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Original Article

Radiation induced oxidative stress and its toxicity in testes of mice and their prevention by *Tinospora cordifolia* extract

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ABSTRACT

Background: Reproductive dysfunctions induced by various environmental toxicants are the prime concern in the today's changing global scenario. Living systems are constantly exposed to ionizing radiation that cause cellular as well as genetic alterations leading to mutations and cell death. To evaluate the deleterious effects of low dose of gamma radiation on testicular tissue and their possible inhibition by *Tinospora cordifolia* root extract (TCE).

Methods: One group of Swiss albino mice was exposed to 2.5 Gy gamma radiation to serve as the irradiated control, while the other group received TCE (75 mg/kg b. wt./day) orally for 5 consecutive days half an hour before irradiation to serve as experimental.

Results: Irradiated animals experienced more severe testicular histopathological lesions and a considerable depletion in different spermatogenic cell counts as compared to that of normal animal. Furthermore, TCE pretreatment effectively prevented radiation-induced alterations in body weight, tissue weight, weight index, tubular diameters and anti oxidative parameter viz. lipid peroxidation, glutathione and catalase activity in testes and restored almost a normal structure of testes.

Conclusion: *T. cordifolia* root extract can be potentially used as an effective radio-protector against radiation induced testicular injuries in mammals.

1. Introduction

Despite the diversity of habitat and cultures around the world, an augment in male infertility has been observed in recent decades and apparently it constitutes an international phenomenon.[1–3] Infertility affects approximately 15% of all couples trying to conceive and male infertility is implicated in almost half of these cases.[4] It has long been suggested that major cause of male infertility may be attributed to oxidative

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stress and the factors that are capable of compromising it by inducing the same in the testicular tissue are ionizing radiation, occupational toxins, altered atmospheric circumstances as well as many infectious conditions, oxygen metabolism, inflammation and life style stressors.[5,6]

In today's changing global scenario, ionizing radiation is considered as most potent cause of oxidative stress mediated by free radical flux which induces severe damage at various hierarchical levels in the living organisms. This flux interferes with oxidation/reduction-based physiological mechanisms of all major cellular components (including water, lipid, proteins, sugars & nucleic acids) existing inside every organ of body system.[7,8] Wide variety of tissue constituting the testicle, together with its importance and accessibility, has made it a favorite site of study among radiobiologists. Therefore, oxidative stress and its role in male infertility have been studied extensively in recent years.

Testis is a highly prolific tissue with fast cellular renewal system along with poor antioxidant defense, and for this reason it becomes an easy target for the radiation-induced free radicals mediated damage. At the level of the testes, oxidative stress is capable of disrupting the steroidgenic capacity of Leydig cells as well as the capacity of the germinal epithelium to differentiate normal spermatozoa which lead to impaired spermatogenesis and infertility through the oxidation of proteins, lipids and DNA of germ cells lineage.[9,10] DNA bases are susceptible to oxidative stress, and per-oxidation of these structures can cause base modification, DNA strand breaks and chromatin cross-linking.[11,12] DNA damage is the crucial event in the radiation-induced reproductive cell death which also may accelerate the process of mutation, germ cell apoptosis, development of persistent testicular atrophy that ultimately results in long-lasting azospermia and infertility.[13]

The mammalian seminiferous epithelium consists of a highly complex yet well-organized cell population, with differentially radiosensitive germ cells.[14] The interstitial cells and Sertoli cells, although intimately associated with the germinal cells, but are reported as radio resistant in nature relatively.[15]

Biological protection of male fertility from radiation hazards is a prime concern since any harmful effect of radiation exposure may pass through generation to generation. The understanding of radiation sensitivity of germ cells and their fortification have paved the way towards development of radio modulatory and radio recovery agent that can be effectively utilized to achieve protection of highly radiosensitive germ cells against the deleterious effects of ionizing radiation.

Research endeavors with synthetic radio-protectors in the past have met with little success primarily due to inherent toxicity at their optimum dose level; hence innovation for an ideal synthetic radio-protector remains elusive till date.[16] Therefore, biological radioprotection has been transformed into a thrust area world wide and path breaking research is being done on radio-protectors of natural origin for diverse applications. The current resurgence of interest in medical and aromatic plants or herbs is a global phenomenon.[17–19]

Herbal drugs offer an alternative to the synthetic compounds and have been considered either non-toxic or less toxic, and this has given impetus to screen for their radio-protective ability.[20,21] Herbal plants and products represent important source of natural antioxidants on account of that have been used in several traditional system of medicine for thousand of years for treating various ailments (including infertility) all over the world.[22] In addition, herbals provide a wonderful platform for the synthesis of new chemical entities and development of novel drugs.

There are over 400 different tribal and other ethnic groups in India. Each tribal group has its own tradition and knowledge about use of natural resources as medicine. *Tinospora cordifolia* (Family: Menispermaceae) finds a special mention for its use in tribal or folk medicine in different parts of the country. In Ayurveda, *T. cordifolia* is mentioned as ''Cure for all problems'' or ''Tridosh shamak'' and used for the treatment of various ailments throughout the centauries.[23] Arial root and stem of the plant are sources of the drug preparation. A number of different active principles constituents including polyphenols (gallic acid, tannins), flanonoids (quercetin), alkaloids (berberine), bitter compound (tinosporin, tinosporic acid and tinosporol), essential oil and a mixture of fatty acids, have been identified as contributing to the observed various medicinal effects.[21,24] Because of all these bioactive components *T. cordifolia* possess several medicinal properties like antioxidant, anti-neoplastic, anti-diabetic, immunomodulator, hepatoprotective, memory booster and longevity promoter etc.[25–27]

In spite of extensive use of TCE in the treatment of various diseases, information related to its beneficial effects on reproductive system and associated functions, special reference to male germ cells, are scarcely or fragmentary. Therefore, the present study was intended to evaluate the modulatory potential of *T. cordifolia* root extract against radiation induced testicular injuries in mammals.

2. Materials & methods

2.1. *Animal care & handling*

The animal care and handling were performed according to the guidelines set by the WHO (World Health Organization, Geneva, Switzerland) and the INSA (Indian National Science Academy, New Delhi, India). Swiss albino mice, 6–8 weeks old weighing 22 ± 2 gm from an inbred colony, were used in the present study. They were maintained under controlled conditions of temperature and light (14 and 10 hr of light and dark, respectively). The animals were provided with standard mice feed (procured from Ashirwad Industries, Chandigarh, India) and water *ad libitum*. Tetracycline water was also given once a fortnight as a preventive measure against infection. Four to six animals were housed in a polypropylene cage containing paddy husk (procured locally) as a bedding throughout the experiment. The Institutional Animal Ethical Committee approved the study.

2.2. *Source of irradiation*

Animals were irradiated by a Co^{60} source in the cobalt therapy unit at Cancer Treatment Center, Department of Radiotherapy, SMS Medical College and Hospital, Jaipur,