preparations made up of herbal drugs)	Increase in memory power, good health, Calmness, and resistance to diseases.	-	Co^{60} Gamma radiation 4Gy	50

Table 3
Isolated active ingredients from medicinal plants with radioprotective activity on liver

S.No.	Isolated active principle	Biological source	Dose administration	Radiation source and Dose	Reference No.
1.	Apigenin	common dietary flavone present abundantly in common fruits and vegetables	15mg/kg b.wt.	Co^{60} Gamma radiation 7Gy	57
2.	Eugenol	main constituent of the essential oil obtained from spices	75, 150, 300mg/kg b.wt.	Co^{60} Gamma radiation 1.5Gy	54
3.	Genistein	found naturally in legumes	200mg/kg	Co^{60} Gamma radiation 8Gy	56
4.	Gymnemic acid	*Gymnema sylvestre*	350mg/kg	Co^{60} Gamma radiation 8Gy	55
5.	Linolenic acid	*Borago officinalis*	150mg/kg	Co^{60} Gamma radiation 1Gy	58
6.	Orientin and Vicenin	*Ocimum sanctum*	50 µg/kg	Co^{60} Gamma radiation 3Gy	52,53

Table 4
Plants with radioprotective activity on liver

S. No.	Biological Source	Common name	Traditional use	Dose	Source and Dose of Radiation	Reference No.
1.	*Acorus calamus* (Araceae)	Sweet Flag	Nervine tonic, hypertensive, tranquilizer, sedative, analgesic, antispasmodic	175mg/kg	Co^{60} Gamma radiation, 8Gy	83, 86
2.	*Adhatoda vasica* (Acanthaceae)	Vasaka	As abortifacient, anti-asthmatic, bronchodilator, antitussive, expectorant, mucolytic	800mg/kg body weight	Co^{60} Gamma radiation; 8Gy	80
3.	*Aegle marmelos* (Rutaceae)	Beal	For diarrhea and dysentery, respiratory disorders, peptic	20mg/kg, 100 mg/kg body weight	Co^{60} Gamma radiation; 6-11Gy	77

			ulcers			
4.	*Allium sativum* (Alliaceae)	Garlic	treatment of arthritis prevent breast cancer, heart diseases, stroke	-	Co^{60} Gamma radiation; 400 rads	62,63
5.	*Amaranthus paniculatus* (Amaranthaceae)	Amaranth, Rajgira	For purifying blood and treating scrofulous sores	800mg/kg body weight	Co^{60} Gamma radiation; 8Gy	82,84
6.	*Boerhavia diffusa* (Nyctaginaceae)	Punarnava	Diuretic, antibacterial, antioxidant and hepatoprotective, antiestrogenic	20mg/kg intra peritoneally	Co^{60} Gamma radiation; 600rads	88
7.	*Centella asitica* (Apiaceae)	Brahmi	Antibiotic, diuretic, blood-purifier, sedative, detoxifier, central nervous system relaxant	100mg/kg	Co^{60} Gamma radiation; 8Gy	71,72,73,74
8.	*Maydis stigma* (Poaceae)	Maize silk	treatment of urinary ailment	75,150,300mg/kg	Co^{60} Gamma radiation; 5Gy	89
9.	*Mentha piperita* (Lamiaceae)	Peppermint	astringent, antiseptic, emetic and stimulant	100mg/kg	Co^{60} Gamma radiation; 6,8,10Gy	92
10.	*Moringa olifera* (Moringaceae)	Drumstick	Circulatory stimulant	125 and 150 mg/kg b.wt.	Co^{60} Gamma radiation; 8Gy	83
11.	*Ocimum canum* (Lamiaceae)	Holy Basil	lowering blood glucose, treatment of fevers, dysentary and tooth problems, parasitic infestations	100mg/kgb.wt.	Co^{60} Gamma radiation; 8Gy	86
12	*Phyllanthus amarus* (Euphorbiaceae)	Bahupatra	anti-viral, hepatoprotective, hypoglycemic	0.1mM concentration	Co^{60} Gamma radiation; 450Gy	76
13.	*Phyllanthus embilica* (Phyllanthaceae)	Amla	treat constipation, reduce fever, benefit the eyes, purify the blood, alleviate asthma,	24µg/ml, 192µg/ml, 60µg/ml	Co^{60} Gamma radiation; 7.4Gy/min	69
14	*Picrorhiza kurroa* (Scrophulariaceae)	Kutki	Treat disorders of the liver and upper respiratory tract, chronic diarrhoea, and scorpion sting.	10mg/kg b.wt.	Co^{60} Gamma radiation; 8Gy	86
15	*Piper longum* (Piperaceae)	Indian long pepper	Aromatic, carminative, gonorrhea, stimulant	5µM - 4mM	Co^{60} Gamma radiation	79
16	*Podophyllum hexandrum* (Berberidaceae)	Indian Podophyllum	Neurological disorders	200mg/kg b.wt.	Co^{60} Gamma radiation; 10Gy	64,65,66
17	*Rosemarinus officinalis* (Lamiaceae)	Rosemary	Regulating blood pressure, antidepressant, diuretic and migraines	1000mg/kg b.wt.	Co^{60} Gamma radiation; 6Gy	61
18	*Rubia cordifolia* (Rubiaceae)	Indian Madder, Manjistha	Treat blood disorders; spread heat, excess heat in the lungs, kidneys, and intestines; reduce swelling	115, 230, 460mg/kg b.wt.	Co^{60} Gamma radiation; 10Gy	67,68
19	*Spinacia oleracea* (Chenopodiaceae)	Spinach	Urinary calculi and leaves are used for lung	1100 mg/kg body wt./day	Co^{60} Gamma radiation; 5Gy	60

			inflammation, febrile affliction and cooling			
20.	*Terminalia chebula* (Combretaceae)	Black myrobalan	Chronic fevers, anaemia and polyuria	80mg/kg	Co^{60} Gamma radiation; 4Gy	81
21.	*Tinospora cordifolia* (Menispermaceae)	Guduchi	Anti-inflammatory, antipyretic, antioxidant, hepatoprotective properties, immuno-potentiating and hypoglycemic	5 mg/kg b.wt.	Co^{60} Gamma radiation; 8Gy	75
22.	*Xylopia aethiopica* (Annonaceae)	African guinea pepper	Dysentery, hyperlipidemia, bronchitis	250mg/kg	Co^{60} Gamma radiation; 5Gy	91

CONCLUSIONS

Protection of liver requires a protector that could work at multiple levels and is able to minimize pathological changes. Several chemicals are there that can protect with good dose reduction factor (DRF) but are toxic to the body. Plants and their products are with low toxicity but are also with low DRF. Plants and their products contain thousands of chemical constituents which may contribute synergistically or antagonistically. Various modes of application like oral, intraperitoneal, intramuscular, subcutaneous or intravenous may affect radioprotection capability of a radioprotector. All the types of radioprotectors have selective distribution rates in various tissues and organs. Body also do have differential acceptability and reaction to the radioprotector. Hepatoprotective formulations of plant medicine may add extra protection to the liver. The search for a good radioprotector is not yet complete. The most appropriate option to protect liver from radiation injury appears to be to develop a proper mixture of various compounds that can provide good DRF with minimum toxicity and side effects.

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