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RESEARCH ARTICLE

EVALUATION OF HERBAL PREPARATION ON RADIATION INDUCED SKIN-INJURY IN HEAD AND NECK CARCINOMA PATIENT AT TERTIARY CARE

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ABSTRACT

Ionising radiations are one of the dominant external factor that exert deleterious effect on human life. The biological effects of the radiation cause damages to DNAs, lipids and proteins. Exposure to high amounts of ionizing radiation causes damage to the hematopoietic, gastrointestinal or central nervous systems. There is a dose dependent effect of radiation on human body. Radiation injury refers to the acute or delayed consequences of exposure of a small part of the body to high doses of ionizing radiation resulting in severe burns acutely whereas long-term injury may affect various organs like eyes resulting in formation of cataract and lung involvement resulting in pneumonia . Damage to the DNA results due to ionizing radiation is the most important factor in cell death. It is followed by altered cell division, depletion of stem cells, organ system dysfunction. The ever increasing use of natural compounds for improving health has tremendously increased in modern times. Hence, there is an urgent need to prevent harmful effects secondary to ionizing radiations. This adverse effect of ionizing radiations on biological systems can be minimized by use of natural radioprotective agents which includes phytochemicals, plants and various herbal preparations of different plant origin.

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INTRODUCTION

There is ever growing research to discover effective and less toxic radioprotective agents. This lead to increasing interest on natural compounds from dietary ingredients and medicinal herbal plants. The crude extracts of these plants constitute several effective radioprotective drugs. They also act as antioxidants and significantly prevent the cellular damage in terms of lipid peroxidation, free radical scavenging activity and protein oxidation. The ability of certain substances to provide protection against the damaging effects of ionizing radiation was first published in 1949 (Dale, 1949). The first report on in vivo radioprotection was reported by Patt *et al* in 1949 (Patt *et al*., 1949), where pre-treatment with a naturally occurring amino acid, cysteine was shown to increase survival of lethally irradiated mice and rats. Later studies showed that aminothiol compounds like cysteine and cysteamine have a structure most favourable for radioprotection and the Sulfhydryl moiety in these compounds are crucial for their radioprotective property (Bacq, 1965). However, these compounds are too toxic at their radioprotective doses and produce serious side effects. The Waller Reed Army Research Institute synthesized and tested over 4,000 compounds and found the most effective compound to be WR-2721 (Amifostine) (Bump *et al*., 1997). It is currently being used in cancer patients to reduce the side effects of radio and chemotherapy. It is limited in use due to its cumulative toxicity on daily administration with radiotherapy, which is manifested as nausea, vomiting, hypotension, allergic reactions, etc (CRC Press, 1997). Thus, there is an urgent need to identify novel, nontoxic and effective compounds to protect humans from radiation induced skin-injury. To address this problem, natural sources especially edible medicinal plants or herbs might provide ideal solution as these are regarded as non-toxic even at higher concentrations. In the view of low cost, easy accessibility and less toxic effects, there is a growing interest on ethno medicines for treating radiation induced injury. Looking into the deleterious effects of radiation, it results in the formation of reactive species i.e reactive oxygen species (ROS), reactive nitrogen species (RNS) and also the generation of free radicals.

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Free radicals can be defined as atoms having an unpaired electron. Because of the presence of unpaired electron, free radicals are highly reactive and are capable of altering all biological molecules including lipids, DNA, and proteins ??? (Sonntang, 1987). Reactive species include hydrated electron, hydrogen radical, hydroxyl radical, hydrogen peroxide, peroxyl radical, O2-.-, singlet oxygen etc resulting from radiolysis of aqueous solutions. Hence the most oxidizing species formed in biological systems during exposure to radiation are O2 and hydroxyl radical. These two ROS along with other reactive species are capable of including severe and undesirable alterations in many biological molecules. The health effects resulting from exposure to ionizing radiation are two categories: stochastic (Probalistic) and deterministic. The stochastic health effect may take several years to develop after radiation exposure, while deterministic effects like cataract induction, hematologic deficiencies, erythema, skin injury and infertility occurs at high doses of radiation. Exposure to high amount of ionizing radiation can also results in damage to the hematopoietic, gastrointestinal, reproductive and central nervous systems. Thus there is always an impending need for a good radioprotective agent, preferably of herbal origin. Several chemical compounds and their analogues have been screened for their radio protective ability.

These synthetic compoundsshows toxicity at their optimum protective dose. To reduce the toxic effects of synthetic compounds, there is a need to explore the new compounds, which could be less toxic and highly effective at non-toxic dose. An intensive area of research promotes the use of natural compounds. The use of natural compounds for improving one's health has augmented in present time. Therefore, it is quite desirable that the choice of alternative radioprotective agents could be from plants or plant products. But, their use as radioprotective agents needs scientific evaluation and validation. Natural radioprotective agents could be more successful and cheaper than synthetic compounds (Weiss *et al*., 2003). An ideal radioprotective agents should have the following properties like possessing free radical scavenging activity by upregulating mRNAs of antioxidant enzymes such as catalase, glutathione transferase, glutathione peroxidase, superoxide dismutase (Weiss *et al*., 2003; Neta,1988), preventing radio oxidative damage, facilitating DNA and cellular repair, immuno modulatory action, facilitating revival of damaged and affected organs, promoting the recovery of hematopoietic and immune functions (Chiu *et al*., 1998), Compaction of DNA (Venkatachalan, 2005), triggering the DNA repair enzymes (Chiu *et al*., 1998), detoxifying the radiation induced reactive species (Vijaylakshmi?? *et al*., 1998),delay of cellular division and inducing hypoxia in the tissues (Nair *et al*., 2001; Hu *et al*., 2014), reduction in lipid peroxidation and elevation in non-protein sulphydryl groups (Devasagayam *et al*., 1996) and inhibiting activation of protein kinase, nitrogen activated protein kinase, cytochrome P-450, nitric oxide. Various herbal plants used in our study for testing radioactive potential are Aloe vera, Azadirachta indica, Curcumin longa and Ocimum sanctum

Aloe vera Its pharmacological activities includes antiseptic, antibacterial, antiviral and antineoplastic effects (Mukherjee *et al*., 2014; Surjushe *et al*., 2008; Yazdani *et al*., 2006). Aloe vera promote wound healing, heals sunburn by increasing collagen content of the granulation tissue. Aloctin A and B, are the active bioactive components which exhibit anti-inflammatory property due to inhibition of eicosanoids.It prevents dermal ischaemia by reversing the effects of thromboxane synthetase.It act synergistically with nitric oxide. It exhibits oxygen radical scavenging action induced by radiation (Vazquez *et al*., 1996; Klein *et al*., 1998).

Ocimum sanctum: It inhibits radiation-induced lipid peroxidation. It possesses anti-tubercular, antiviral, antifungal and anti-inflammatory properties (Kartikeyan *et al*., 1999, Mondal *et al*., 2009; Baliga *et al*., 2013). Ocimum sanctum promotes recovery and regeneration of haemopoietic progenitor cells in mice bone-marrow. It augments NK cells, T-cells and IL-2 production by its immunostimulatory action. Two flavinoids, Orientin and Vicenin are the radioprotective agents isolated from Ocimum sanctum and it provide protection from Gamma-irradiation in animal model of mice by protecting against bone-marrow damage, as measured by chromosomal aberrations and stem cell survival using the exogenous colony-forming unit spleen assay(Sen, 1993; Khanna *et al*., 2003).

Azadirachta Indica: Neem products have been observed to be antihelmintic, antifungal, antidiabetic, antibacterial, antiviral, contraceptive and sedative properties(Biswas *et al*., 2002; Subapriya *et al*., 2005; Drabu *et al*., 2012; Pandey *et al*., 2014). In-vivo, it enhances macrophage phagocytosis, expression of MHC-II antigen, IgM and IgG (Immunostimulatory property). In-vitro, it stimulates IL-1, IFN-γ, TNF-α production. It exhibit antioxidant action against RNS produced by radiation (Ganguli, 2002; Biswas *et al*., 2002).

Curcuma longa: Curcuma longa rhizome is widely used in Indian cuisine as well as in traditional medicine. Pharmacological activities include anti-inflammatory, anti-HIV, Anti bacterial, antitumour, antioxidant and nematocidal effects (Gupta *et al*., 2012; Panchat charam *et al*., 2006; Cho *et al*., 2013). The active component-diferuloylmethane has been reported to render radioprotective effects. Curcumin inhibits benzopyrene induced skin tumors in swiss mice and selectively inhibits radiation induced signal transduction pathways (Reddy *et al*., 1994; Nagabhushan *et al*., 1992).

Aims and Objective

To evaluate efficacy of Herbal preparation in cancer patients receiving radiotherapy or chemo-radiation in patients of head and neck cancer.

MATERIALS AND METHODS

Inclusion criteria

Sixty patients of Head and neck carcinoma more than 18 years of age of either sex and willing to give informed consent will be included in the study. The local application of the herbal paste over skin will begin from day one of radiotherapy till four weeks after completion of radiotherapy.

Exclusion criteria

Patients known to or allergic to ingredients of Herbal paste will be excluded from the study.

Preparation of herbal paste

A viscous gel-like material will be collected from the incised leaf of Aloe vera plant. Fresh Ocimum sanctum leaves, Azadirachta indica leaves (50 grams each) and Curcuma longa roots (5 gram) will be grounded into a paste with the help of mixer/ginder. This paste will be properly mixed with 100gram of Aloe vera juice.

Study Protocol

60 patients of Head and neck cancer will be divided into two groups of 30 patients each:

Group I- received polyherbal paste containing Aloe vera gel, Ocimum sanctum, Azadirachta indica and Curcuma longa.
Group II – act as a control.

Efficacy will be judged by comparing Group I and Group II-patients on RTOG-grading.

Evaluation of skin toxicity and mucosal reaction is done as per RTOG-criteria.

Grade	Description
0	No change over baseline
1	Follicular, faint or Dull erythema/epilation/dry squamation/decreased sweating
2	Tender or bright edema, patchy moist desquamation/ moderate edema
3	Confluent, moist desquamation, pitting edema
4	Ulceration, Haemorrhage, necrosis

RESULTS

For measuring radiation-induced reactions, Non-parametric test like chi-square test was applied and number of patients in different grades was calculated as per RTOG-criteria.

Table 1. Mucosal Reactions [RTOG]

4TH WEEK- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	02	19	09	0
Drug Group	02	22	06	0

P < 0.01

5TH Week- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	0	12	18	0
Drug Group	0	16	14	0

P = 0.72

6th Week-No of Patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	0	3	21	6
Drug Group	0	8	22	0

P < 0.01

7TH Week- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	0	0	25	5
Drug Group	0	6	24	0

P < 0.01

6TH Month- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	4	22	04	0
Drug Group	08	21	01	0

P = 0.00 ie < 0.01

Table. 2 Skin Reactions [RTOG]

4TH Week- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	0	24	06	0
Drug Group	02	28	02	0

P < 0.01

5TH Week- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	0	18	12	0
Drug Group	0	22	08	0

P < 0.052 [borderline significant]

6TH Week- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	0	08	12	10
Drug Group	0	09	21	0

P< 0.057

7TH Week- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	0	01 [3.3%]	21	08
Drug Group	0	10 [33.3%]	20	0

P < 0.01

6TH Month- No of patients	Grade 0	Grade 1	Grade 2	Grade 3
Control	03	16	10	01
Drug Group	10	18	02	0

P < 0.01

For measuring radiation-induced mucosal reactions, Non-parametric test [chi-square test] was applied and number of patients in different grades was calculated as per RTOG-criteria.

- At 4th week, comparing two groups as a whole, treatment with herbal paste prevented radiation induced mucosal ulceration in group II-patients and was considered to be statistically significant [P<0.01].
- At 6th and 7th week, comparing two groups as a whole, in Group-II patients, herbal treatment was again statistically significant in healing mucosal ulcers and prevented patients going to Grade-III.
- Even at 6th-month, difference between two groups was statistically significant. [P<0.01]
- For measuring radiation induced skin-injury, again chi-square test was applied, since data was qualitative and number of patients going into different grades was assessed by RTOG-criteria.
- At 4th -week, comparing two groups, difference between two groups was statistically significant in preventing skin -reactions. [P<0.01]
- At 5th week, difference between two groups in preventing skin reactions was borderline significant. [P<0.052].
- At 7th –week, difference between two groups was statistically significant and herbal paste treatment prevented patients going into Grade-III of skin reactions.
- At 6th month, again difference between two groups was statistically significant.

DISCUSSION

Present study revealed a marked beneficial effects of herbal gel containing Azadirachta indica, aloe vera, Ocimum sanctum and Curcuma longa on radiation induced skin injury in patients with Head and neck carcinoma. Beneficial effect of herbal preparation may be due to their antioxidant free radical scavenging and immunostimulant properties of ingredients present in these plants. It is well established that exposure to ionizing radiation causes production of reactive oxygen species[ROS] and reactive nitrogen species [RNS] also the generation of free radicals. Free radicals are highly reactive and are capable of altering all biological molecules including lipids, DNA and proteins (Yamini *et al*., 2010). Reactive species include hydroxyl radical [OH], H_2O_2, peroxyl radical [ROO], O_2^{--} and singlet oxygen [$1O_2$]. However, most oxidizing species formed in biological systems during exposure to radiation are O_2 and OH. These two ROS with other reactive species are capable of inducing severe and undesirable changes in many biological molecules (Metller *et al*., 2002). Radiation injury may be acute or delayed type. Exposure of a small part of body to high doses of ionizing radiation results in erythema, skin injury or severe burns (Mettler *et al*., 2002). Damage to the DNA results due to ionizing radiation is the most important factor in cell death. Ionizing radiation also results in damage to the haematopoietic, gastrointestinal, CNS and reproductive systems (Yamini *et al*., 2010).

Major mechanisms responsible for radiation induced damage are related to oxidative stress / damage, production of free radicals and immunomodulation. Therefore, well known antioxidant, free radical scavenging and immunostimulant effects of all the natural plants used in the preparation of herbal gel (Adatirachta indica, Aloe vera, Ocimum sanctum and Curcumin longa] are responsible for radioprotective effects and to promote wound healing in patient undergoing radiotherapy for the treatment of head and neck carcinoma. Aloe vera leaf gel is reported to produce antioxidant (Singh *et al*., 2000) free- radical scavenging, immunostimulant (Pugh *et al*., ultraviolet-B protecting activity (Lee *et al*., 1999), anti-inflammatory (Hormann *et al*., 1994), antiburn, antibacterial, antiallergic properties and acceleration of wound healing (Hormann *et al*., 1994). Thus, all these properties reported in the literature for Aloe vera can well explain the beneficial effect of herbal gel in protecting the skin and mucosa following exposure of radiotherapy.

Azadirachta indica is reported to exert antioxidant, free-radical scavenging, immunomodulatory (Sai *et al*., 1997), anti-inflammatory (Bhargava *et al*., 1970), anti-allergic, antibacterial and wound healing properties (Thaker *et al*., 1986). These properties of A. indica are helpful in preventing radiation induced injuries in patients undergoing radiotherapy treatment for carcinoma of head and neck. Antioxidant effects of Ocimum sanctum leaf extracts have been confirmed by various workers. Gupta *et al*., 2006, demonstrated antioxidant properties of Ocimum sanctum. Increased lipid peroxidase activity reported to be reversed by ocimum sanctum treatment (as observed from reductions in malanoaldehyde levels) and stabilized the rise in superoxide dismutase activity (Ragvendra *et al*., 2009).

Dietary supplementation of Ocimum sanctum leaves (2g/day) has been shown to decrease MDA levels (42.4%) in rabbits. Godwani *et al*., 1988, demonstarted immunostimulant effects of Ocimum sanctumaqueous and methanolic extracts in rats. Radiation protective effects of Ocimum sanctum has also been reported. Ocimum sanctum protects against radiation lethality and bone marrow damage in mouse and has strong radical scavenging activity in-vitro (Ganasoundari *et al*., 1998). Uma Devi *et al*., 1999, reported that pre-treatment with Ocimum sanctum extract checked the radiation induced depletion of GSH and reduced the radiation induced lipid peroxidation in liver of the mouse. Therefore well established antioxidant, free radical scavenging and radioprotective effects of ocimum sanctum are beneficial in protecting against radiation injury.

Antioxidant (Masuda *et al*., 1993), free radical scavenging(Bonte *et al*., 1997) immunomodulatory (Ammon *et al*., 1992) , anti-inflammatory (Ali *et al*., 1995), antihistaminic, anti-allergic and skin protective effects (Bonte *et al*., 1997) of curcuma longa are responsible for preventing skin damage induced by radiotherapy. Therefore, it is clear from available literature for each plant that these possess marked antioxidant, free radical scavenging , immunomodulatory or even radiation protective properties and combination of all these natural products definitely provide synergistic effect, which may be responsible for observed excellent prophylactic as well as interventionary effects of the herbal gel on the skin in patients undergoing radiotherapy for carcinoma of head and neck. Since infection delays the wound healing, strong anti-bacterial and anti-fungal properties reported for A indica, Aloevera, ocimum sanctum and Curcuma longa is certainly helpful in accelerating wound healing by preventing infections. Therefore, antibacterial and antifungal properties of herbal gel is also beneficial.

Conclusion

Herbal paste in our study prevented post-radiation induced mucosal and skin-reactions in patients of head and neck carcinoma. The protective effects persisted for 6 month. Thus herbal paste made in our study exhibited radioprotective potential.

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