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MELATONIN AND SESAMOL EVALUATION FOR RADIATION INJURY

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ABSTRACT

The radiation, specifically the Infra Red (IR) has high penetration power and can penetrate human body to treat/destroy any abnormal/normal tissue. IR (Gamma radiation, X-ray) has been used medically for diagnostic and therapeutic purposes, e.g., PET-CT, CT scan, MRI and cancer radiotherapy. Gamma radiation is known to cause high amount of damage to biomolecules as protein, fats, carbs and DNA. Most consequences of IRare due to its damaging effects on genetic material of highly dividing cell, leading to growth arrest (cell cycle arrest), apoptosis, necrosis and tissue degeneration. The extension of effects are manifested as mucositis, skin erythema, rashes, hair defoliation, severe pancytopenia, neutropenia, thrombocytopenia, Malabsorption, GI bleeding, immunosuppression, secondary infections, and cancer.Melatoninis a direct free radical scavenger as well as indirect antioxidant. Melatonin shows it's effects by stimulating antioxidant enzymes and suppressing prooxidative enzymes activity. Additionally, Melatonin also has antitumor and radiosensitizing properties. Therapy with Melatonin may prevent tumor progression. Thus, it seems that, in the future, melatonin may improve the therapeutic gain in radiation oncology treatments. Thermal denaturation studies on irradiated calf thymus DNA were also carried out with sesamol and melatonin. Sesamol demonstrated greater radioprotective efficacy in both plasmid DNA and calf thymus DNA. It is proposed that the greater radioprotective efficacy of sesamol could be due to its greater capacity for scavenging of free radicals compared to melatonin. The results will be helpful in understanding the mechanisms and development of sesamol as a radioprotector.

Keywords: *Antioxidant, Antitumor, Free radicals, Melatonin, Radiation,Radioprotective, Sesamol.*

INTRODUCTION

Radiation is the spectrum of energy that travels through space and can be divided into two types: ionizing and non-ionizing. Ionizing radiation (IR) is called so, because it ionizes the medium through which it travels. Ionizing radiation when travels through body it ionizes biomolecules that are present throughout cells and tissues (e.g, X-ray). Like X-rays, radio waves, radar, radiant heat, and visible light (non-ionizing radiation) are forms of electromagnetic radiation. They all have the same velocity, c, but they have different wavelengths and, therefore, different frequencies. However, the ionizing radiation have shorter wavelengths and consequently, a larger photon energy. As a result, X- and -rays can break chemical bonds and produce biologic effects. [1].

The discovery of IR basically, X-ray is credited to German physicist Wilhelm Conrad Rontgen in 1895 and subsequent discoveries in 1896 by Becquerel on natural radioactivity, and Curie in 1898 found radioactive radium have marked golden era of physics. But soon, Edison, Tesla, and Gubbe reported radiation-injury in eyes and skin in 1896 [2]. The iconic image of bone, accidently taken by X-ray, excited medical community and unaware of the threat, rapid developments led to technology (X-ray machine) and rapidly spread from research laboratory to diagnostic laboratory in hospitals and till today is main diagnostic tool for imaging. In 1902, the first case of radiation induced cancer was reported in the hand of a radiologist. Soon, many cases of radiation injury were reported like blistering, skin erythema, ulceration, leukemia [3].

The radiation exposure thus, can be divided into planned/therapeutic exposure (medical and diagnostic) and accidental exposure or intentional exposure to general public and armed forces (nuclear bomb, nuclear accident). Nuclear and radiation accident is defined by the International Atomic Energy Agency (IAEA) as "an event that has led to significant consequences to people, the environment or the facility"[4]. The nuclear accidents have occurred in past as in Hiroshima Nagasaki in 1914 in Japan, later in Chernobyl (1986), Fukushima (2011), and Mayapuri (2010) incident in Delhi. The prime example of a "major nuclear accident" is Chernobyl disaster in 1986 in which a reactor core was damaged and significant amounts of radioactive isotopes were released. Different scenarios such as nuclear explosion, accidents involving nuclear reactor, accidental radioactive spillage, nuclear attack, etc warrants the exposure to civilians, cleanup workers, first responders and armed forces [5,6].

The health effects due to IR may be classified as stochastic effects and deterministic effects. Stochastic effects occur by chance and may occur at any dose of radiation exposure, while deterministic effects occur after a minimum threshold exposure to radiation that may vary from person to person [7].Whole body irradiation (WBI), at significant doses, leads to the onset of acute radiation syndrome (ARS) [8]. ARS is defined by the National Council on Radiation Protectionand measurements as a "range of signs and symptoms that reflect severe damage to specific organ systems and that can lead to death within hrs or up to several months [9]. Exposure to high dose of radiation causes huge adverse effects on health, as anemia, immunosuppression (hematopoietic syndrome), diarrhoea, vomiting, GI bleeding (gastrointestinal

syndrome), and dizziness, disorientation, neurovascular problems (Neurovascular syndrome). All sub-syndrome, i.e, hematopoietic, gastrointestinal and cerebrovascular, are combinedly known as ARS. ARS is main cause of death due to accidental radiation exposures. [10-12].

The clinical manifestation of ARS depends on the absorbed dose. Hematopoietic system is most sensitive, gastrointestinal is affected at higher dose and subsequentlycerebrovascular involvement followed by multi organ dysfunction. The manifestations and pathology associated with ARS involve interactions between radiosensitive organ systems and thus form a complex disease. Higher doses of irradiation may result in combination of all sub-syndromes leading to ARS [13,14]. Thus, medical management of irradiation must address the risk associated with ARS [15-18].

NEED FOR RADIATION COUNTER MEASURES, PAST EFFORTS AND CURRENT CHALLENGES

Medical management of radiation injuries thus is a complex problem and much of the knowledge is based on clinical experiences from radiotherapy patients, actual accidental exposure cases are rare and therefore appropriate guidelines required to be followed. Radiation exposure in unplanned situations (nuclear accidents) are often unavoidable for emergency responders. Understanding of radiobiology and demonstration of chemical compounds that can protect cells if introduced prior to radiation with ample demonstrations in small animal models convinced possibility of developing radiation countermeasure agents. Strategies for development of radioprotectors for radiation emergency operations, radiation workers and even patients undergoing radiotherapy are necessary. Thus, for all such scenarios, controlled or uncontrolled, where radiation exposure is anticipated, using a pharmacological agent (radioprotector) is most prudent strategy, to prevent deleterious effects to human being. Such approach (using radioprotector) would be of large utility in clinical interventions (e.g., diagnostic imaging, radiotherapy), for occupational workers and to a great extent for first responders in radiation accidents/ terror attacks.

At present no radioprotector is approved for planned exposure scenarios. Undertaking military operations in combat zones with radiation environment is another area where radioprotectors are necessary for protection of soldiers health. Radioprotector will also be useful for enhancing therapeutic efficacy of radiotherapy by providing protection to surrounding normal tissues. Radiation countermeasures fall into three broad classes: protectors, mitigators and therapeutics. Radioprotectors are administered before exposure to prevent damage. Radiation mitigators are to be administered after radiation exposure, that is before exposure symptoms manifest, to accelerate recovery or repair. Radiation therapeutics or treatments are given after symptoms manifest to stimulate repair or regeneration [19-21].

Radioprotector development is an important area of radiation countermeasure program. It is envisaged that by the use of safe radioprotector as single prophylactic dose near-term mortality can be reduced and restrict radiation-induced damage that cause long/short-term adverse health effects. Also, it could be useful in ameliorating the harmful effects of the radiotherapy and permitting the safe uses of higher doses of radiation [21,23]. There is an urgent need for radiation countermeasure development that are safe and effective for human use. Until now, only Amifostine (WR2721) is reported to be developed as radioprotector, but it causes severe toxicity in human, and hence, was restricted to head and neck cancer radiotherapy as cytoprotective approved by USFDA [24,25]. However, in last five decades, numerous chemical and biological molecules have been evaluated through screening and assessment in animal models (mostly for radioprotectors) using both in-vitro and in-vivo models [22,26]. To date no radiation countermeasure is available/approved by USFDA for ARS in humans [27,28].

Concerted efforts through Radiation countermeasure program and importantrole played by Armed forces radiobiology research institute few molecules have reached investigational new drug status and ready for further evaluation [29]. Hence, the urgent need for the development of radioprotector, that can prevent or reduce the radiation associated damage, has provoked the research presented here to focus on the development of melatonin and sesamol as radioprotectors. Nevertheless, the described molecules are reported antioxidantcandidates for development as “dual utility” drugs, that is it could be used both as radiation prophylaxis and mitigative/ therapeutics to make radiation therapy safer and/or more effective. Antioxidants offer several advantages over the range of other chemical and biological radioprotective agents. They are readily available in the market with low toxicity over a wide range of dosage; they are potentially attenuating radiation-induced chromosomal aberration, DNA damage, mutagenesis, transformation and the clastogeniety [30-32].

Melatonin (N-acetyl-5-methoxytryptamine) is a potential natural antioxidant and chief secretory product of pineal gland in the brain. It has many important physiological and pharmacological roles discovered and reported [33]. Other than conventional role in circadian rhythm[34], it is found to have roles in immune functions[35-37], cancer therapy [38,39], intractable epilepsy[40], neurodegenerative disorders [41,43] such as Alzheimer's, Parkinson's and Huntington's disease [42], nutritional antioxidant [43-45]and radioprotection [46,47] etc. A plethora of investigation suggests that melatonin pre-treatment protects biological molecules from oxidative injury caused by free-radicals including hydroxyl, peroxyl, lipid-peroxyl radicals, singlet oxygen, hydrogen peroxide, nitric oxide (NO), peroxynitrite anions [48]. Further, melatonin plays vitalrole in scavenging free radicals, destroying toxic reactive oxygen species (ROS) and reactive nitrogen species (RNS) directly (receptor-independent manner) and indirectly (by increasing expression and activity of antioxidative enzymes; SOD,

GST, CAT, GPx) as well as by inhibiting the action of prooxidant enzyme (nitric oxide synthase) [49-53].

Another molecule, sesamol (3, 4-methylenedioxyphenol) is an antioxidant form sesame oil [54,55]. It has reported to decrease radiation-induced micronuclei, dicentric counts, thiobarbituric acid reactive substances (TBARS), and increases GSH, SOD, CAT and GPx [56-58]. Sesamol also prevents radiation induced lethality in WBI mice by inhibiting lymphocytes DNA strand breaks, splenic injury, gastrointestinal injury, lipid peroxidation and increasing antioxidants enzymes levels (GSH, GST, CAT) [57,59]. Sesamoland melatonin have strong antiradical scavenging properties in comparison to other reference antioxidants molecules [60].

RESULT AND DISCUSSION

Radiation exposure caused 7 fold increase in the TUNEL+ cells, while treatment with melatonin was able to reduce it (radiation induced TUNEL +cells) by 2.2 folds while sesamol reduced it by 1.5 fold. The combination treatment (ses+mel) reduced the same by 3.1 fold, on day 6th of radiation treatment. The results of this study demonstrated the beneficial effects of ses+mel on gastrointestinal microenvironment by protecting the epithelial cells. Apoptosis, [324] a major cell death type induced by radiation, initiates following the DNA damage turns out to be irreparable. Intestinal crypt epithelial cells are prone to apoptosis following IR exposure because the intestinal epithelium is one of the fastest proliferating tissues in the body. Ses+mel treatment effectively reduced IR-induced apoptosis as shown by TUNEL and Goblet cell count as well. Apart from apoptosis, the studies have identified immediate DNA damage protection, induced by IR, to be important for cell survival. Mechanistically, ses+mel not only prevent DNA damage but also enhance the total antioxidant capacity and expression of antioxidant enzymes in irradiated mice. Though the efficacy of individual treatment of sesamol and melatonin are in line with the previously reported studies through i.p route [61-66] and oral route for sesamol [67], but, the combination ses+mel provides an added advantage over individual melatoninand sesamol.

CONCLUSION

Analysis of results depicted that botn the Melatonin and Sesamolmarkedly protected from the radiation induced injury.

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