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The potential role of L-carnitine against cardio and haematotoxicity of gamma radiation in male albino rats.

A Thesis

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بسم الله الرحمن الرحيم

(وَقُل رَّبِّ زِدْنِي عِلْما)

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List of Abbreviations

AC	Acyl-carnitine
ADH	Alcohol dehydrogenase
ADP	Adenosindiphosphate
ALC	Esterified L-carnitine
ALDH	Aldehyde dehydrogenase
AR	Aldose reductase
AST	Aspertate amino trasferase
ATP	Adenosin triphosphate
BB	Butyrobetaine
BBD	Butyrobetainedioxygenase
CACT	Carnitine–acylcarnitinetranslocase
CAT	Catalase
Ch	Cholesterol
CoA-SH	Coenzyme A
COT	Carnitineoctanoyltransferase
CPK	Creatine phosphokinase
CPK-MB	Creatine phosphokinase myokard band
CPT	Carnitinepalmitoyltransferase
CPT-1	Carnitinepalmitoyltransferase 1
CPT-1A	Carnitinepalmitoyltransferase 1 (liver)
CPT-1B	Carnitinepalmitoyltransferase 1 (muscle)
CPT-1C	Carnitinepalmitoyltransferase 1 (brain**)**
CPT-2	Carnitinepalmitoyltransferase 2
CrAT	Carnitineacetyltransferase
cTnI	Cardiac troponin I
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
FC	Free carnitine
GPx	Glutathione peroxidase
GSH	Glutathione
GST	Glutathione S-transferase
H&E –	*Hematoxylin and eosin*

List of Abbreviations (Cont.)

HMG-CoA reductase	(3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
H_2O_2	Hydrogen peroxide
Hb	Hemoglobin
Hct %	Hematocrit percentages
HDL	High density lipoprotein
HDL-c	High density lipoprotein cholesterol
HF	Heart failure
HNE	4-Hydroxynonenal
$HO_2^{\bullet}$	Hydroperoxyl
HTML	Hydroxytrimethyllysine
HTN	Hypertension or high blood pressure
IHD	Ischemic heart disease
IMM	Inner mitochondrial membrane
L·	Lipid radical
LC	L- carnitine
LCFAs	Long chain fatty acids
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-c	Low density lipoprotein cholesterol
LOO·	Lipid peroxy radical
LOOH	Lipid hydroperoxide
MCD	Muscular carnitine deficiency
MDA	Malondialdehyde
MI	Myocardial infarction
mtDNA	mitochondrial DNA
NAD^+	Oxidized nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
nDNA	nuclear DNA
$NO^{\bullet}$	Nitric oxide
NOSs	Especially nitric oxide synthases
O_2	Oxygen
$O_2^{\bullet-}$	Superoxide anion

List of Abbreviations (Cont.)

Octn1, Octn2 & Octn3	Organic cation/carnitine transporters
OCTN2	Organic cation/carnitine transporter 2
OFR	Oxygen-free radicals
$OH^{\bullet}$	Hydroxyl
OMM	Outer mitochondrial membrane
ox-LDL	Oxidized low-density lipoprotein
PLP	pyridoxal phosphate (the active form of vitamin B_6)
PLs	Phospholipids
PUFAs	Especially polyunsaturated fatty acids
RBCs	Red blood corpuscles
RIHD	Radiation induced heart disease
RNA	Ribonuclic acid
RNI	Reactive nitrogen intermediate
RNS	Reactive nitrogen species
$RO^{\bullet}$	Alkoxyl
$RO_2^{\bullet}$	Peroxyl
ROI	Reactive oxygen intermediate
$ROO^{\bullet}$	Peroxyl
ROS	Reactive oxygen species
RT	Radiation therapy
SCD	Systemic carnitine deficiency
SOD	Superoxide dismutase
TG	Triglyceride
THP	Trimethyl hydrazinium propionate
TMABA	Trimethyl aminobutyraldehyde
TMABA-DH	Trimethyl aminobutyraldehyde dehydrogenase
TML	Trimethyl lysine
TMLD	Trimethyl lysine dioxygenase
Vit C	Vitamin C
Vit. E	Vitamin E
VPA	Valproate
WBC	White blood cells

Abstract

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The potential role of L-carnitine against cardio and haematotoxicity of gamma radiation in male albino rats.

Key words: cardiotoxicity, haematotoxicity, total antioxidant capacity, oxidative stress, L-carnitine.

The current study was designed to examine the beneficial effect of pre or post-irradiation of oral intake of L-carnitine (300 mg/kg of B. Wt.) in preventing the cardiotoxicity, haematotoxicity, oxidative stress, disturbed lipid profile and hypoglycemia caused by exposure to a single dose of 6Gy gamma radiation in male albino rats. The rats were arranged equally into 5 groups (10 rats in each group): control, L-carnitine, irradiated, irradiated group treated with L-carnitine and irradiated group pretreated with L-carnitine. After 21 days of irradiation CK, CK-MB, AST, LDH, troponin-I, total antioxidant, MDA, cholesterol, triglyceride, HDL-c, LDL-c and glucose were evaluated from serum and blood elements were assumed from blood in addition to histological examination of the heart.

Whole body γ-irradiation led to a significant elevation in the levels of cardiac enzymes (CK, CK-MB, AST and troponin I), MDA, cholesterol, TG, LDL-c and reticulocytic count and a significant decrease in serum level of LDH enzyme, HDL-c, glucose and blood element (WBCs, platelets, RBCs, Hb and Hct) as compared to their corresponding normal control group with remarkable changes in the heart histology.

Administration of L-carnitine to rats before and after γ-irradiation led to improvement of the studied parameters that were altered due to radiation exposure. The cardiac enzymes, MDA, cholesterol, TG, LDL-c showed more significant decrease in the irradiated group treated with L-carnitine compared to the pre-irradiated one while, Hb, WBCs and platelets experienced significant increase in the second group compared to the first leading to the suggestion that combination of pre and post intake of L-carnitine in irradiated rats is recommended to protect radio-resistant and radio sensitive organs as well.

Introduction

Radiotherapy is frequently used as a part of cancer treatment to achieve tumor control. Over the last half century, radiation therapy (RT) has evolved to become one of the cornerstones of treatment for various types of cancers. It is estimated that more than 50% of patients with cancer are treated with radiotherapy (**Yusuf *et al*., 2011)**.

Although radiotherapy treatment has been widely used as an effective tool to kill tumor cells, it might produce harmful effects to surrounding healthy tissues **(Sezen *et al*., 2008 and Ostrau *et al*., 2009).** It is well known that ionizing radiations induce oxidative stress on target tissues, mainly through the generation of reactive oxygen species (ROS) resulting in imbalance of the pro-oxidant antioxidant equilibrium in the cells. It also attacks diverse cellular macromolecules such as DNA, lipids and proteins, eventually inducing cell death **(Boerma and Hauer- Jensen, 2011).**

The heart is a vital organ and generates intense oxidative imbalances because of its intense activity. Moreover, the heart presents a less potent antioxidant system when compared to other body tissues (**de Freitas *et al*., 2013)**.

During radiotherapy (RT) of mediastinal tumours (lymphomas, breast cancer, and lung cancer), frequently a part of the heart is included in the treatment field and may receive significant doses of ionizing radiation **(Hilbers *et al*., 2012).** Clinical reports indicated that a considerable number of patients who receive this therapy develop cardiovascular complications.