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Radiomodulatory effects of *Aloe vera* on hepatic and renal tissues of X-ray irradiated mice

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ABSTRACT

The present study was aimed to explore the protective role of *Aloe vera* gel extract against hepatic and renal damage caused by X-ray exposure to mice. Male balb/c mice were divided into four groups: control, *Aloe vera* gel extract [AV] (50 mg/ kg b.w on alternate days for 30 days), X-ray (2 Gy) and AV + X-ray. X-ray irradiation enhanced the serum levels of liver function indices and chromosomal abnormalities in liver. Kidney function markers were found to be deranged and were accompanied by reduced glomerular filtration rate indicating renal dysfunction. Irradiation caused histopathological and biochemical alterations in both tissues which was associated with enhanced reactive oxygen species (ROS), lipid peroxidation (LPO) levels, lactate dehydrogenase (LDH) activity and enhanced apoptosis as revealed by TUNEL assay and DNA fragmentation. The administration of Aloe vera gel extract to X-ray exposed animals significantly improved their hepatic and renal function parameters which were associated with a reduction in ROS/LPO levels, LDH activity and chromosomal abnormalities as compared to their irradiated counterparts. *In vitro* assays revealed effective radical scavenging ability of *Aloe vera* gel extract, which may be linked to its potential in exhibiting antioxidant effects in *in vivo* conditions. This data suggested that *Aloe vera* may serve to boost the antioxidant system, thus providing protection against hepatic and renal damage caused by X-ray.

1. Introduction

Living beings are chronically exposed to natural as well as artificial sources of radiation such as cosmic rays, radon decay, radioactive wastes, nuclear accidents & tests, nuclear reactors, medical & therapeutic procedures. The widespread application of radiation in medicine and industry is continuously enhancing the risk of radiation health hazards [1]. Considering the imminent health risks due to radiation exposure, there has been growing interest in developing radioprotectors.

Although certain synthetic radioprotectors like amifostine have shown encouraging results but have been limited in use because of their severe side effects [2]. Natural radioprotectors may be better suited since they are less/non-toxic than the synthetic compounds at their optimum protective doses [3].

The medicinal use of *Aloe vera* was recognized in the 1930s with its reports of successful treatment of X-ray and radium burns [4]. *Aloe barbadensis Miller (Aloe vera)* belongs to the family of asphodelaceae (Liliaceae) [5]. *Aloe vera* has been reported to possess a wide range of properties including immunomodulation, anti-inflammation, antifungal and radioprotection [6]. It is a popular medicinal plant which contains many important components such as minerals, vitamins,

Abbrevations: A/G, albumin globulin ratio; ABTS, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid; AV, *Aloe vera*; BHT, butylated hydroxytoluene; BUN, blood urea nitrogen; CAT, catalase; CDNB, 1-chloro-2, 4-dinitrobenzene; cpm/gm, counts per minute per gram; CREAT, creatinine; D-BIL, direct bilirubin; DAB, diaminobenzidine; DAP, dose area product; dGycm^2, deci Gray square centimeter; DPPH, 1,1-diphenyl-2- picrylhydrazyl; DTNB, 5,5′-dithiobis-(2-nitrobenzoic acid); EDTA, ethylene diamine tetra acetic acid; EtBr, ethidium bromide; GFR, glomerular filtration rate; GR, glutathione reductase; GSH, glutathione reduced; GSH-Px, glutathione peroxidase; GSSG, glutathione oxidized; GST, glutathione-S-transferase; Gy, gray; H&E, haematoxylin and eosin; H_2O_2, hydrogen peroxide; IU, international units; LDH, lactate dehydrogenase; LPO, lipid peroxidation; NADH, nicotinamide adenine dinucleotide reduced; NADPH, nicotinamide adenine dinucleotide phosphate reduced; NBT, nitro blue tetrazolium; ROS, reactive oxygen species; SGOT, *serum glutamic oxaloacetic transaminase*; SGPT, serum glutamic pyruvic transaminase; SOD, superoxide dismutase; TAE, tris-acetate-EDTA; T-BIL, total-bilirubin; TUNEL, terminal deoxynucleotidyl transferase mediated dUTP nick end labeling

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carbohydrates, glycoproteins, barbaloin, aloe-emodin, β-sitosterol, acemannan, anthraquinones etc [7]. We have recently demonstrated that administration of *Aloe vera* gel extract to mice conferred protection against testicular damage induced by X-ray irradiation [8]. Several other studies have indicated that *Aloe vera* provided protection against radiation induced intestinal injury, skin reactions, hepatic damage etc. [9–11].

Interaction of ionizing radiation with biological system results in overproduction of reactive oxygen species such as superoxide radical ($O_2\cdot^-$), hydroxyl radical (OH·), hydrogen peroxide (HO2·) etc. which triggers a chain of reactions resulting in production of lipid peroxides and thus ensuing detrimental effects [12]. Exposure to ionizing radiation has been reported to cause damage to haematopoietic, gastro-intestinal, abdominal, central nervous system [13]. However, the detrimental effects of radiation are tissue specific [14]. Rapidly dividing cells are most sensitive to ionizing radiation because of high turnover rate [15].

Liver has been considered as a highly radiosensitive organ and its damage upon radiation exposure could have enormous detrimental effects because it is involved in numerous metabolic functions [16,17]. Kidney has been reported to be moderately radiosensitive and is capable of regenerating after radiation induced cytotoxic injuries [18]. However, some studies have revealed that the kidneys are amongst the most radiosensitive organ of the abdominal system [19]. Irradiation induced alterations in biochemical parameters revealed hepatic and renal dysfunction in mice, suggesting their vulnerability to radiation exposure [20–22].

Considering the previous reports, the present study was designed to evaluate the potential of *Aloe vera* gel extract in offering protection to hepatic and renal tissues of mice against deleterious effects of X-ray irradiation.

2. Materials and methods

2.1. Chemicals

Glutathione oxidized (GSSG), Glutathione reduced (GSH), nicotinamide adenine dinucleotide phosphate reduced (NADPH), thiobarbituric acid (TBA), 5′-5′-dithiobis-2-nitrobenzoic acid (DTNB or Ellman's reagent), 1-chloro-2,4-dinitrobenzene (CDNB), bovine serum albumin (BSA), colchicine, nitroblue tetrazolium (NBT) were purchased from reputed Indian manufacturers (Sisco Research Laboratory Pvt. Ltd., Central Drug House Pvt. Ltd., Himedia Pvt. Ltd.). 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), 1,1-Diphenyl-2-picrylhydrazyl (DPPH), 2′,7′- Dichloro-dihydrofluorescein diacetate (DCFH-DA) and Ethidium bromide (EtBr) were obtained from Sigma chemicals co (St. Louis, MO, USA). Diagnostic kits for serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), bilirubin, albumin, urea and creatinine were obtained from Reckon Diagnostic Pvt. Ltd (ENZOPAK, India). Technetium-99 m diethylene-triamine- pentaacetate (^{99m}Tc-DTPA) was obtained from the Department of Nuclear Medicine (PGIMER, Chandigarh). Other chemicals used were procured from Indian firms and were of highest purity and analytical grade.

2.2. Preparation of aqueous extract of Aloe vera gel

Aqueous extract of *Aloe vera* gel was prepared in our laboratory according to the method described previously [7,8,23]. The phytochemical analysis of this extract indicated the presence of carbohydrates, tannins and anthraquinones [7].

2.3. Determination of antioxidant activity of aqueous Aloe vera gel extract

2.3.1. 2, 2′-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid (ABTS) radical scavenging assay

ABTS radical scavenging activity of aqueous *Aloe vera* gel extract was determined according to the method described previously [24]. ABTS radical cation ($ABTS\cdot^+$) is a blue/green chromophore produced by the reaction between ABTS solution (7 mM) and 2.45 mM ammonium persulphate (APS). The reduction of blue/green coloured $ABTS\cdot^+$ by hydrogen donating antioxidants was measured at 734 nm. $ABTS\cdot^+$ scavenging capacity of extract was compared with that of butylated hydroxytoluene (BHT) and percentage inhibition was calculated according to the formula:

$$\text{ABTS radical scavenging activity (\%)} = [(Ac - As)]/(Ac)] \times 100$$

where, Ac is the absorbance of ABTS radical + ethanol; As is the absorbance of ABTS radical + sample extract/ standard.

2.3.2. 1, 1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay

DPPH radical scavenging capacity of aqueous *Aloe vera* gel extract was determined according to the method described previously [25]. This assay is based on the ability of antioxidants to donate hydrogen atoms to DPPH radical which produces the reduced form of DPPH. The change in color from violet (DPPH radical) to yellow (reduced DPPH) was measured at 517 nm. The DPPH radical scavenging ability of extract was compared with that of BHT and percentage inhibition was calculated according to the formula:

$$\text{DPPH radical scavenging activity (\%)} = [(Ac - As)]/(Ac)] \times 100$$

where, Ac is the absorbance of DPPH radical + ethanol; As is the absorbance of DPPH radical + sample extract/ standard.

2.4. Quantitative analysis of various components of aqueous Aloe vera gel extract

2.4.1. Phenol sulphuric acid assay (Dubois method) for quantification of carbohydrates

The phenol sulphuric acid method detects all classes of carbohydrates, including mono, di, oligo and polysaccharides and therefore determines total carbohydrates in the samples [26]. The treatment with concentrated sulphuric acid causes hydrolysis of glycosidic linkages of carbohydrates forming hydrolysed neutral sugars which, when partially dehydrated form furfural derivatives. The yellow-orange coloured complex developed by condensation of furfural derivatives with phenol was measured at 490 nm. Varying dilutions of glucose from a stock solution (1 mg/ml) were used to obtain a standard curve and carbohydrate concentration was determined from the same.

2.4.2. Determination of total flavonoids

The total flavonoid content of *Aloe vera* gel extract was estimated according to the previously reported Aluminium-chloride ($AlCl_3$) colorimetric assay [27]. In this method, $AlCl_3$ reacts with the C-4 keto groups and either the C-3 or C-5 hydroxyl group of flavonoids forming a complex which has absorbance maxima at 420 nm. The total flavonoid content was determined by using a standard curve of Quercetin (0.1 mg/ ml) and expressed as mg of Quercetin equivalent (mg/g).

2.4.3. Elemental analysis of Aloe vera gel extract

The elemental composition of aqueous *Aloe vera* gel extract was determined using Wavelength Dispersive X-ray fluorescence WD-XRF (Bruker S8 Tiger).

2.5. Whole body X-ray irradiation of animals

Whole body irradiation of mice was carried out by using an X-ray

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