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Radioprotective Role of Some Bacteria Belonging to Actinomycetales against Gamma Irradiation-Induced Oxidative Stress in Male Albino Rats

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ABSTRACT

Background: radiation protection concepts and philosophy have been evolving over the past several decades. The inadvertent exposure of human from various source of radiation causes ionization of molecules, setting off potentially damaging reactions via free radicals production. Development of radioprotectants and mitigators is the therapeutic approach to ameliorate the negative health impact of radiation exposure. The majority of substances with biological activity used in medicine are produced by actinomycetes and fungi. **Aim:** the aim of the present study is to evaluate the radioprotective role of the antimicrobial active metabolite of *Streptomyces atrovirens* Rahman as antioxidant against gamma irradiation that induced some biochemical alterations in rats.

Material and Methods: animals were pretreated with antimicrobial active metabolite of *Streptomyces atrovirens Ab1* using suitable stomach tube for two weeks prior to radiation exposure. The levels of malondialdhyde (MDA), glutathione content (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutamic oxaloacetic transaminase (ALT), glutamic aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) activities, also total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL- C) were estimated. **Results:** the results revealed that exposure to ionizing radiation resulted in significant elevation in the levels of MDA content, ALT, AST, ALP and GGT activities and concentration of TC, TG and LDL-C, meanwhile, showed significant depletion in GSH content and SOD, CAT and GPx activities and HDL-C concentration. **Conclusion:** it could be concluded that, the administration of the antimicrobial active metabolite of *Streptomyces atrovirens Ab1* pre-whole body gamma irradiation resulted in sufficient amelioration against radiation effects on the biochemical aspects examined in the present study.

Key words: *Ionizing Radiation, Actinomycetes, Streptomyces and Antioxidants.*

INTRODUCTION

Free radicals are believed to play a role in more than sixty different health conditions, including the ageing process, cancer, radiation damage, atherosclerosis[1]. Antioxidants work in several ways by reducing the energy of the free radicals, stop the free radical from forming in the first place, or interrupt an oxidizing chain reaction to minimize the damage of free radicals[2].

The development of radioprotective agents has been the subject of intense research in view of their potential for use within a radiation environment; however, no ideal, safe synthetic radioprotectors are available to date, so the search for alternative sources has been ongoing for several decades[3,4].

People are exposed to natural radiation sources as well as human-made sources on a daily basis. Natural radiations come from many sources due to naturally occurring radioactive materials in soil, water, air and cosmic rays. Human-made sources range from nuclear power generation to medical uses of radiation for diagnosis or treatment[5].

Radiation is known to produce various reactive oxygen species (ROS) in biological systems such as superoxide, hydrogen peroxide and hydroxyl radical reaction[6]. The range of antioxidant defense available within the cell and in the extracellular fluid should be adequate to protect oxidative damage[7].

Radiation therapy (RT) is considered to be one of the most popular and important tools to care cancer[8]. The radio-sensitivity of normal tissues particularly organs away from the tumor sites are suggested to limit the therapeutic gain[9].

Detrimental effect of ionizing radiation occurs mainly due to free radicals generated through the decomposition of cellular water[10]. However, organisms have protective systems against free radical reaction, for example, endogenous antioxidants and antioxidative systems.

Exposure to radiation can be classified into three types based on exposure situation; planned exposure, resulted from intended introduction and operation of radiation

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sources with specific industrial, researches or medical purposes[11]. Existing exposure, is the exposure to radiation already exists, such as exposure to Radon and natural background radiation and emergency exposure, resulted from an expected events such nuclear accidents, malicious attacks and require prompt response[12].

Exposure can also be classified based on dose /dose rate into acute exposure in which energy from radiation is absorbed over a few hours or days and leads to acute effects which occur within several hours to months after exposure and Chronic exposure in which energy is absorbed over longer period and leads to Chronic effects which occur several years after exposure[13].

Development of radioprotectants and mitigators is the therapeutic approach to ameliorate the negative health impact of radiation exposure.

Radioprotectants are compounds that are designed to reduce the damage in normal tissues by radiation and to be effective must be present before or at the time of radiation while mitigators may be used to minimize toxicity when applied even after radiation has been delivered[14].

Radioprotective treatments that have been proposed over the past decades include thiol compounds, growth factors, cytokines[15] and natural antioxidants[16].

Finding effective and safe radioprotective agent to ameliorate radiation-induced damage is still a challenge and lead to increasing interest on agents from natural sources. Various strategies have been developed to protect the biological systems by interfering the development of the radiation-induced damage[17].

The majority of substances with biological activity used in medicine are produced by actinomycetes and fungi[18].

Actinomycetes account for approximately 7000 of the metabolites reported in the dictionary of natural products[19]. They are responsible for the production of about half of discovered active secondary metabolites and mainly by Streptomyces species[20].

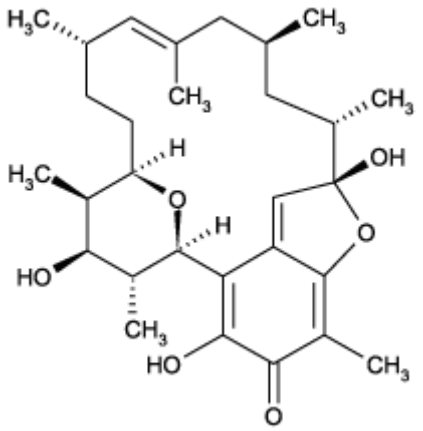
MATERIALS AND METHODS

Tested material:

Metabolites of *Streptomyces atrovirens Ab1* were screened for antimicrobial activity against dermatophytes then fractionated and purified.

Chemical structure of the purified antimicrobial metabolite was elucidated in Microanalytical Center, Faculty of Science, Cairo University using Nuclear magnetic resonance (NMR),Mass spectroscopy, Infrared (IR) and Ultraviolet (UV) spectroscopy.

Interpretation of results indicated molecular weight of about 786.6 and chemical formula of $C_{29}H_{42}O_6$ and following structural formula:



Current study aim to examine the radioprotective activity of the active antimicrobial metabolite after daily oral administration of 250µg/Kg b.w./day before exposure to (8 Gy) whole body gamma radiation.

Radiation source

Rats irradiation was performed in the Atomic Energy Authority, Cairo, Egypt with a dose rate 0.667 Gy/min using Gamma cell 40 (Cesium-137) manufactured by the Atomin Energy of Canada Ltd.

Animals:

48 male albino rats weighting 125±10 g. were obtained from the laboratory of animal colony, Ministry of health, Egypt.

Rats were housed in wire cages in room temperature maintained at 25 ± 5 ℃ and given food and water *ad libitum.* Animals were housed at 12 h light/dark cycle throughout the experimental period according to[21] and kept for one week before experiment start for acclimatization.

Experiment design

After acclimatization, rats were divided into four groups each of twelve rats and treated as following;

Group A: (Control group) maintained on standard diet.
Group B: (Treated group) rats received daily (250µg/Kg b.w./day) of tested material suspended in distilled water for two weeks by gavage[22].
Group C: (Irradiated group) rats fed standard diet and exposed to single dose (8 Gy) of whole body gamma radiation.
Group D: (pre-Treated, + irradiated group) rats received daily (250µg/Kg b.w./day) of tested material suspended in distilled water for two weeks by gavage then exposed to a single dose of whole body gamma radiation at a dose of (8 Gy) and left for one week before slaughtering[23].

Biochemical analysis

Blood samples were immediately collected after slaughtering in clean centrifuge tubes from the hepatic portal vein and then centrifuged at 4000 rpm for 15 minutes to separate serum.

Serum samples were used for estimation of reduced glutathione content (GSH)[24], activities of superoxide dismutase (SOD)[25] , catalase (CAT)[26] and Glutathione peroxidase (GPx)[27], Lipid peroxidation (LPO) as Malonaldialdehyde level (MDA)[28], triglyceride (TG) by the enzymatic colorimetric method[29], total cholesterol (TC) [30], high density lipoprotein cholesterol (HDL-C) [31], low density lipoprotein cholesterol (LDL- C)[32], activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT)[33], Alkaline Phosphatase (ALP) [34] and Gamma Glutamyl Transferase (GGT)[35].

Histological examination

Liver tissues from rats of each group were taken immediately after slaughtering and washed with normal saline solution to remove blood, then fixed in 10% neutral formalin.

Liver tissues were dehydrated in different grades of alcohol, and processed for paraffin embedding. Sections of 5µm were cut using a rotary microtome. The sections were processed and passed through graded alcohol series, stained with Haematoxylin and Eosin, cleared in Xylene and examined microscopically[36].

RESULTS

Table (1) presented MDA level, GSH content and SOD, CAT and GPx activities of rats exposed to single dose of radiation with and without antimicrobial active metabolite of *Streptomyces atrovirens Ab1* administration.

Irradiated group recorded very high significant elevation ($P<0.001$) in MDA level, as compared with the corresponding non-irradiated group. In addition, it is evident from table (1) that irradiation caused significant depletion ($P<0.05$) in GSH content and GPx activity and high significant decrease in CAT activity ($P<0.01$) and very high significant depletion in SOD activity ($P<0.001$). Groups treated with antimicrobial active metabolite of *Streptomyces atrovirens Ab1* pre-irradiation turned the value of MDA level to its normal value, also caused amelioration in GSH content and SOD, CAT and GPx activities.

The data in table (2) revealed that whole body gamma irradiation resulted in high significant increase in serum TC ($P<0.01$) and very high significant increase ($P<0.001$) in TG, LDL concentration meanwhile, showed significant decrease in HDL concentration. Groups treated with the antimicrobial active metabolite of *Streptomyces atrovirens Ab1* pre-irradiation resulted in sufficient amelioration in all investigated parameters.

Table (3) showed that, whole body gamma irradiation resulted in very high significant elevation in ALT, AST, ALP and GGT activities ($P<0.001$) as compared with the corresponding non-irradiated group. Treated groups by antimicrobial active metabolite of *Streptomyces atrovirens Ab1* pre-irradiation caused sufficient amelioration in all investigated parameters.

DISCUSSION

Gamma rays act either directly or by secondary reactions to produce biochemical lesions that initiate series of physiological symptoms. Ionizing radiation is known to induce oxidative stress through the generation of reactive oxygen species (ROS) resulting in imbalance of the prooxidant and antioxidant activities, ultimately resulting in cell death[37]. Numerous attempts were made to investigate different means for controlling and protection from radiation hazards using chemical, physical and biological means. Changes in LPO, GSH content, SOD, CAT and GPx activities have often been used as an index of oxidative stress[37].

The present results revealed a significant increase in lipid peroxiadtion associated with

depletion in GSH level due to radiation exposure. It was argued that the oxidant/antioxidant imbalance due to oxidative stress due to the exposure to gamma radiation is the main cause of the excessive formation of peroxides as MDA[38]. This response of antioxidant activity was attributed to the acute period of inflammatory processes developed during radiation exposure, which is characterized by the accumulation of lipid peroxidation products[39]. The decrease in antioxidant enzyme activities and increase in the free radicals may be the main cause of irradiation–induced peroxidation and disturbance of cell activities. The significant acceleration in lipid peroxidation is attributed to peroxidation of the membrane unsaturated fatty acids due to free radicals propagation concomitant with the inhibition in bio-oxidase activity[40].

Our results revealed that, whole body gamma irradiation of rats at 8 Gy produced a significant increase in the level of MDA, these results were in agreement with **Sener** [41] and **Guney**[42]. They reported that this elevation might be due to inhibition of antioxidant enzyme activities.

Whole body gamma irradiation with 8 Gy caused a decrease in the content of GSH. Glutathione content represents a key cellular defense mechanism against oxidative injury and lowered concentration of GSH is due to the increased formation of ROS. Hydrogen peroxide which is produced during oxidative stress can cause extensive damage and GSH levels are greatly decreased[43,44]. The present results were in agreement with those of **Mathur** [45] who concluded that the reduction in GSH content was due to the exhaustion of the antioxidant system as an attempt to detoxify the free radicals generated by radiation.

After applying 8 Gy gamma irradiation, the activity of SOD dropped significantly when compared to control group. In our observation, the significant decrease in SOD activity after 8 Gy gamma irradiation leads to increase in the formation of O_2^- and H_2O_2 . This decline may be due to inactivation of SOD by ROS[46,47].

The activity of CAT significantly decreased after 8 Gy whole body gamma irradiation and this is in agreement with previous observations of **De**[48] and **Thresiamma**[49]. Radiation, causes enzyme deficiencies which arise as a result of enormous production of free radicals in the system at high concentrations, hydrogen peroxide is converted to oxygen and water by CAT, which is predominantly localized in the peroxidases[50].

GPx, markedly decreased after applying 8 Gy gamma irradiation when compared to the control group. GPx is a defense enzyme against hydrogen peroxides and other hydroperoxides. In the present study, it might be due to its utilization by the enhanced production of ROS, which interacts with the enzyme molecules causing their denaturation and partial inactivation. These results are in agreement with those of **Kregel**[51] and **Park** [52].

According to the present findings, antimicrobial active metabolite of *Streptomyces atrovirens Ab1* provided subcutaneously protects against biological effects caused by gamma irradiation. This protection may be due to its stimulating effects on antioxidant system or ability to prevent and/or react with the free radicals to convert them into non-harmful forms due to the presence of quinone methide group in its structure, the group responsible for the antioxidant activity of flavonoids[53].

The present results reflected significant increase in the level of total cholesterol and triacylglycerol after radiation exposure of (8 Gy). These data are in harmony with **Abu Ghadeer** [54] who reported that the increased level of triacylglycerol in serum may be related to inactivation of lipoprotein lipase enzyme as a result of whole body irradiation.

Weiguo[55] recorded that, after radiation exposure, an increase in 3-hydroxy-3-methyl glutaryl CoA (HMG-COA) reductase activity, which is the rate limiting enzyme in cholesterol synthesis, was accompanied by increased cholesterol content. **Fielding** [56] illustrated that the hyper-cholesterolemia attributed to the decrease in lecithine cholesterol acetyl transferase, leading to decrease in cholesterol esterification of rat serum.

Hypercholesterolemic effect could be attributed to destruction of cell membrane and enhanced released to cholesterol into the serum[57] and/or disturbance in (HDL-H) receptors[58].

The amelioration resulted from antimicrobial active metabolite of *Streptomyces atrovirens Ab1* pre-irradiation may be due to its beneficial effects on membrane permeability leading to the

maintenance of a higher level in serum. These may be due to that tested treatment is rich in antioxidants, these results were agreement with **Lawenda**[59] ,that reported that antioxidant help to destroy free radicals particles that can damage cell membrane and may contribute to the aging process as well as the development of a number of conditions, including heart disease and cancer.

Serum transaminases activities are the most widely used parameter as a measure of hepatic injury, due to its ease of measurement and high degree of sensitivity. It is useful for the detection of early damage of hepatic tissue and requires less effect than that for a histological analysis[60].

Whole body gamma irradiation (8 Gy) caused significant increase in the transaminase activities compared to control group. The changes in the enzymatic activity after irradiation are related to either the release of enzymes from radiosensitive tissues or to the extensive breakdown of liver parenchyma. Furthermore, the change in tissues permeability due to irradiation could enhances the release of transaminase enzymes from their subcellular sites of production to extracellular process and consequently to blood circulation[61].

Histological examination of liver samples of irradiated group showed hepatocytes damage and necrotic degeneration. While, examination of pretreated group showed normal histological architecture and enzymes level.

Present study investigated the beneficial radioprotective effect of the antimicrobial active metabolite of *Streptomyces atrovirens Ab1* on antioxidant system biochemical indicators when administrated at a dose of 250µg/Kg b.w./day for fifteen days prior to whole body exposure to gamma radiation.

The antioxidant activity of tested treatment is a result for the presence of quinone methide group in its structure, this group is responsible for the antioxidant activity of flavonoids[53] and its formation is the key step in the antioxidant reaction of ferruginol.

Quinone methides are analogous compounds to quinones, wherein a carbonyl oxygen has been replaced by a methylene group. There are three isomers of quinone methides: ortho-, para- and meta-, but the ortho- and para- types which are the most common[62].

It could be concluded that, the administration of the antimicrobial active metabolite of *Streptomyces atrovirens Ab1* pre-whole body gamma irradiation resulted in sufficient amelioration against radiation effects on the biochemical aspects examined in the present study.

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Results

Table 1- Effect of whole body gamma irradiation and/or pretreatment with *Streptomyces atrovirens Ab1* antimicrobial metabolite on rats serum superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) activities, reduced glutathione content (GSH), and Lipid peroxides as malondialdehyde level (MDA).

Parameter / Group	CAT U/mL	SOD U/mL	GSH mg/dL	GPx U/mL	MDA µ mol/dL
Group A (Control)	24±1.7	62.4±5.9	45±3.4	72±5.8	76±5.7
Group B (Treated)	23±1.5 -4.2%	61±4.6 -2.2%	47±3.6 +4.4%	69.8±5.4 -3.0%	75.7±6.2 -0.4%
Group C (Irradiated)	15.8±1.2** -34.1%	33±2.2*** -47.1%	32.3±2.1* -28.2%	55±3.9* -23.6%	132.5±9.3*** +74.3%
Group D (Treated+Irradiated)	21±1.5 -12.5%	59.7±4.2 -4.3%	40.9±3.7 -9.1%	65±4.6 -9.7%	91±5.5 19.7%

- Results expressed as average ± SE (Standard error)
- Significant difference from control at * P <0.05, ** P <0.01 and *** P <0.001 as judged by Student t-test.
- % of change.

Table 2- Effect of whole body gamma irradiation and/or pretreatment with *Streptomyces atrovirens Ab1* antimicrobial metabolite on rats serum lipid profile (Triglyceride (TG), Total cholesterol (TC), High density lipoprotein cholesterol (HDL-C), and low Density Lipoprotein cholesterol (LDL- C)).

Parameter / Group	TC mg/dL	TG mg/dL	LDL mg/dL	HDL mg/dL
Group A (Control)	92.6±7.8	83.5±6.6	44.7±3.2	33.9±2.2
Group B (Treated)	95.8±7.6 +3.4%	83.7±6.8 +0.23%	43.2±3.0 -3.3%	33.6±2.1 -0.8%
Group C (Irradiated)	121.6±10.3** +31.3%	155.7±13.0*** +86.4%	84.2±6.9*** +88.3%	24.8±2.0* -26.8%
Group D (Treated+Irradiated)	95.9±7.2 +3.5%	102.4±8.9* +22.6%	52.6±4.3 +17.6%	28.2±1.9 -16.8%

- Results expressed as average ± SE (Standard error)
- Significant difference from control at * P <0.05, ** P <0.01 and *** P <0.001 as judged by Student t-test.
- % of change.

Table 3- Effect of whole body gamma irradiation and/or pretreatment with *Streptomyces atrovirens Ab1* antimicrobial metabolite on rats serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline Phosphatase (ALP) and gamma glutamyl transferase (GGT).

Parameter / Group	ALT U/L	AST U/L	ALP U/L	GGT U/L
Group A (Control)	62.7±4.4	33.6±2.8	7.4±0.55	4.0±0.28
Group B (Treated)	61.2±4.0 -8.4%	32.3±2.5 -3.8%	7.5±0.53 +1.3%	4.0±0.30 100%
Group C (Irradiated)	112.5±10.6*** +79.4%	60.0±4.9*** +78.5%	14.8±1.1*** +100.0%	8.1±0.69*** +102.5%
Group D (Treated+Irradiated)	82.6±6.3** +9.6%	41.3±3.5* +22.9%	9.6±0.74* +29.7%	5.4±0.38** +35.0%

- Results expressed as average ± SE (Standard error)
- Significant difference from control at * P <0.05, ** P <0.01 and *** P <0.001 as judged by Student t-test.
- % of change.

Histological examination results

Microscopical examination of rats liver tissue of control group (Fig. 1) and treated group (Fig. 2) showed normal histological architecture with normal hepatic lobule and normal hepatocytes arrangement in cords around the central vein (CV).

On the other hand, rats liver tissue of the 8Gy irradiated group showed changes in liver architecture and appearance of apoptotic and necrotic (N) tissues and fatty changes (F) (Fig. 3) as compared to that of pretreated and irradiated group which showed preserved histological architecture and significantly reduced number of apoptotic and necrotic cells (Fig. 4).

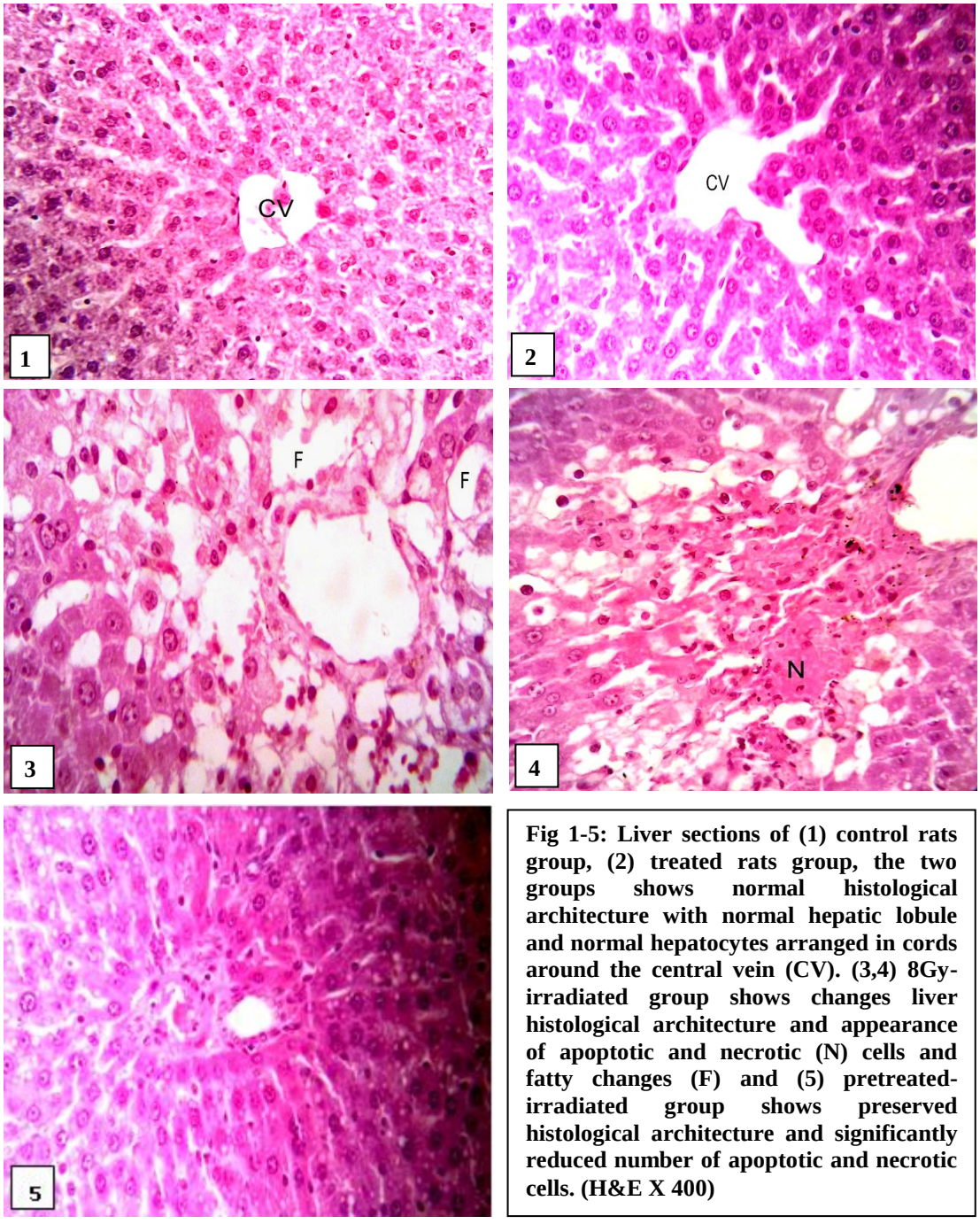

Fig 1-5: Liver sections of (1) control rats group, (2) treated rats group, the two groups shows normal histological architecture with normal hepatic lobule and normal hepatocytes arranged in cords around the central vein (CV). (3,4) 8Gy-irradiated group shows changes liver histological architecture and appearance of apoptotic and necrotic (N) cells and fatty changes (F) and (5) pretreated-irradiated group shows preserved histological architecture and significantly reduced number of apoptotic and necrotic cells. (H&E X 400)