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Impact of Low Dose of Gamma Radiation on Liver in Mice

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ABSTRACT: This work aims to investigate whether the pre-exposure to low dose/low dose rate (40 mGy, 2.2 mGy/hour) γ-radiation as a priming dose can produce a protective effect in mice.Mice were divided into Group I (control), Group II (L); exposed to 40 mGy, Group III (H); exposed to 4 Gy, and Group IV (L+H); exposed to 40 mGy 24 hours before the exposure to 4Gy. The molecular and biochemical changes related to oxidative stress, DNA damage, apoptosis, and mitochondrial activity in the liver were studied 4 hours after irradiation. Exposure to 40 mGy before 4 Gy induced a significant increase in the levels of Nrf2, Nrf2 mRNA, TAC, and mitochondrial complexes I & II accompanied by a significant decrease in the levels of LPO, 8-OHdG, DNA fragmentation, TNF-α, caspase-3, and caspase-3 mRNA compared with H group. Exposure to 40 mGy before 4 Gy induced a significant increase in the levels of Nrf2, Nrf2 mRNA, TAC, and mitochondrial complexes I & II accompanied by a significant decrease in the levels of LPO, 8-OHdG, DNA fragmentation, TNF-α, caspase-3, and caspase-3 mRNA compared with H group. Exposure to low-dose γ-radiation before a high dose provides protective mechanisms that allow the body to survive better after exposure to a subsequent high one via reducing the oxidative stress, DNA damage, and apoptosis-induced early after irradiation. However, further studies are required to identify the long-term effects of this low dose.

KEYWORDS: mice, liver, gamma radiation, low dose, damage, apoptosis, mitochondrial activity

I.INTRODUCTION

Genomic DNA was extracted from liver of mice by using GeneJET™ Genomic DNA Purification Kit (cat# K0721) (Thermo Scientific, USA) according to the manufacturer's instructions.[17] The isolated DNA was measured at 260/280 nm to assess DNA concentration and purity, then 500 ng of DNA was pipetted[1] onto a 1% agarose gel containing 100 ng/mL ethidium bromide, and electrophoresis was performed. Lipid Peroxidation (LPO) and Total Antioxidant Capacity (TAC) was identified by centrifugation. [16]Nuclear Factor Erythroid 2-Related Factor-2 (Nrf2), Tumor Necrosis Factor Alpha (TNF-α) and Caspase-3 Proteins were recorded in mice. Statistical analysis [2]was performed using IBM SPSS software (version 23.0; IBM Corp., Armonk, NY, USA), and data were presented as means ± S.D. One-way ANOVA was used to determine statistically significant differences between group's means and post hoc test (LSD) for pairwise comparisons.[3] Pearson correlation coefficients were calculated to evaluate the association between relevant parameters. [15]The criterion for significance was $p<.05$.[18]

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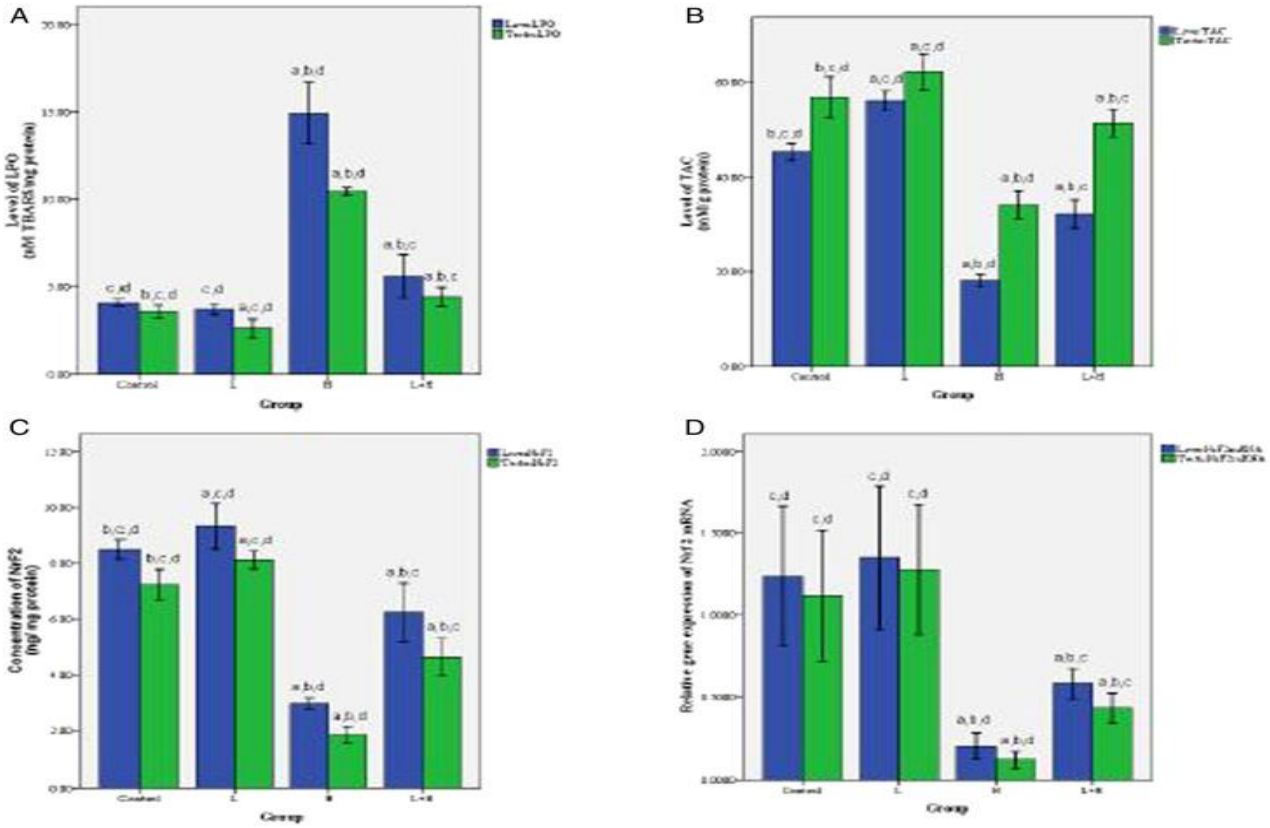

Oxidative stress markers in the liver (blue) of old mature miceand liver (green) of young mice. (A): Level of Lipid peroxidation (LPO); (B): Level of Total antioxidant capacity (TAC); (C): Concentration of Nuclear factor erythroid 2-related factor-2[19] (Nrf2); (D):Fold change of Nrf2 mRNA relative to Glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Data are expressed as mean ± SD (n = 10). a: significant compared to L group, c: significant compared to H group, d: significant compared to L ± H group ($P < .05$).[14]

II.DISCUSSION

Degree of DNA fragmentation was elevated in liver. Beside the oxidative stress and DNA damage markers[13], the protective effect of low dose before high dose exposure was proven by determination of TNF-α concentration as an inflammatory marker and the activity of caspase-3 as an apoptosis marker in the liver of mice.[4]

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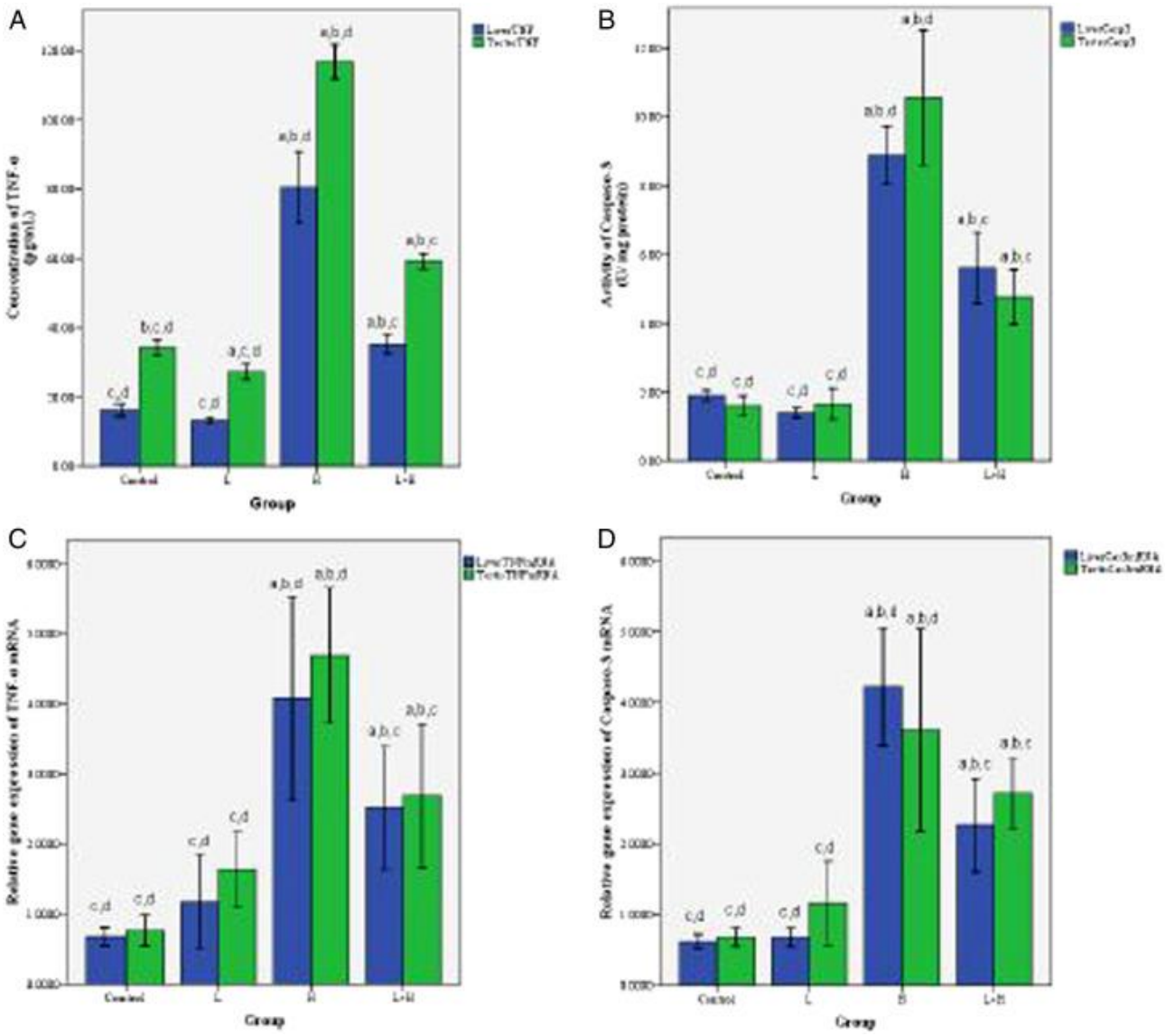

Inflammation and apoptosis markers in the liver (blue) of mature mice and liver (green) of young mice. (A): Concentration of tumor necrosis factor alpha (TNF-α); (B): Activity of Capase-3; (C): Fold change of TNF-α mRNA relative to Glyceraldehyde 3-phosphate dehydrogenase (GAPDH);[20] (D): Fold change of Caspase-3 mRNA relative toGlyceraldehyde 3-phosphate dehydrogenase (GAPDH).[12] Data are expressed as mean ± SD (n = 10). a: significant compared to L group, c: significant compared to H group, d: significant compared to L ± H group ($P < .05$).

Table 1.

Pearson Correlation Coefficients of Nuclear factor erythroid 2-related factor-2 and 8-Hydroxy-2′-Deoxyguanosine with Other Parameters in the live of mature and young mice.[11]

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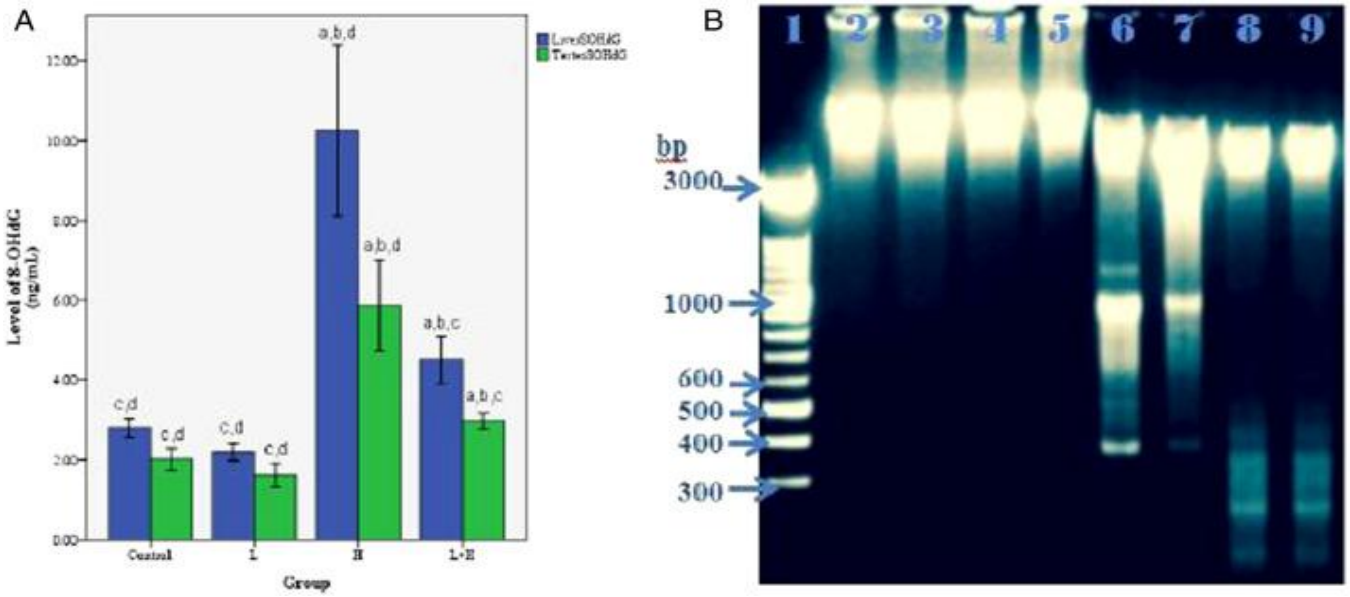
Parameter	Correlation coefficient (r) of Nrf2		Correlation coefficient (r) of 8-OHdG	
	In Liver mature	In liver young	In Liver mature	In liver young
LPO	−.889**	−.915**	.884**	.934 **
TAC	.946**	.925**	−.889**	−.877 **
Nrf2	1		−.908**	−.902 **
TNF-α	−.943**	−.953**	.892**	.962**
Caspase-3	−.956**	−.926**	.935**	.974**
8-OHdG	−.908**	−.902**	1	
Complex I	.629**	.886**	−.683**	−.739**
Complex II	.823**	.914**	−.761**	−.869**

III.RESULTS

Exposure to low doses of ionizing radiation has been shown to provide benefits for biological systems. [21]Previous studies indicated that low doses of ionizing radiation would stimulate different mechanisms that have effects on different cell types of physiological systems.[5] Therefore, it has been accepted that the radiation[10] hormesis phenomenon exists, which means that exposure to low dose ionizing radiation stimulates beneficial biological effects however, exposure to a high dose induces critical cellular responses in different organs in the body[22]. The testis is one of the most radiosensitive organs, and the liver is the main organ that controls systemic metabolism and maintains homeostasis in response to external stimuli, so they are easily affected by ionizing radiation.[6]



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Damage of DNA markers in the liver (blue) mature mice and liver (green) ofyoung mice. (A): level of 8-hydroxy-2'-dexyguanosine (8-OHdg). Data are expressed as mean ± SD (n = 10). a: significant compared to L group,[23] c: significant compared to H group, d: significant compared to L ± H group (P < .05). (B); DNA fragmentation agarose gel electrophoresis. Lane 1: DNA ladder; Lane 2, 4, 6 & 8: DNA from liver of mice of control, L, H and L+H groups; respectively. Lane 3, 5, 7 & 9; DNA from liver of mice of control. L, H and L ±H groups, respectively.[24]

The present study was conducted to understand the effects of exposure to low dose/low dose rate of γ-radiation (40 mGy, 2.2 m Gy/hour) before exposure to a higher dose (4 Gy, .425 Gy/minute),[25] at the first time to the best of our knowledge, on oxidative stress, DNA damage, mitochondrial activity, and apoptotic markers in the liver of mature and young mice[7]

IV.CONCLUSIONS

According to the results obtained in this study, low dose/low dose rate γ-radiation -as a priming dose—may induce a protective effect against the early damaging effect of γ-radiation, challenge dose, in mice. [9]This effect might be attributed to the reduction of DNA damage induced[27] early after irradiation and activation of anti-oxidative and anti-apoptotic mechanisms via modulating the Nrf2-mediated antioxidant response pathway, and mitochondria-mediated caspase activation & apoptosis. However, further studies are required to identify the long-term effects[26] of this low dose.[8]

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