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Original Article

# Green silver nanoparticles ameliorate oxidative stress and apoptosis induced by gamma irradiation in rat pancreas

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## Abstract

Radiation-related toxicity is a major concern for certain tissues and organs in radiation oncology practice. In abdominal tumor radiation treatment, the pancreas is particularly sensitive to radiation and should be considered at risk. The primary causes of acute pancreatitis after exposure to gamma radiation are oxidative damage and reactive oxygen species (ROS). The purpose of this study is to assess the efficacy of matcha silver nanoparticles (M-AgNPs) in mitigating oxidative stress and apoptosis induced by gamma radiation in the pancreas of female rats. Rats were exposed to 6 Gy of gamma radiation and subsequently administered an oral treatment with matcha (M) or M-AgNPs (10 ml/kg/day) for 14 days. We examined apoptotic markers such as caspase 3, B-cell lymphoma-2 (BCL2), and B-cell lymphoma-2-associated protein X (BAX) to evaluate their impact on cell survival. Additionally, the study investigated the modulation of antioxidants, glutathione S-transferases (GST), and malondialdehyde (MDA). The findings indicated that the administration of M-AgNPs for two weeks post-radiation exposure is more efficacious in diminishing lipid peroxidation and suppressing apoptotic indicators compared to conventional M treatments. M-AgNPs significantly ($p < 0.05$) reduced the elevation of MDA and demonstrated a considerable ($p < 0.05$) increase in GST. Moreover, it exhibited a markedly elevated level ($p < 0.05$) of BCL-2 and a significantly decreased level of Bax and caspase-3 ($p < 0.05$) in comparison to irradiated rats. The results of the histopathological investigations showed a notable enhancement in the histological characteristics of pancreatic tissue. In conclusion, the finding indicated that the AgNPs synthesized from matcha could potentially mitigate the adverse effects of radiation exposure. Further investigation is required to elucidate specific molecular pathways and their long-term consequences.

**Keywords**: Gamma radiation, Matcha, Silver nanoparticles, Oxidative stress, Apoptosis, Pancreas

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## Introduction

While radiation therapy (RT) is a highly efficacious method for addressing malignant tumors, it has the potential to inflict damage on adjacent healthy tissues and give rise to severe adverse effects (Rezaeyan et al., 2016). The pancreas is indeed very sensitive to irradiation and should be considered an organ at risk during radiation treatment for abdominal tumors. Previous studies by Gemici et al. (2013) established that abdominal irradiation induces substantial structural and functional alterations in pancreatic tissue. Also, Wydmanski et al. (2016) discovered in a prior investigation that abdominal irradiation resulted in exocrine functional loss of pancreatic tissue in a subset of patients.

In RT, reactive oxygen species (ROS) are produced through the radiolysis of water in extracellular environments, and these highly reactive entities are detrimental to both tumor cells and nearby normal tissues (Zou et al., 2017). Moreover, radiation can provoke endogenous ROS generation in mitochondria and modify mitochondrial membrane permeability, thereby enhancing ROS production (Kim et al., 2015). Elevated levels of ROS can disrupt intracellular redox homeostasis (Kim et al., 2019), leading to cellular dysfunction and lipid peroxidation, which indicate oxidative stress and elevated malondialdehyde (MDA) levels (Wang et al., 2017; Zhang and Gurunathan, 2016). Moreover, when the level of ROS-induced DNA damage exceeds the cell's ability to repair, the cell activates the apoptotic pathway. Consequently, it is imperative to implement strategies to mitigate oxidative damage and its consequences resulting from radiation exposure.

Antioxidants are crucial for reducing oxidative damage resulting from radiation exposure. Cells possess an effective antioxidant system, comprising enzymes and non-enzymatic substances, that mitigates the detrimental effects of free radicals. Antioxidants can effectively suppress and/or treat chronic illnesses by obstructing or decelerating the interactions of biomolecules with free radicals through electron transfer, hence impeding the oxidative process. Antioxidant defense includes various mechanisms. These include delaying or inhibiting the production of free radicals; scavenging free radicals; converting free radicals into less toxic compounds; delaying the formation of secondary toxic active species; interrupting chain propagation reactions; enhancing the endogenous antioxidant defense system through synergistic interactions with other antioxidants; and chelating metal ions (Adwas et al., 2019; Costa et al., 2021).

Several disorders linked to oxidative stress are predominantly handled and treated according to the antioxidant properties of plant extracts. Furthermore, the notable antioxidant characteristics demonstrated by some nanomaterials present a compelling possibility to develop innovative regimens with enhanced and tailored efficacy. For instance, studies have demonstrated that the capacity of gold, silver, and selenium nanoparticles to eliminate redox-active radicals can mitigate oxidative stress (Saad et al., 2017; Sood and Chopra, 2017; Thilagavathi et al., 2016).

According to a recent study by Ali et al. (2024), coating or doping nanoparticles with alternative materials reduces their negative effects, enhances stability, and reduces agglomeration. The green biosynthesis of metal nanoparticles utilizing medicinal plant extracts is a significant research focus due to its relevance in various fields, particularly in medicine administration (Chaudhuri et al., 2016). It is a suitable alternative to chemical methods due to its cost efficiency and environmental friendliness (Njue et al., 2020). Plants include many bioactive compounds that help the synthesis of metal nanoparticles by serving as reducing and stabilizing agents (Begum et al., 2022).

Silver nanoparticles (AgNPs) have been the subject of extensive research due to their cost-effectiveness and various advantageous properties, including optical, antimicrobial, anticancer, and antioxidant (Vijayan et al., 2018; Suresh et al., 2014). As a consequence, the fabrication of particles on a nanoscale has emerged as a promising therapeutic alternative (Bejarbaneh et al., 2023). Polyphenolic compounds are natural compounds found in some plants, such as matcha green tea (M). M is the unfermented and finely ground green tea powder (Koláčková et al., 2020). It has many antioxidant and anti-inflammatory compounds (Kochman et al., 2020). The electron-donating capability of the phenolic compounds in matcha, which contributes to its higher total phenolic content, enables the reduction of silver ions to nanoscale silver particles. Recent studies indicate that nanoparticles

created from bioactive phytochemicals have superior beneficial and effective qualities compared to conventional herbal medications (Habeeb et al., 2022). Consequently, the purpose of this study is to assess the efficacy of the biosynthesized M-AgNPs in mitigating oxidative stress and apoptosis induced by gamma radiation in the pancreatic tissue of female rats.

## Material and Methods

### Material

Matcha green tea (Camellia sinensis) was bought from ILEAF NATURLS in the United States. Silver nitrate (99.0%) and polyvinylpyrrolidone-stabilized AgNPs were procured from Sigma Aldrich. All supplementary chemicals were of analytical grade and procured from reputable commercial providers.

### Preparation and characterization of M-AgNPs

According to our previous research methodology (Hamed et al., 2023), M-AgNPs were created. M was used in the biogenic synthesis and green sonochemical approach to make AgNPs. M-AgNPs were characterized using a variety of methods, including dynamic light scattering (DLS), high-resolution transmission electron microscopy (HR-TEM), Fourier-transform infrared spectroscopy (FTIR), and thermogravimetric analysis (TGA).

### Experimental animal groups

Rats were exposed to a single dose of whole-body gamma radiation (γ-Rad) at a rate of 0.33 Gy/min. γ-Rad at the designated dose of 6 Gy has the potential to stimulate apoptosis by inducing oxidative stress (Hamed and Hammad, 2023). In this study, we used 36 Wistar albino female rats, each weighing between 180 and 200 g, and divided them into six groups: the control group (C) received deionized water orally. The M group was given 10 ml/kg/day of M orally for a period of 14 consecutive days (Ninsiima et al., 2023). The MN group received 10 ml/kg/day of M-AgNPs orally over a 14-day period. Rats in the R group received a single dose of 6 Gy of whole-body γ-Rad, after which they received no treatment for the duration of the experiment. After 24 hours of receiving a single dose of whole-body γ-Rad (6 Gy), the MR group administered 10 ml/kg/day of M orally for 14 consecutive days. The MNR group received 10 ml/kg/day of M-AgNPs orally for 14 consecutive days after receiving a single dose of whole-body γ-Rad (6 Gy).

### Sample preparation

Twenty-four hours after the final administration of M and M-AgNPs, the rats were euthanized for sample collection. Pancreas tissues were swiftly collected from the rats in various groups (10% wt/v) and homogenized in a Teflon apparatus using a cold PBS solution containing 0.16 mg/ml heparin. The homogenates underwent centrifugation at 4,000 rpm for 15 minutes at 4 °C. The transparent supernatant was employed to assess biochemical parameters subsequent to centrifugation.

### Oxidative stress evaluation

Oxidative stress was measured using commercial kits (Bio-Diagnostic Company). Assessment of lipid peroxidation by measuring MDA. MDA was assessed via its reaction with thiobarbituric acid (TBA), resulting in the formation of colorful thiobarbituric acid reactive products (TBARs), which were quantified spectrophotometrically at 532 nm. MDA concentrations were measured in nmol/g of tissue. The GST kit assay quantifies overall GST activity (including cytosolic and microsomal) by assessing the conjugation of 1-chloro-2,4-dinitrobenzene (CDNB) with reduced glutathione. The GST activity was determined at 340 nm in the sample and expressed in U/gm of tissue.

### Apoptotic markers evaluation

ELISA kits were used to determine caspase-3 (Cat. No. CSB-E09785r; CUSABIO, Wuhan, China), BAX (Cat. No. SEB631Ra; Cloud-Clone Corp., USA), and BCL-2 (Cat. No. E-EL-R0648; Elabscience®, USA)

in pancreas homogenate samples, according to the manufacturer's instructions.

### Histopathological examination

After fixation with 10% formol saline, pancreatic tissue was washed and dehydrated in alcohol. Dehydrated specimens were cleaned in xylene, sealed in paraffin blocks, and sectioned at 4-6 µm thickness. Before histological analysis under an electric light microscope (Bancroft et al., 2013), tissue sections were deparaffinized with xylol and stained with H&E. Pancreatic tissue H&E sections were evaluated for the severity of apoptosis at ten distinct fields and

200x magnification using a three-point scale: (parenchyma apoptosis—0: absent, 1: focal (<5%), 2: sub-lobular (<20%), 3: lobular (>20%). The analysis was performed in a blinded manner (Heindl et al., 2015).

### Statistical analysis

Results were presented as mean values accompanied by standard error. The data were statistically examined utilizing one-way ANOVA, followed by Tukey's HSD multiple comparisons as a post-hoc test to identify significant differences across groups. The statistically significant level was set at $P < 0.05$. The software SPSS statistical version 20 (SPSS® Inc., USA) was used for all statistical analyses.

## Results

### Impact of M and M-AgNPs on oxidative stress

The results of our study indicated that the concentrations of MDA and GST did not significantly ($p > 0.05$) rise in the M group (77.76 ± 1.41 and 1.51 ± 0.14, respectively) when compared to the control group (74.96 ± 2.19 and 1.24 ± 0.05 for MDA and GST). Furthermore, we detected no significant decrease ($p > 0.05$) in the MDA concentrations between the MN group (62.60 ± 4.05) and control groups. However, a substantial elevation in GST ($p < 0.05$) was noted in the MN group (1.77 ± 0.06) in comparison to the control groups. On the contrary to the control group, the radiation group demonstrated a significant reduction in GST levels (0.29 ± 0.02; $p < 0.05$) and a considerable increase in MDA levels (123.66 ± 3.57; $p < 0.05$) (Figures 1A and 1B).

The data presented in Figure 1A clearly indicates that the MNR group significantly (98.48 ± 2.18; $p < 0.05$) mitigated the rise in MDA when compared to the irradiated group. However, the MR (111.93 ± 2.58) and R groups showed no significant decrease ($p > 0.05$). In addition, MDA concentrations were significantly ($p < 0.05$) lower in the MNR group compared to the MR group. The GST concentration in the MR (0.82 ± 0.04; $p < 0.05$) and MNR (0.98 ± 0.02; $p < 0.05$) groups was considerably greater than the irradiated group, as displayed in Figure 1B. This study's results indicated that M-AgNPs enhance cellular antioxidant defenses and exhibit significant antioxidant efficiency in mitigating gamma radiation-induced oxidative stress in the pancreas.

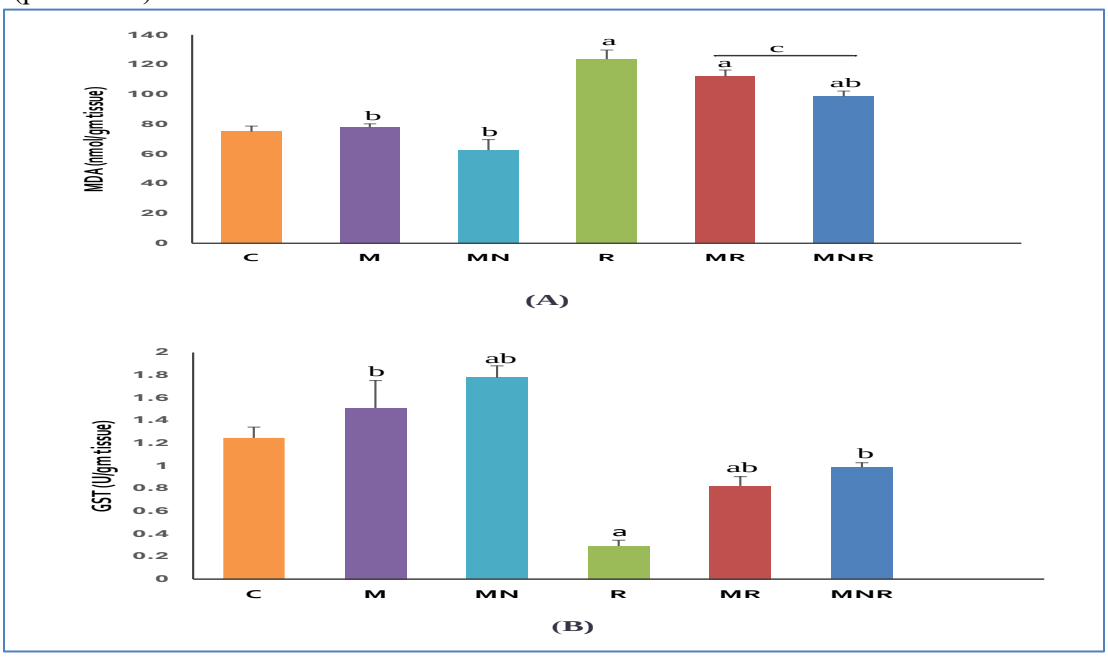


**Figure 1.** Effects of M and M-AgNPs on oxidative stress markers in the pancreas. (A) MDA and (B) GST. Values were reported as means ± SE (n = 6). a = significant vs. the control group at $p < 0.05$; b = significant vs. the irradiation group at $p < 0.05$; c = significant between the MR and MNR groups at $p < 0.05$.

## Impact of M and M-AgNPs on apoptotic markers

The present investigation assesses the impact of M and M-AgNPs on pancreatic apoptotic markers. We evaluated the levels of BCL-2, Bax, and caspase-3 in all experimental groups. The M group exhibited significant increases in Bax (194.56 ± 2.92; $p < 0.05$) and caspase 3 levels (0.49 ± 0.047; $p < 0.05$), while BCL2 levels (0.87 ± 0.03) did not increase significantly when compared to the control group (110.56 ± 0.72; 0.34 ± 0.003; 0.83 ± 0.04 for Bax, caspase 3, and BCL2). Additionally, the MN group significantly elevated Bax levels (240.90 ± 7.87; $p < 0.05$) compared to the control group, while caspase 3 did not significantly increase (0.47 ± 0.006), and BCL2 (0.80 ± 0.02) levels did not significantly decrease.

Furthermore, in contrast to the control group, the radiation group exhibited a notable decrease in BCL2 levels (0.49 ± 0.04; $p < 0.05$), while Bax and caspase-3 levels significantly increased (514.73 ± 6.65, $p < 0.05$; 0.81 ± 0.051, $p < 0.05$, respectively) (Figure 2). Additionally, the findings of our study indicated that the MR and MNR groups exhibited a substantially higher concentration of BCL-2 (1.16±0.11, $p < 0.05$; 1.36±0.04, $p < 0.05$, respectively) than the radiation group. In addition, the MR and MNR groups demonstrated a significantly reduced concentration of Bax level (383.56±4.31, $p < 0.05$; 417.2±7.60, $p < 0.05$) and caspase-3 level (0.52±0.023, $p < 0.05$; 0.45±0.03, $p < 0.05$) compared to the radiation group. Moreover, it is notable that in the treated groups, the M treatment demonstrated a significant decrease in Bax levels compared to M-AgNPs.

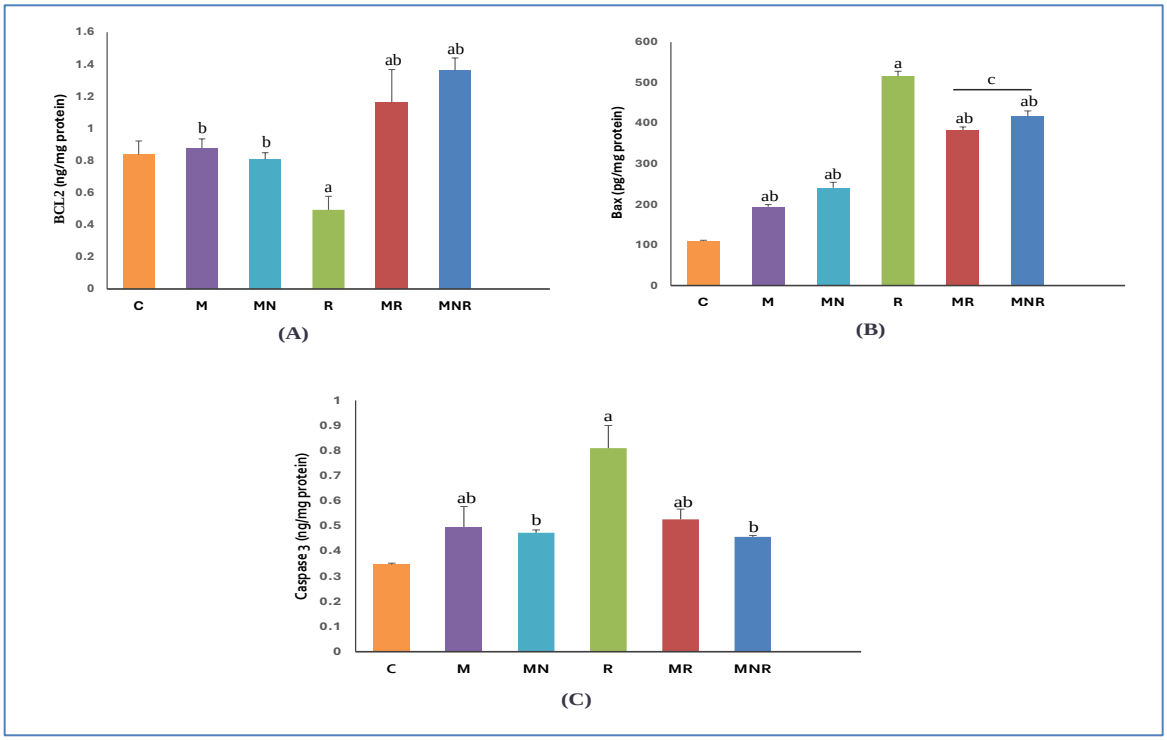


**Figure 2.** Impact of M and M-AgNPs on apoptotic markers: (A) BCL2, (B) Bax, and (C) Caspase 3 in the pancreas. Values were reported as means ± SE (n = 6). a = significant vs. the control group at $p < 0.05$; b = significant vs. the irradiation group at $p < 0.05$; c = significant between the MR and MNR groups at $p < 0.05$.

## Histopathological finding

A section of pancreatic tissue from the control, M, and MN animal groups revealed a pancreas with a normal architecture. Both the exocrine and endocrine tissues of the pancreas exhibited typical histological characteristics. The lobules of the pancreas varied in size and morphology. The cellular components of the islets of Langerhans were organized normally, and the acinar structure contained typical proteinous eosinophilic materials. The pyramidal cells

comprising the acinar cells had acidophilic cytoplasm at their apex. The exocrine components of the pancreas are densely packed with acinar cells and organized into small lobules; they receive a score of 0 (figure 3a-b-c). The radiation-exposed animal group exhibited apoptosis of a subset of Langerhans cells. The acinar epithelial lining of the pancreas exhibited degenerative alterations accompanied by the absence of typical lobular architecture. Certain acinar cells exhibited vacuolation accompanied by nucleus pyknosis of score 3 (figure 3d). The animal group MR exhibited a significant quantity of Langerhans's cells undergoing apoptosis, with eosinophilic apoptotic bodies interspersed among them. Loss of normal lobular architecture accompanied by variable degenerative changes in the pancreatic acini; certain acinar cells exhibited vacuolation accompanied by pyknosis of their nuclei (figure 3e). In contrast, the histological appearance of the pancreatic lobules and islets of Langerhans improved notably in the animal group MNR. A subset of acinar cells exhibited pyknotic nuclei that were intensely stained, while the vast majority of acinar cells displayed vesicular nuclei. A few numbers of apoptotic Langerhans's cells were observed at score 1 (figure 3f).

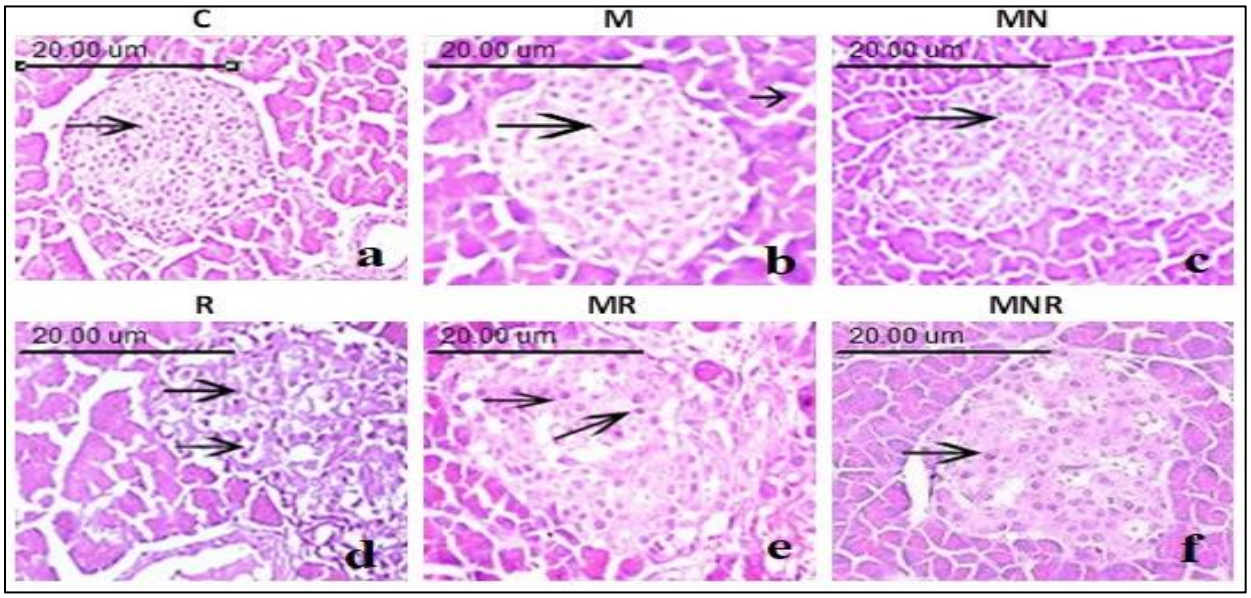


**Figure 3.** Photomicrograph of pancreatic tissue section showing: (a,b,c) normal architecture of Langerhans's islets and acini; arrow (d) numerous numbers of apoptotic Langerhans's cells; arrow (e) greater numbers of apoptotic Langerhans's cells arrow (f): Few numbers of apoptotic Langerhans's cells arrow (H&EX 200).

## Discussion

In radiation oncology, radiation-related toxicity is a crucial clinical consideration. The pancreas, due to its close proximity to the stomach and duodenum, may be unintentionally exposed to radiation during irradiation of the gastro-duodenal region (Zucca et al., 2020) or through total body irradiation. So, this study aims to investigate the potential impact of biosynthesized M-AgNPs in mitigating oxidative stress and apoptosis induced by γ-radiation in the pancreatic tissue of female rats.

Contact with ionizing radiation (IR) produces ROS like hydroxyl radicals, superoxide, singlet oxygen, and hydrogen peroxide, which react with cellular components (Deng et al., 2019), causing morphological, metabolic, and cytotoxic changes due to oxidative stress and ROS, which damage lipids, proteins, and DNA (Hashim et al., 2020; Kamran et al.,

2021). Furthermore, Alattar et al. (2022) indicated that oxidative stress induces inflammation. In the present study, whole-body irradiation with a single radiation dose of 6 Gy elevated the MDA levels of pancreatic tissues. This aligns with research by Rezaeyan et al. (2016), who demonstrated that IR induces ROS within cells via water radiolysis, which subsequently assaults the fatty acids in the cell membrane and causes lipid peroxidation. Our results are also in line with those of other studies that used animal models and found that irradiation led to a significant rise in pancreatic MDA levels (Olgaç et al., 2006).

Contrarily, after irradiation, MDA levels were considerably lower in the M-AgNPs treatment (MNR group) than in the irradiated group. Nevertheless, the MR and R groups exhibited no substantial difference. Furthermore, the MNR group had substantially lower MDA concentrations than the MR group. This demonstrates that the M-AgNPs substantially reduced the increase in MDA, which correlates with oxidative stress and cellular damage. The results of this study are consistent with those of Guntur et al. (2018). Furthermore, a prior study indicated that AgNPs synthesized from green tea exhibited enhanced scavenging activity relative to green tea alone (Ruchikaa and Sehgala, 2020); this increase in scavenging efficacy may be ascribed to the increased surface area. The coating of polyphenolic residues on the surface of AgNPs may augment the interaction and ability of polyphenols in M to donate hydrogen to free radicals.

IR can adversely affect the antioxidant system; glutathione S-transferase (GST) is a crucial component of the cellular antioxidant system and plays key roles in preserving cellular homeostasis (Singh and Reindl, 2021). In the current investigation, GST levels markedly diminished in pancreatic tissues 14 days following irradiation. The present findings align with previous research indicating that IR might adversely affect the antioxidant system, leading to diminished levels and activity of antioxidant enzymes (Zhu et al., 2019).

However, following irradiation, the M or M-AgNPs treatment resulted in an increase in GST levels, indicating enhanced antioxidant defense mechanisms. Our results align with prior research indicating that plant-derived nanoparticles, such as silver, augmented the antioxidant activity of the respective molecules in the extract (Duman et al., 2016; Kanipandian et al., 2014). Moreover, a study by Al-Shmgani et al. (2017) indicates that AgNPs demonstrate antioxidant potential. Furthermore, our results indicated that the antioxidant activity of M-AgNPs surpassed that of matcha alone. Our findings correspond with those of Abdel-Aziz et al. (2014), who noted that plant extracts containing AgNP exhibited elevated amounts of total phenolic compounds and total flavonoids in comparison to the plant extract utilized independently. Nonetheless, certain studies indicate no alteration or a reduction in ROS following AgNP treatment (Qian et al., 2015; Gallorini et al., 2016; Pereira et al., 2018). The study's findings indicated that M-AgNPs can augment cellular antioxidant defenses and show considerable antioxidant effectiveness in mitigating gamma radiation-induced oxidative stress in the pancreas.

Apoptosis, a eukaryotic mechanism of cell death regulated by genetics, facilitates the controlled elimination of cells in order to preserve homeostasis and normal development (Singh et al., 2019). The cell survival and death are regulated by the equilibrium of pro-apoptotic and the anti-apoptotic BCL2 family proteins. The proteins in the BCL-2 family are divided into two groups: those that promote survival (BCL-2) and those that promote cell death (BAX) (Luna-Vargas and Chipuk, 2016). Radiation-induced oxidative stress can initiate cell death by activating the mitochondria-dependent apoptotic machinery. Apoptotic cell death involves the progressive activation of many cysteine-dependent aspartate-directed proteases, commonly referred to as caspases. Furthermore, Chung et al. (2015) indicated that γ-radiation induces cell death via apoptosis and ROS generation. Elevated ROS levels trigger apoptosis by regulating the phosphorylation and ubiquitination of BCL2 family proteins, leading to the overexpression of pro-apoptotic genes (e.g., BAX) and the downregulation of anti-apoptotic genes (e.g., BCL2) (Li et al., 2004).

Our findings indicated that radiation caused a considerable reduction in BCL2 levels, whereas Bax and caspase-3 levels markedly rose. This finding is consistent with Changizi et al. (2021), who demonstrated that radiation markedly downregulated the BCL2 gene while upregulating the BAX and CASP3 genes. The significant decrease in Bcl-2 expression corresponds with prior research demonstrating the downregulation of this anti-apoptotic protein following radiation exposure

(Rajabathar et al., 2023). In addition, the substantial increase in Bax expression highlights the pro-apoptotic signaling, which is consistent with studies linking elevated Bax levels to radiation-induced apoptosis (Mukherjee et al., 2022). Moreover, it was noted that heightened caspase-3 expression resulted from augmented oxidative stress caused by radiation (Li et al., 2015).

Conversely, our study's findings revealed that the MR and MNR groups demonstrated a significantly elevated level of BCL-2 compared to the radiation group. Furthermore, the MR and MNR groups had a markedly decreased level of Bax and caspase-3. M-AgNPs may inhibit apoptosis by diminishing lipid membrane peroxidation and oxidative stress, which are critical mediators of apoptosis. The distinctive phytochemical features of M-AgNPs, characterized by a high concentration of antioxidants such as catechins, along with their physicochemical attributes that augment biological activity, may facilitate their capacity to suppress apoptosis. Moreover, the combination of matcha's antioxidant-rich phytochemicals with the powerful properties of AgNPs may produce a synergistic effect, whereby the whole therapeutic outcome exceeds the individual effects of each component.

## Conclusion

Radiation-related toxicity is a major concern for certain tissues and organs in radiation oncology practice. So, this study aims to investigate the potential impact of M-AgNPs in mitigating oxidative stress and apoptosis induced by γ-radiation in the pancreatic tissue of female rats. The results showed that administering M-AgNPs for two weeks after being exposed to six gray gamma radiation is more effective in reducing lipid peroxidation and suppressing apoptotic indicators than the conventional M treatment. The findings indicate that M-AgNPs could potentially act as effective agents in mitigating damage resulting from ionizing radiation exposure. M-AgNPs' unique phytochemical characteristics and their physicochemical characteristics enhance biological activity. Moreover, the combination of matcha's antioxidant-rich phytochemicals with the powerful properties of AgNPs may produce a synergistic effect, whereby the whole therapeutic outcome exceeds the individual effects of each component. Further investigation is required to elucidate specific molecular pathways and their long-term consequences.

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**Disclaimer:** None

**Conflict of Interest:** None

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## Contribution of Authors

Khateeb S: Conceptualized study and supervised the research work, acquired funds, interpreted data and edited the final draft of manuscript.
Hamed NS: Designed the experiment and analyzed the data.
Aljohani R, Almudayni M, Albalawi M & Alharthany K: Prepared the initial draft of the manuscript, analyzed and interpreted data.

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