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Radioprotective effects of Silymarin, a natural medical herb, in modulation and prevention of radiation induced damages

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ABSTRACT

Radiotherapy is the most common cancer treatment modality applying ionizing radiation. In majority of the cases, RT necessarily affects on normal tissues around the tumor. Silymarin is one of the most important chemical ingredients of the milk thistle. Silymarin composed of six flavonolignans that Silibinin, with 40-50%, is the most one. In view of the innumerable beneficial effects of silymarin in the management of ROS-mediated diseases, it was felt that silymarin could act as a promising radiation countermeasure agent. In this review paper we introduce Silymarin as herbal radioprotectors.

Keywords: Radioprotective, Silymarin, Modulation, Prevention, Irradiation

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INTRODUCTION

Radiation biology

Radiotherapy (RT) is the most common cancer treatment modality applying ionizing radiation. In majority of the cases, RT necessarily affects on normal tissues around the tumor **[1]**. Exposure of the tissues result in oxidative stress due to water radiolysis and producing ROS (reactive oxygen species) (e.g. $OH^{\bullet}$, $H^{\bullet}$, H2O2, and H_3O^{+}), consuming cellular antioxidant supply and react with DNA, RNA, proteins, cell membrane's lipids, etc **[2]**. that induce cell dysfunction resulting cell death. Radiation damage to the biological systems is happening via two processes: a) direct effect, in which radiation energy is absorbed through target molecules of DNA and or RNA, resulting in molecular injury **[3]**. b) Indirect effect, in which the molecule is chemically altered through reactions with free radicals (FṘ) and ROS produced primarily from the radiolysis of water. The final effect of direct or indirect radiation damage is disturbance of molecular structure and function, leading to change cell metabolism. Lipid per oxidation happens after irradiation or FṘ assault. This introduces to manufacture of short chain fatty acid derivatives, lipid-lipid cross-link and protein-protein as well as lipid-protein cross-link, oxidation of accessible amino acids, protein denaturation, and scission of disulphide bonds in proteins. Consequently, these alterations can be changed membrane fluidity and permeability, which could trigger the release of potent physiological mediators **[4]**. Activity of enzymes related with these membranes may be changed by the disturbance of lipid microenvironment and protein structure. In summary, RT injures normal cells around the tumor and patient may experiences certain symptoms during RT course or later on **[5]**.

Due to the immense applications of unplanned radiation exposure as well as planned RT, radiation protection is an important issue. Scientists have developed treatment strategies in order to reduce the side effects of RT and facilitate the healing of radiation damages in normal tissues **[6]**. Studies in the improvement of radioprotectors (RPs) have focused on screening various biological and chemical compounds. During the last decades, several synthetic and natural agents have been investigated for their potential as a RP. For instance, the radioprotective effects of antioxidants, cytoprotective factors, immune-modulators, vitamins and DNA binding molecules have been evaluated in-vitro and in-vivo worldwide **[7]**. However, the plan was imperiled when synthetic compounds was administrated in RT to reduce the unwanted radiation side effects. Contradictory, available clinical results show that it is difficult to make a clear decision to deny or accept application of synthetic RPs during RT in a conclusive method. While, clinical trials in which the effects of antioxidant vitamins, as an adjacent modality with RT, against the acute opposed side effects were evaluated demonstrate that application of high doses antioxidants, could improve treatment effectively; up to now there is no ideal synthetic RP available that not only does not have cumulative or irreversible toxicity, but also can be easily administered and provides efficient long-term protection against radiation. In contrast, researchers reported various herbal products for FṘ-mediated conditions in human's disease and disorders. Studies to access efficient with low toxicity RPs leads to growing interest on natural compounds. Scientists extracted several effective RPs from the plants; however, improvement of a safe, effective, and nontoxic RP for clinical application is still under investigation. Thus, several procedures have been developed to prevent patients by interfering in the improvement of ionizing radiation injuries. One of the most famous herbal RP is Silybum Marianum, generally known as Milk Thistle. Silymarin is one of the most important chemical ingredients of the milk thistle **[7]**. Silymarin composed of six flavonolignans that Silibinin, with 40-50%, is the most one. In this review paper we introduce Silymarin as herbal RP **[8]**.

Failures of the current RPs and Silymarin characteristics as an herbal RP

The early progression of RPs led to the finding of synthetic thiol ingredients; although they had certain undesirable side effects **[9]**. Hence, researchers planned studies for the novel RPs that not only could be more efficient with less toxicity, but also they could be more acceptable for prescription. In the last decade, a number of synthetic compounds, chelating agents and natural antioxidants have been tested for their capabilities to protect RT-induction injuries. The main focus was, of course, on natural and synthetic agents, such as organometallic compounds and biological response adjusters. Immunomodulators are non-cytokine agents, suggesting as an option to motivate hematopoietic stem cells **[10]**. These could invigorate growth, differentiation and proliferation of hematopoietic' stem cells, hence preventing and repairing radiation induced injuries. In our diet there are different natural ingredients that are including antioxidants, e.g. enzyme, minerals materials and vitamins **[11]**. Decreasing of oxidation injury by natural antioxidants prepares a sort of defense against radiation damage. Furthermore, researchers have been improved more synthetic super oxide dismutase (SOD) mimetic substances, with a metal ion, such as Cu, Fe, Mn and Zn. Most of these drugs had a variety of radiation protection in patients treated by RT. Up to now WR-2721 is the best chemical RP; although it is not prescribe in RT of all cancer patients due to its harmful side effects and extremely high price. Thus, the intention in the RP improvement tilted to RPs in which the fundamental function is FṘ scavenging. The efficiency of RP is stated as dose reduction factor (DRF) that is calculated by plotting the survival fraction 30 days after RT versus the RT dose **[12]**.

In the recent years scientists have worked the radioprotective investigation towards the phytochemicals and plant extracts. Arora et. al. explained status of the present and future prospective of herbal RPs focusing on the potential of natural compounds based RP drug discovery. Man has been used plants for curing diseases from very long time ago and it continue till now. Nowadays, roughly 70% of the world's healthcare is based on application of plants and herbal products. Researches reveal that some of the plants and their extracts have been prosperously used to treat FṘ-mediated sicknesses and disorders for instance cancer, Parkinson, Alzheimer disease, atherosclerosis, arthritis rheumatoid, aging, and inflammatory diseases **[13, 14]**. Thus, it would be reasonable to expect that plants may contain several ingredients that can protect versus ROS-mediated injuries. Many of herbal medicinal plants investigated for their radioprotective efficiency and the results have proven their RP effects **[15]**. The radioprotective efficacy of the herbal extracts consist of a plenty of components including cell proliferation stimulators, anti-inflammatory and antimicrobial agents, immunostimulants, as well as antioxidants, some of which may perform in isolation and in combination with other compounds from the same one. Majority of the researches applying herbal products have focused on investigation of radioprotective efficiency of entire extracts or polyherbal formulas, and in certain cases, fractionated extracts and isolated components. Several researches have been reported to be radioprotective in different model systems. Some of the products including antioxidant have the capability to moderate harmful effects of ionizing radiation in biological systems and bio-molecules that include cruciferous

vegetables (e.g. broccoli and cabbage), Mentha arvensis Linn (mint), Podophyllum hexandrum Linn. (Himalayan May apple), Spirulina platensis, and green tea (polyphenols), bixin (carotenoid), Gingko biloba Linn. extract (flavone glycosides and terpene lactones), and milk thistle (Silymarin) **[16]**. Many of the works utilizing phytochemicals have concentrated on assessment of radioprotective efficiency of total extracts or polyherbal formulas and in a number of cases a part of the extracts and isolated ingredients, for their capability to protect against radiation-induced chromosomal aberrations and micronuclei formation. Although many plants potentially demonstrate having different biological actions that could be related to the appeasement of ionizing radiation-induced injuries in mammalian systems; only a few of them have been evaluated systematically. Some of the herbal products such as vitamins, flavonoids, carotenes, and polyphenols, are known to illustrate antioxidant characteristics **[16]**. Silymarin for its unique properties, e.g. no toxicity, bioactive flavonoid, approved herbal hepatoprotectant; uses widely around the world, as a dietary antioxidant, in order to protect against many of disorders and diseases as well as their treatment.

Many in vitro and in vivo models have been illustrated anti-inflammatory, antioxidant, and anti-carcinogenic characteristics of Silymarin versus the inflammatory responses, oxidative stress, and chemical carcinogen-induced tumor promotion. Furthermore, studies have shown that Silymarin increases aspartate glutamyltranspeptidase (GGT) and -aminotransferase (ALT) and of the plasma. Additionally, Silymarin is used as a topical ointment for treatment of breast cancer worldwide. Moreover, Silymarin is known to adjust proinflammatory pathways via down regulation of cyclooxygenase-2 (COX-2) and 5-lipooxygenase (LOX); therfore, protection of hepatic cytochrome P450 detoxification system engaging hepatic cytochrome P450 enzyme activities **[17]**. Silymarin is able act as a RP for liver by maintaining membrane permeability and protecting hepatic glutathione exhausting. Moreover, Silymarin not only acts as a hepatoprotective factor; but also it has protective effects versus different drugs of nephrotoxic nature. Studies demonstrate that Silibinin protects hepatocytes, since it can block the hepatotoxin receptors available on the membrane of the hepatocyte; thus, it protects cells against death and apoptosis. Additionally, studies show that Silynmarin prevents from hepatotoxins by decreasing the quantity of oxidized Glutathione (GSH) in the liver and intestine; motivate the ribosomal RNA polymerase and protein synthesis resulting in intensified regeneration of hepatocytes **[18]**. In mouse it has been proved that Silymarin could prevent liver versus fumonisin B1 –induced injury and sepsis-induced acute lung and brain damage. The strong hepatoprotective influence of Silymarin versus cytotoxicity and apoptosis happened by Ochratoxin A (OTA), has been illustrated in cultured primary rat hepatocytes **[19]**. The hepatoprotective effects of OTA, in Aflatoxin B1, have also been presented in case of albino male Wistar rats. Studies on broiler chickens reveal that Silymarin derived -phospholipid complex is engaged in decreasing toxicity of aflatoxin B1 (AFB1). Furthermore, potential impacts of Silymarin as used in adjacent by vitamin E versus (OTA)-induced immunotoxic outcomes in White Leghorn cockerels have also been illustrated**[20]**. Moreover, prevention impacts of Silymarin on L-arginine-induced genotoxicity demonstrated in lymphocyte culture in-vitro. Silymarin includes phytochemicals components such as lignans and flavonoids. Studies elucidated that these compounds individually have substantial influence opposite different pathological symptoms as well as having radioprotective characteristics. Silymarin can extend the DNA repairmen time, as it can elevates G2/M phase arrest. Additionally Silymarin down regulates the ethanol-induced oxidative damage and increases the activities of Interleukin-10 (IL10), tumor necrosis factor α, γ -interferon and vascular endothelial growth factor **[21]**. Silymarin is also known to downregulate some anti-apoptotic gene manufactures engaged with reproduction of tumor cells. It has been revealed to possess chemo-preventive characters and protects prostate and skin cancer **[22]**.

Lignans and flavonoids exist in Silymarin particularly have been elucidated having anti-radiation properties. Ordinarily, certain chemical components have been evaluated for RP capability. However, the individual applicability of most of the synthetic agents remained limited, because of their toxicity at an optimum dose. In order to decrease toxicity of a synthetic component, one needs to investigate the ingredients; which could be more efficient and less toxic **[23]**. An extensive field of research interest advances such kind of constituents lies in the application of natural ingredients. Application of natural agents for enhancing one's health has increased in the modern age. Thus, this would be quite logic that the selection of alternative RPs falls on plants and plant extracts. However, application of these extracts or plants, as RPs needs investigation in a scientific manner. When this is done, a natural RP could be more efficient than a chemosynthetic agent. In summary, an effective and suitable RP must physiologically has the following characters: 1) FṘ scavenger; 2) Radiooxidative damage; 3) Facilitate DNA and cellular repair; 4) Immunomodulation; and 5) Facilitate repopulation of damaged and affected organs **[24]**.

Furthermore, "the natural RPs perform their protective effect through certain processes as shown in the following section: 1) FṘs scavenging (antioxidant process); 2) Up regulate mRNAs of antioxidant enzymes such as catalase,

glutathione transferase, glutathione peroxidase, superoxide dismutase; 3) Promoting the recovery of hematopoietic and immune functions; 4) Compaction of DNA; 5) Triggering the DNA repair enzymes; 6) Detoxifying the radiation induced reactive species; 7) Delay of cellular division and inducing hypoxia in the tissues; 8) Reduction in lipid peroxidation and elevation in non-protein sulphhydryl groups; and 9) Inhibit activation of protein kinase, nitrogen activated protein kinase, cytochrome P-450, nitric oxide" **[25]**.

"In order to take in account herbal drug as RPs, one must consider the following items:
1. The exact composition
2. Mechanism of action of each component
3. Possibility of synergistic action between different components
4. Exploration regarding mechanism of action as RPs
5. Elimination of the toxic components from the extract
6. Pharmacokinetics of the different components in the body organs
7. Some physico-chemical parameters like membrane permeability, interaction possibilities with cellular and nucleolar membranes, diffusion coefficient of the components, interaction possibilities with body fluids, biodistribution etc **[26]**.

Nowadays, human exposure to ionizing radiation is increasing due to the improvement in science and technology. The development of radioprotective drugs is important to prevent patients from the side effects of radiotherapy, as well as the public from unwanted irradiation **[27]**.

CONCLUSION

Nuclear and radiological accidents can result in moderate to severe radiation damages and massive mortality. The harmful effect of γ-radiation on biological systems is well known. Plants are inherently gifted with the capability to resistant against the deleterious radiation from the sun. Intensive exposure to ionization radiation by accidental, occupational or therapeutical purpose causes cellular damage mainly by formation of excessive ROS or by FṘs. Recently, interest of radiation protection has tilted to evaluate the radioprotective potential of plants and herbs in the hope that one day it will be possible to find a suitable pharmacological agent(s) that could protect humans against the harmful effects of ionizing radiation. Thus, it can be said that plants are supplied with certain prevention components to protect themselves from the radiation stimulated injuries and oxidative stress. The use of phytochemicals in radioprotection has received much attention in the last decade owing to certain discoveries with special properties as antioxidants. Generally, they are popular because the phytochemicals have less toxicity in human; as many of these are used alternatively in Asian countries for centuries. Furthermore, preclinical studies showed that they are available more easily, inexpensive and good radioprotection. The radioprotective activity of phytochemicals may be mediated via certain mechanisms such as FṘ scavenging, improvement in the antioxidant status, and anti lipidperoxidation potential, conferred due to the presence of variety of phenolic hydroxyl groups attached to the ring structure. Polyphenols especially flavonoid glycosides, isoflavones and their derivatives (quercetin, catechin, myricetin, luteolin, orientin, naringin, apigenin, etc.) have ketone groups conjugated to aromatic rings which are activated by electron donor substituents, thus inhibiting energy transfer, suppressing oxidative stress and stabilizing redox processes in cells. The polyphenols may upregulate mRNAs of antioxidant enzymes such as catalase, glutathione transferase, glutathione peroxidase, and superoxide dismutase, thus counteracting the oxidative stress induced by ionizing radiations. Up-regulation of DNA repair genes and inhibition of genes such as protein kinase C (PKC), mitogen activated protein kinase (MAPK), cytochrome P-450, and nitric oxide may also protect against radiation-induced DNA damage. Herbal extracts efficiently restore the disturbed equilibrium during radiation injury, in a collective and holistic manner owing to their varied phytochemical spectrum. Finally, studies may be designed to bring out lead radioprotector molecules in the market with patient acceptable profile. The multifarious activities exhibited by Silymarin, including hepatoprotective, gastroprotective, antioxidative, renoprotective and anti-inflammatory, and its efficacy in recent clinical trials for treatment of a large number of diseases goes on to prove its safety and efficacy in humans. In view of the innumerable beneficial effects of silymarin in the management of ROS-mediated diseases, it was felt that silymarin could act as a promising radiation countermeasure agent **[28]**.

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