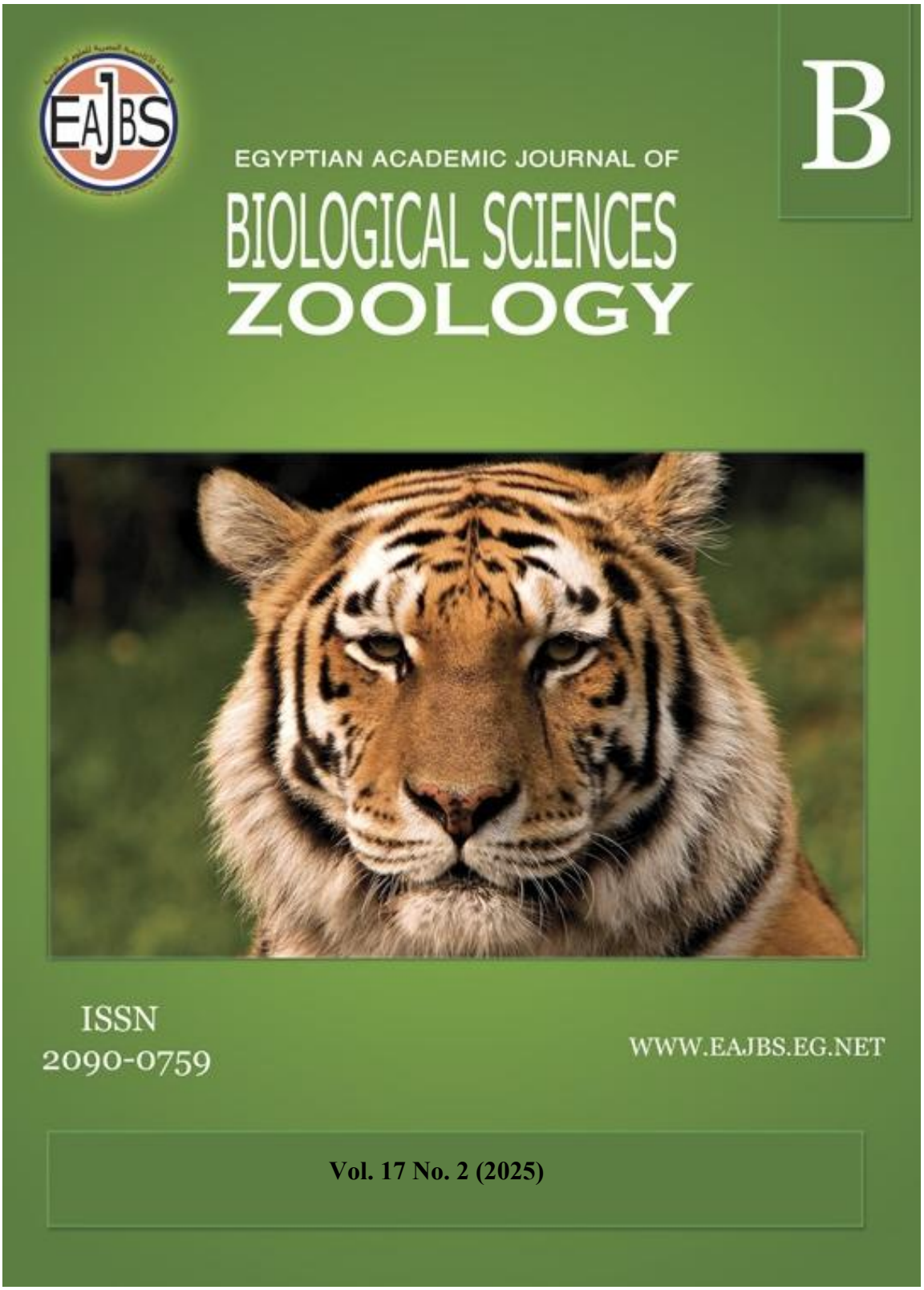

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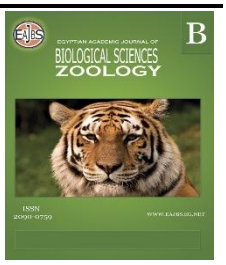
Citation: *Egypt. Acad. J. Biolog. Sci. (B. Zoology) Vol. 17(2) pp:25-53 (2025)*
DOI: 10.21608/EAJBSZ.2025.449823

Egypt. Acad. J. Biolog. Sci., 17(2):25-53(2025)

Egyptian Academic Journal of Biological Sciences
B. Zoology
ISSN: 2090 – 0759
Res. Ethics No.: 03-2025-0020
http://eajbsz.journals.ek b.eg/



The Possible Therapeutic Effect of Nanoparticles of *Moringa oleifera* Leaves Extract and \ or Low Doses of Gamma Radiation on Liver Injury Induced in Rats by Acute Pancreatitis

Safaa M. Abd El-hameed[1]*; Mona M. El-Tonsy[1]; Neamat H. Ahmed[2] and Hemmat M. Abdelhafez[1]

[1]Zoology and Entomology Department, Faculty of Science AL-Azhar University (Girls)-Naser city-cairo, Egypt.
[2]Cell Biology& Histology National Center for Radiation Research and Technology Egyptian Atomic Energy Authority, Cairo, Egypt.
***E-mail:** safaa_magdy@outlook.com

ARTICLE INFO
Article History
Received:29/7/2025
Accepted:27/8/2025
Available:1/9/2025

Keywords:
Acute pancreatitis, nano-*Moringa oleifera low dose* , γ-irradiation, liver, β-amyloid protein, apoptosis.

ABSTRACT

Background: The hallmark of acute pancreatitis (AP) is exocrine pancreatic inflammation, which is linked to acinar cell damage and a systemic and local inflammatory response. Liver function is closely related to the progression and prognosis of AP. Nanoparticles can improve drug release efficiency and enable regulated release with fewer adverse effects. An essential herbal plant, *Moringa oleifera* is used to treat inflammation, cancer, liver and heart problems, wounds, and pain. According to radiation hormesis, a natural synthesis of reactive oxygen species (ROS) sufficient to activate the defensive mechanisms and induce a positive health effect, a low dosage of ionizing radiation (IR) is necessary for life. **Aim of the work:** This study is designed to evaluate the impact of nano-*Moringa Oleifera* leaves extract and/or low dose gamma irradiation on acute pancreatitis induced by L-arginine on the liver tissues of rats**. Materials and Methods:** Fifty adult male rats were categorized into five separate groups. Group I: control group (C), group 2: positive control group (PC): L-arginine (250 mg/100g body weight) was administered intraperitoneally to the rats twice at 1-hour intervals, every other day for 14 days to cause acute pancreatitis, group 3: nano-*Moringa oleifera* treated group (NM): the positive control animals were treated with nano-*Moringa oleifera* (50 mg/kg/day) daily for 14 days, group 4: gamma irradiated group (IR): the positive control animals were exposed to 0.25 Gy x2 / week for 2weeks, group 5: nano-*Moringa oleifera* + gamma irradiated treated group (NM + IR): the positive control animals were treated with **NM** (50 mg/Kg/day) for 14 days and were exposed to 0.25 Gy x2/week/2weeks.The experimental rats were sacrificed after one day of treatments; liver functions, Random blood sugar (RBS) level, Insulin level, histopathological and histochemical changes in liver tissue were evaluated**. Results:** rats suffering from PC revealed a significant increase in AST, ALT and RBS while a significant decrease in insulin, along with severe liver tissue damage. Treatment of experimental animals suffering from PC with NM and γ-irradiation either alone or combined, a remarkable decrease AST, ALT and RBS, while remarkable increase in insulin level, resulting in notable amelioration of liver tissue damage. **Conclusion:** To minimize the liver damage induced by acute pancreatitis, it is recommended to use nano-*Moringa oleifera* and low dose of γ-irradiation, either separately or in combination.

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INTRODUCTION

One of the gastrointestinal conditions linked to considerable morbidity and subsequent death is acute pancreatitis (Zhou *et al*., 2024).

Systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and hypermetabolism are the main causes of the high death rate associated with severe acute pancreatitis (SAP), which is marked by rapid progression and a host of complications. There are two primary peaks in AP death: the first peak, which comes early and is linked to the beginning of MODS in the first week, and the second peak, which is closely linked to infections (Beger *et al*., 1997). There was a positive correlation between the severity of AP and the incidence and severity of liver injury, even in patients who did not develop MODS. This resulted in a longer course of AP. Since the liver contains the highest number of macrophages (Kupffer cells, KCs) in the body, it plays a crucial role in the management of bacteremia, systemic endotoxemia, and vasoactive byproducts. The mortality rate for patients with SAP who have liver failure can reach 83%, per previous research (Halonen *et al*., 2002). The equilibrium between the antioxidant and oxidant systems is disrupted in AP. Rats with duct obstruction in an animal experimental model produce a significant amount of oxygen free radicals (OFR) during the early stages of AP (Uruñuela *et al*., 2002). Acute pancreatitis brought on by L-arginine (ARG) was assessed as a new and unique type of experimental pancreatitis (Borai *et al*., 2017). In addition to being a substrate for nitric oxide synthase, L-arginine is known to cause oxidative and nitrosative stress. There is some evidence to suggest that in this model of pancreatitis, these pathways may also play a role in pancreatic damage. Reduction of oxidative stress is the goal of therapies for L-arginine pancreatitis (Hardman *et al.,* 2005).

Formulations of herbal drugs based on nanotechnology have garnered interest because of their increased activity and ability to solve problems related to herbal medicine. (Dewi *et al.,* 2022). Many natural and synthetic polymers have been investigated over the years for the creation of nanoparticles; however, due to their biocompatibility and biodegradability, poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and their copolymers (PLGA) have been the subject of many research. Compared to other polymers used in medication and gene delivery, PLGA has several benefits, such as biodegradability, biocompatibility, and FDA-approved human usage. By hydrolytically cleaving the ester connection to lactic and glycolic acid, the PLGA copolymers break down within the body. These monomers are readily broken down by the body's Krebs cycle and expelled as water and carbon dioxide (Jain, 2000).

Over the past few decades, *Moringa oleifera'*s (*Mo*) medicinal and therapeutic value has been praised. It is the *Moringaceae* species that is most commonly grown (Fahey, 2005). The benefits of *Mo*'s leaves, blooms, seeds, seed oil, stem bark, and roots for health and nutrition have been well-documented (Promkum *et al*., 2010). Because of its documented antibacterial, antioxidant, antiulcer, cytoprotective, cardiovascular, antidiabetic, anticancer, and neuroprotective qualities, it can be used as a nutritional supplement or to treat a variety of clinical problems (Rao *et al*., 2001; Omotoso *et al*., 2018). Additionally, *Mo* can raise total antioxidant activity (TAC) and improve insulin resistance (Tuorkey, 2016). Numerous *Mo* tree sections are presently being researched for potential benefits on the treatment of metabolic illnesses, including type 2 diabetes. In animal studies, *Mo* exhibits antihyperglycemic properties (Azad *et al*., 2017). Soliman *et al.* (2024) confirmed that, based on nutritional and biochemical characteristics for natural plant sources and functional soft cheese, nano-encapsulated *Moringa oleifera L*. seed extract and *Ocimum tenuiflorum L*. leaf extract demonstrated a possible anti-hyperglycemic impact without any adverse reactions.

Low-dose radiation (LDR) increases the production of normal cells, immunological responses, DNA damage repair, antioxidant capability, and apoptosis in some cancer cell types, among other biological actions both *in vitro and in vivo* (Farooque *et al*., 2011). Lower liver

doses in conventional fractionation are less likely to cause persistent enzyme abnormalities. For instance, in stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma (HCC), ALT/AST levels normalized in some patients (Jia *et al*., 2021). To treat liver damage caused by acute pancreatitis in rats caused by L-arginine, the present research sought to investigate the possible therapeutic benefits of extract from nano-*Moringa Oleifera* leaves and/or low dosage gamma irradiation.

MATERIALS AND METHODS

Experimental Animals:

The experimental animals for the various studies conducted in this work were fifty adult male albino rats (*Rattus rattus*) weighing 180–200g, which were acquired from the Egyptian Holding Company for Biological Products and Vaccines (Cairo-Helwan, Egypt). Before the experiment began, the animals were acclimated to the lab environment. The animals were housed in specially designed cages with 10 rats each, under regulated conditions of temperature and relative humidity (continuous temperature of 25–27 °C with a 12-hour light/dark cycle) for two weeks prior to the experimental procedure. Standard rodent pellets were used to feed the animals.

The research ethics committee (REC) authorized this study procedure, which is planned and administered in compliance with the CIOMS and ICLAS International Guiding Standards for Biomedical Research Regarding Animals 2012 (Warnecke *et al.,* 2008).

Radiation Facility:

Egyptian National Center for Radiation Research and Technology (NCRRT), located in Cairo, conducted the gamma cell-40 irradiation. The gamma cell-40, a cesium-1 irradiation device, is produced by Atomic Energy of Canada Ltd. Experimental animals were administered 0.25 Gy x2 /week for two weeks at a dose rate of 0.423 Gy/min (Frey *et al.*, 2015). This was calculated using the Dosimetry Department's guidelines from the NCRRT at the time of the experiment.

L-arginine Monohydrochloride:

The supplier of L-arginine monohydrochloride (CAS No. 53308-83-1) was Sigma Chemical Company (Sigma, USA). Reagents with a purity grade of more than 95%.

Pancreatitis Models (induction of pancreatitis):

To induce acute pancreatitis, the animals received repeated intraperitoneal injections of L-arginine at a rate of 250 mg/100g body weight twice at one-hour intervals, every day for ten days (Hegyi *et al.,* 2004; Kui *et al.,* 2015).

After diluting L-arginine-HCl in saline, its pH was brought down to 7.4 by NaOH. A fresh L-arginine solution was made before to every experiment (Kui *et al.,* 2015**).**

Preparation of Nano-*Moringa:*

Plant Materials:

At the National Research Center in Dokki, Giza, Egypt, the Egyptian Scientific Society of *Moringa* (ESSM) provided the aqueous extract of *Moringa oleifera* leaves (MOL)

Preparation of *Moringa* Leaves Extract-Loaded PLGA-PEG Nanoparticles:

Abd-Rabou *et al.* (2017), claim that a minor modification was made to the nanoparticle production method. To create poly D, L-lactide-co-glycolide (PLGA) nanoparticles, 100 mg of PLGA polymer was dissolved in 3 milliliters of chloroform to create an initial emulsion. An O/W emulsion was produced using a microtip probe sonicator (VC 505, Vibracell Sonics, Newton, USA) in an aqueous polyvinyl alcohol (PVA) solution (12 ml, 2% w/v).

Three separate nano-formulations of polyethylene glycol-blended PLGA (PLGA-PEG) were created using three different PLGA-PEG ratios (1:2, 2:1, and 1:1) in order to create PLGA-PEG nano-void. These were then added to the watery PVA solution prior to emulsification with the PLGA polymer. To enable the organic solvent to evaporate, the

emulsion was shaken for eight hours. After two washes with double-distilled water, an excess of PVA was eliminated the next day by ultracentrifugation at 50,602g for 20 minutes at 4 °C (Sorvall Ultraspeed Centrifuge, USA).

Moringa leaf extract (ML)-encapsulated PLGA-PEG nanoparticles (MLn) were similarly created for medicinal applications by adding a certain concentration before emulsification.

Analysis of Particle Size and Zeta Potential:

Using a Zeta Sizer (Nano ZS, Malvern Instruments, UK) and a red laser with a wavelength of λo=633 nm (He–Ne, 4.0 Mw), photon correlation spectroscopy (PCS) was used to quantify the particle size and zeta potential of the PLGA-PEG NPs. One milligram of the NPs was dissolved in one milliliter of water, which was then diluted ten times with water, and the readings were taken for at least 120 seconds. In the same way, materials were put in an electrophoretic cell with a potential of ±150 mV for zeta potential measurements.The nanocomposites were maintained at 25.0±0.1 °C.

Transmission Electron Microscope (TEM):

Using a transmission electron microscope (TEM, Philips CM-10, FEI Inc., Hillsboro, OR, USA), the particle morphology of the NPs was investigated. Formvar-coated copper grids were filled with 100 µg/ml of the nano-suspensions. Once the samples had completely dried, they were stained with 2% w/v uranyl acetate (Electron Microscope Services, Ft. Washington, PA). Soft Imaging Viewer software and a digital microscope were used for image capture and analysis.

Experimental Design:

The adult male albino rats in the experiment were divided into five groups (n=10) as follows:

G1: **Negative control group(C):** untreated normal animals.

G2: **Positive control group (PC)**: animals were administered intraperitoneal injections twice at 1h intervals with L-arginine (250mg/100g) to induce acute pancreatitis**.**

G3: Nano-*Moringa oleifera* treated group (NM): The positive control animals were given a daily dose of nano-*moringa oleifera* leaves extract (50 mg/kg/day) for 14 days.

G4: Gamma-irradiated group (IR): for two weeks, positive control animals were exposed to 0.25 Gy x2 /week.

G5: Nano-*Moringa oleifera* + gamma irradiated treated (NM + IR): the positive control animals were treated with **NM** (50 mg/Kg/day) for 14 days and were exposed to 0.25 Gy x2/week/2weeks.

Rats in each group were given isoflurane anesthesia, and samples of liver tissue and blood serum were taken after a day of treatment. To separate the plasma for additional biochemical analysis, blood samples were drawn in sterile heparinized syringes and centrifuged for 10 minutes at 3000 rpm. As quickly as feasible, the entire liver of each animal was removed, cleaned with isotonic ice-cold saline, fixed in 10% neutralized formalin, and embedded in paraffin for histopathological and histochemical analysis.

Biochemical Analysis:

Estimation of Liver Functions:

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were measured by the kinetic method of Murray and Kaplan (1984 a&b respectively) using a commercial kit obtained from SPINREACT Company, Spain.

Estimation of Glucose Level:

Using the stated enzymatic colorimetric approach, the glucose level was determined by Tietz (1986).

Estimation of Insulin Level:

Insulin level was carried out according to the method of Reeves *et al.* (1984), using kits of Bio Source Europe S.A. Company.

Histological and Histochemical Analysis:

Liver samples were immersed in 10% neutralized formalin for 24 hours before being dehydrated and fixed in paraffin wax. Sections (5 μm) were cut using a microtome, collected on glass slides, and stained with hematoxylin and eosin stains (H & E) for histological investigation (Bancroft *et al.,* 1996). Collagen fibers were stained by using Masson's Trichrome (Mao *et al.,* 2016). Amyloid-β protein was detected by Congo red technique (Bancroft and Gamble, 2008). Paraffin-positive slides were stained with 5 μg/ml propidium iodide and 50 μg/ml acridine orange in phosphate-buffered saline, and they were analyzed using fluorescence microscopy to assess apoptosis and necrosis in accordance with Bank (1988).

Statistical Analysis:

All statistical analyses were performed using the statistics package for Windows Version 15.0. (SPSS Software, Chicago, IL). The average standard error was used to present the results for continuous variables. Using one-way analysis of variance (ANOVA), the values were compared, and p values below 0.05 were deemed statistically significant.

RESULTS

1- Characterization of Nano-*Moringa* particles:

Moringa leaves extract nanoparticles (MLn)-based PLGA-PEG nanoparticles (poly D-L-lactide-co-glycolide-polyethylene glycol) were prepared using three different nano-formulations with three different ratios of PLGA-PEG (1:2, 2:1, and 1:1), which were then added to the aqueous PVA (Polyvinyl Alcohol) solution before the droplet size of *Moringa* leaves extract nanoemulsion was measured. Formulations No. 3 for MLn-based PLGA-PEG nanoparticles demonstrated excellent stability. Formula 3 (F3): Zeta potential (-39.60±3.52) is more stable, the nano-size (141.772±14.5) is the smallest, and the polydispersity index (0.05±0.01) is uniform in size and shape (Table 1 and Figs.1, 2&3).

As seen in Figure 4, the morphology of MLn-based PLGA-PEG nanoparticle sample F3 was examined using transmission electron microscopy (TEM). TEM revealed rounded particles with an encircling capsule and core (Fig. 4A). The TEM of F3 nanoparticles in Figure 4B displays a range of diameters for a few chosen particles, from 148.42 to 152.40.

Table 1: The effect of PLGA: PEG ratios on the particle size and zeta potential of MLn-based PLGA-PEG nanoparticles.

Formulation	PLGA	PEG	Nano-Size (nm)	PDI	Zeta potential (mV)
F1	1	2	190.137± 6.5	0.5± 0.02	-13.23±3.32
F2	2	1	341.995±15.4	0.6±0.03	-5.27± 1.29
F3	1	1	141.772±14.5	0.05± 0.01	-39.60± 3.52

Notes: MLn; *Moringa* leaves extract nanoparticles, PLGA; poly D-L-lactide-co-glycolide, PEG; polyethylene glycol, F1; formula 1 (ratio 1:2), F2; formula 2 (ratio 2:1), and F3; formula 3 (ratio 1:1), PDI; polydispersity index, S.E.; standard error.

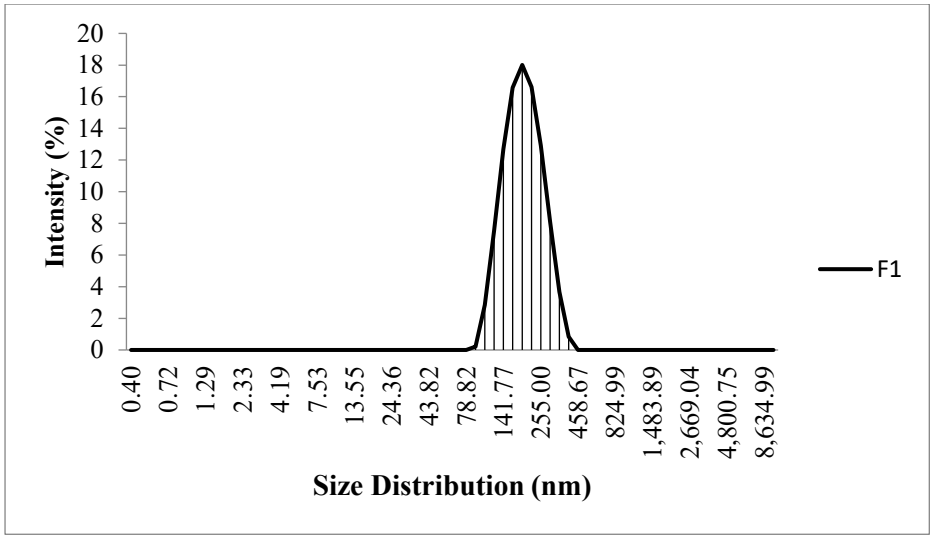

Fig. 1: Size distribution of formula 1 F1.

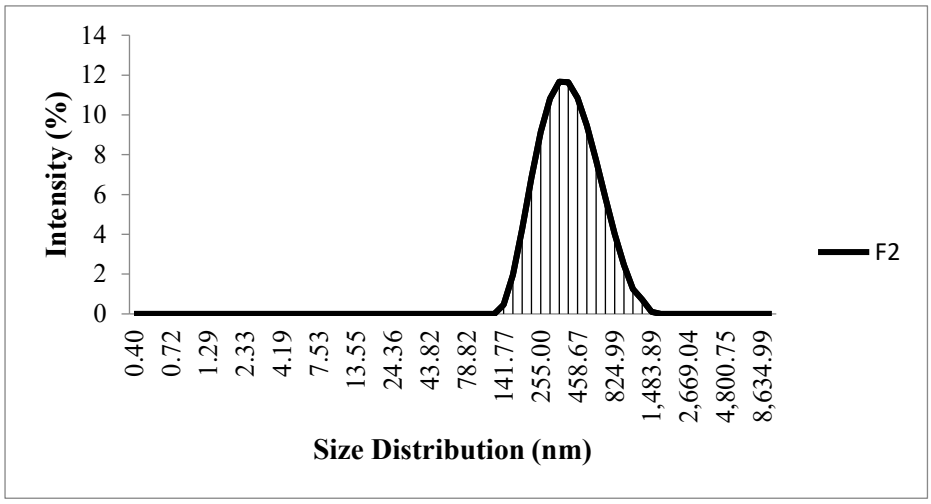

Fig. 2: Size distribution of formula 2 F2.

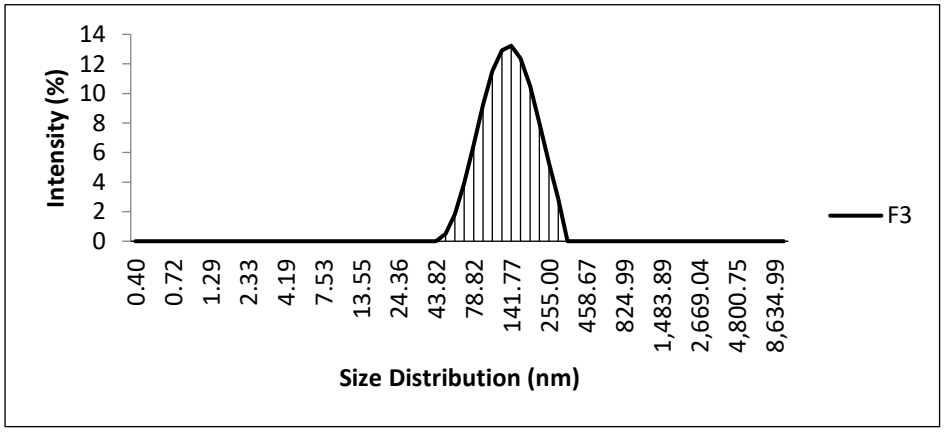

Fig. 3: Size distribution of formula 3 F3.

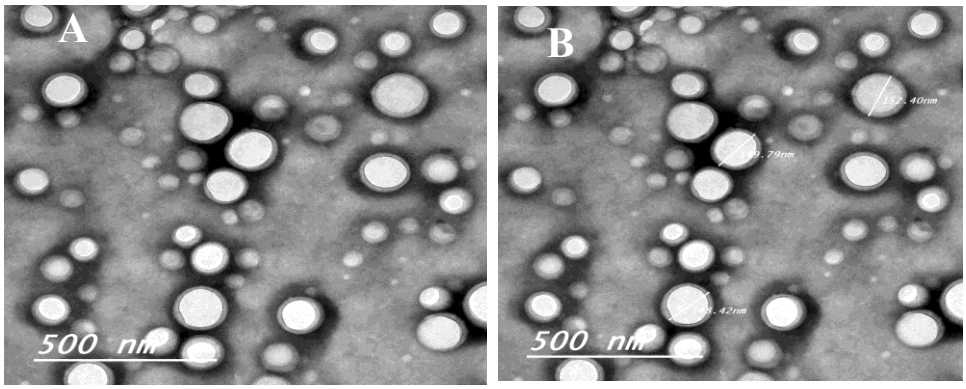

Fig. 4: Characterization of F3 nanoparticles. A) TEM of F3 nanoparticles showing rounded particles containing core and surrounded capsule. B) TEM of F3 nanoparticles showing some sizes of selected particles.

Biochemical Results:

1-The Liver Functions:

A group of rats suffering from PC revealed a significant increase in AST and ALT (73.45% and 48.51% respectively) in comparison with the control group.Treatment of experimental animals, suffered from PC with nano- *Moringa* and γ-irradiation either alone or combined a remarkable, decrease in AST (-27.14%,-27.12%and -32.81% respectively) and ALT levels(-18.93%,-19.31% and -19.04% respectively)were observed when compared with the PC group **(**Table 2**)** .

Table 2: Effect of nano- *Moringa oleifera* leaves extract and /or low doses of gamma irradiation on AST and ALT levels of adult male albino rats suffering from pancreatitis.

Parameter	AST(U/L)			ALT(U/L)		
Time / Groups	One day of treatment			One day of treatment		
	Mean± S.E	% change (C)	% change (PC)	Mean± S.E	% change (C)	% change (PC)
Control (C)	99.25±1.68	0.0 %	-42.35%	45.17±2.29	0.0 %	-32.66%
Positive control (PC)	172.15±3.97 a	73.45%	0.0 %	67.08±1.36 a	48.51%	0.0 %
Nano-*Moringa* (NM)	125.42±2.99 ab	26.37%	-27.14%	54.38±1.15 ab	20.39%	-18.93%
IR	125.46±0.42 ab	26.41%	-27.12%	54.13±1.15 ab	19.84%	-19.31%
Nano- *Moringa* (NM+IR)	115.67±1.30 ab	16.54%	-32.81%	54.31±1.35 ab	100.31%	-19.04%

N=10. Each value represents the mean ± standard error (SE), where (a) Significant from control at $P \leq 0.05$. (b) Significant from positive control at $P \leq 0.05$. **AST:** aspartate aminotransferase, **ALT:** alanine aminotransferase.

2- Estimation of RBS and Insulin Levels:

A group of rats suffering from pancreatitis (PC) revealed a significant increase in RBS (27.49%) while a significant decrease in insulin (-36.9%) levels in comparison with the control group.

Treatment of experimental animals suffering from PC with NM and γ-irradiation either alone or combined, a remarkable decrease in RBS level (-15.44%, -13.04% and -14.04% respectively) was observed. In comparison, a remarkable increase in insulin level (53.77%, 56.6% and 52.83%, respectively) was noticed when compared to the PC group **(**Table 3**)**.

Table 3: effect of nano-*Moringa oleifera* leaves extract and/or low doses of gamma irradiation on RBS and insulin levels in adult male albino rats suffering from pancreatitis**.**

Parameter	RBS (mg/dl)			Insulin(U/ml)		
Time / Groups	One day			One day		
	Mean± S. E	% change (C)	% change (PC)	Mean± S.E	% change (C)	% change (PC)
Control (C)	182.50±3.95	0.0 %	-21.56%	1.68±0.08	0.0 %	58.49%
Positive control (PC)	232.67±3.35 [a]	27.49%	0.0 %	1.06±0.08 [a]	-36.9%	0.0%
Nano- Moringa (NM)	196.75±3.12 [ab]	7.81%	-15.44%	1.63±0.03 [b]	-2.98%	53.77%
gamma-irradiated group (IR)	202.33±2.96 [ab]	10.87%	-13.04%	1.66±0.02 [b]	-1.19%	56.6%
Nano- Moringa (NM+IR)	200.21±3.21 [ab]	9.7%	-14.04%	1.62±0.03 [b]	-3.57%	52.83%

N=10. . Each value represents the mean ± standard error (SE). (a) Significant from control at P ≤ 0.05. (b) Significant from positive control at P ≤ 0.05. **RBS:** random blood sugar.

Histological Observations:

The histological pattern of the control rats' liver tissue showed that the central vein had a normal structure, with hepatocyte cords radiating from it and being divided from one another by blood sinusoids. Bile ducts, a branch of the hepatic artery, and a branch of the hepatic portal vein are all located in the portal area (Figs. 5 A&B). Normal distribution of collagen fibers in the portal area and thin bundles of collagen fibers support the wall of the central vein, walls of hepatocytes and blood sinusoids in the control group (Figs. 5 C&D). Sections in the liver tissue of rats of the PC group showed hydropic degeneration in most hepatic cells with the presence of apoptotic nucleoli, liver steatosis and slightly elongated and corrugated wall of the central vein (Fig. 6 A). A highly distorted portal area containing lymphocytic infiltration around the portal vein, with hemolyzed blood cells inside was also observed (Fig. 6 B). Highly increased collagen fibers in and around the walls of the hepatic portal vein, the bile duct and the arterial wall as well as increased collagen fibers distribution in and around the central vein and in the sinusoidal spaces (Figs. 6 C&D). Sections in the liver tissue of the NM treated group showed somewhat normal architecture of the liver tissue with few hemolyzed blood cells inside the central vein (Fig. 7 A) and some inflammatory cells around the portal area (Fig. 7B). Apparently normal distribution of collagen in the central and hepatic portal veins was also recorded (Figs. 7 C&D). On the other hand, sections in liver tissue from IR treated group showed the presence of hepatocytes with hydropic degeneration and apoptotic nuclei. Also, some liver steatoses were observed in Figurs. 8 A&B, a nearly normal appearance of collagen fibers was also observed (Figs. 8 C&D). At the same time, sections from liver tissue of the NM+IR treated group showed somewhat normal architecture of liver tissue while the central vein was slightly elongated (Fig. 9 A). Also, well developed portal area of liver tissue, but the hepatic portal vein was congested with highly hemolyzed blood cells inside it (Fig. 9B). Additionally, a normal collagen fiber distribution was noted (Figs. 9 C&D).

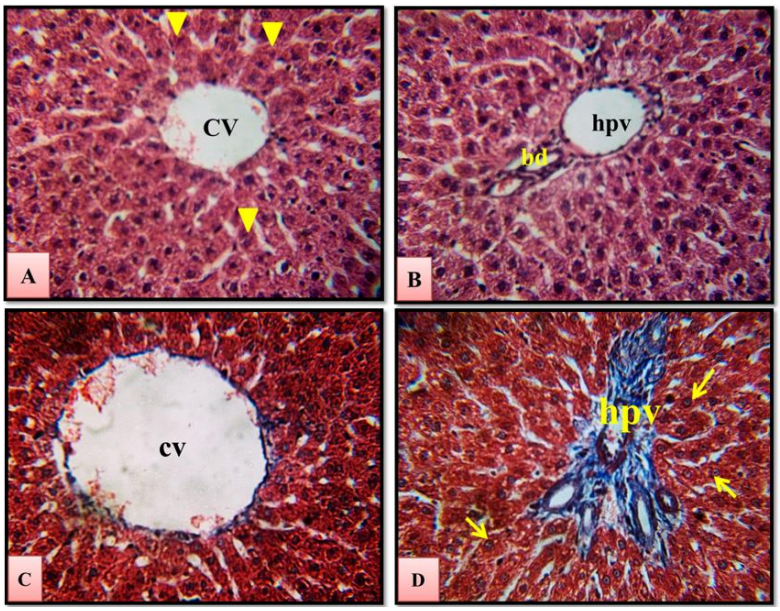

Fig. 5: photomicrographs of sections in the liver tissue of rats of the control group showing: **A&B:** normal structure of the central vein **(cv)**, cords of hepatocytes (▼) radiating from it and separated from each other by blood sinusoids. The portal area contains a branch of the hepatic portal vein **(hpv)**, a branch of the hepatic artery and bile ducts **(bd)**.

(H&E stain A&B X 400)

C&D: thin bundles of collagen fibers support wall of the central vein **(cv)** , walls of the hepatocytes **(arrows)** , blood sinusoids, bile duct and hepatic portal vein **(hpv)**.

(Masson trichrome (MT) stain A and B X 400)

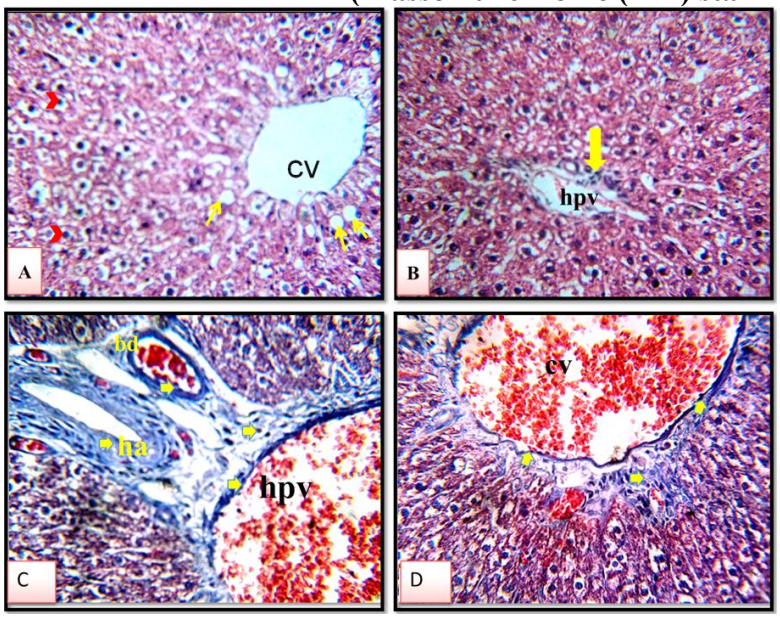

Fig. 6: photomicrographs of sections in the liver tissue of rats of the positive control group suffering from pancreatitis showing: **A:** hydropic degeneration in most hepatic cells (➔) with the presence of apoptotic nucleoli (➤), liver steatosis and slightly elongated and corrugated wall of the central vein **(cv)**.

B: highly distorted portal area**(hpv)** which contains lymphocytic infiltration **(bold arrow)** around the portal vein, with hemolyzed blood cells inside it. **(H&E stain A,B X 400)**

C: highly increased collagen fibres (➡) in and around walls of the hepatic portal vein **(hpv)**, the bile duct **(bd)** and in the arterial wall **(ha)**.

D: increased collagen fibers distribution in and around the central vein **(cv)** and in the sinusoidal spaces. **(MT stain C& D X 400)**

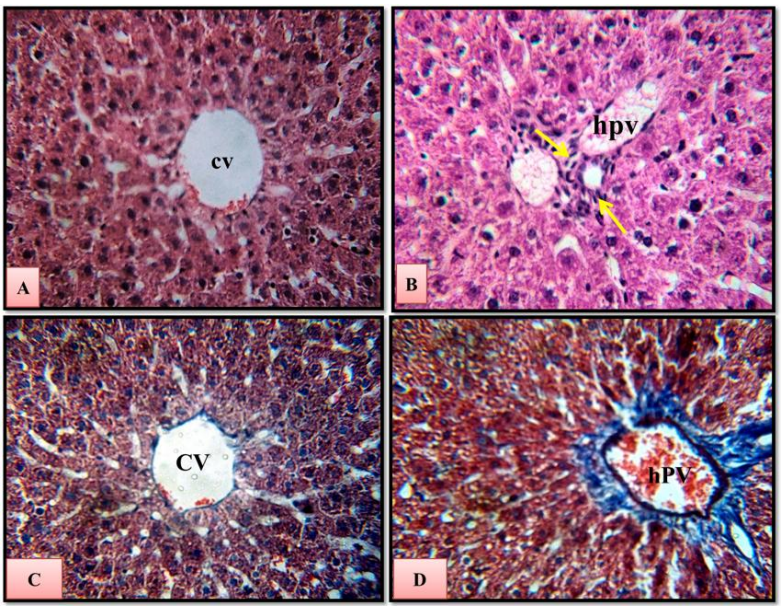

Fig. 7: Photomicrographs of sections in the liver tissue of rats suffering from pancreatitis treated with nano- *Moringa* showing:
A: somewhat normal architecture of liver tissue with a few hemolyzed blood cells inside the central vein **(cv)**.
B: somewhat normal architecture of liver tissue with the presence of some inflammatory cells (↑) around the portal areas**(hpv)**. **(H&E stain A and B X 400)**
C&D: somewhat normal distribution of collagen fibers in the central **(cv)** and hepatic portal veins **(hpv).** **(MT stain C and D X 400)**

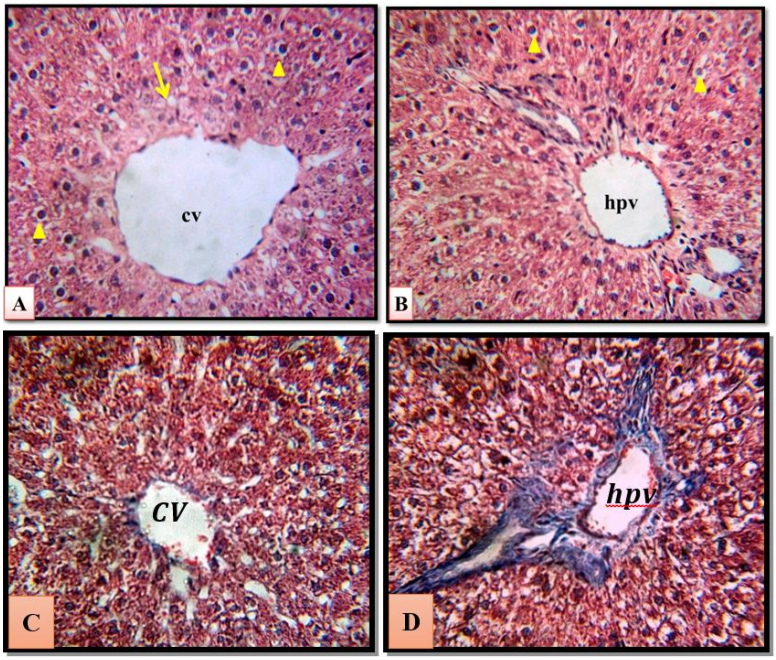

Fig.8: photomicrographs of sections in the liver tissue of rats suffering from pancreatitis exposed to low doses of gamma radiation showing:
A&B: somewhat normal appearance in the central**(cv)** and prtal areas **(hpv),** while the presence of hepatocytes suffering from hydropic degeneration (↓) and apoptotic nuclei (▼). Also, some liver steatosis was observed.
C&D: nearly normal appearance of collagen fibers in the central **(cv)** and hepatic portal areas **(hpv)**.

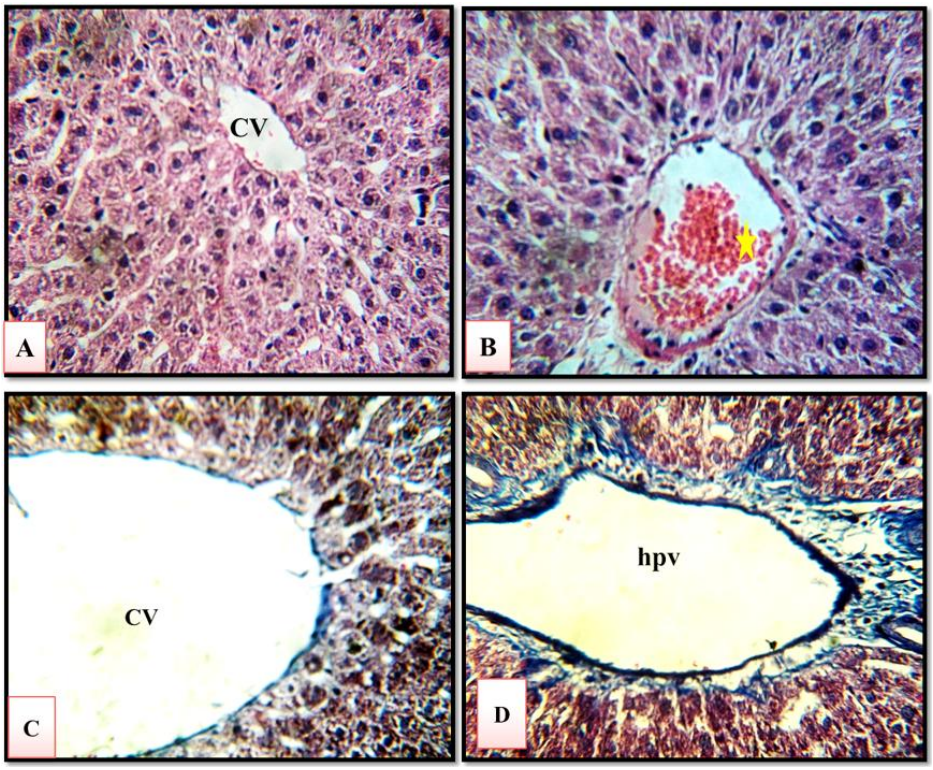

Fig. 9: photomicrographs of sections in the liver tissue of albino rats suffering from pancreatitis treated with nano-*Moringa* and irradiation showing:
A: somewhat normal architecture of liver tissue but the central vein **(cv)** is slightly elongated.
B: well developed portal area of liver tissue, but the hepatic portal vein is congested with highly hemolyzed blood cells inside it **(star)**. **(H&E stain C, D X 400)**
C&D: nearly normal distribution of collagen fibers in the central **(cv)**and portal**(hpv)** areas of liver tissue. **(MT stain A, B, C and D X 400)**

Histochemical Results of The Liver Tissue:
β– amyloid Protein:

Figure (10 A) represented the normal deposition of β– amyloid in the liver tissue of albino rats of the control group. Meanwhile, in the PC group, the liver tissue sections showed densely stained β- amyloid (Aβ) proteins (Fig. 10 B). Moreover, sections in the liver tissue of the NM treated group showed decreased β- amyloid (Aβ) proteins deposition all over the liver tissue (Fig.10 C). Furthermore, sections in the liver tissue of the IR treated group showed mild to moderate deposition of β- amyloid (Aβ) plaque in hepatocytes (Fig. 10 D). At the same time, sections in the liver tissue of the NM+ IR treated group showed faintly stained β–amyloid proteins deposition (Fig. 10 E).

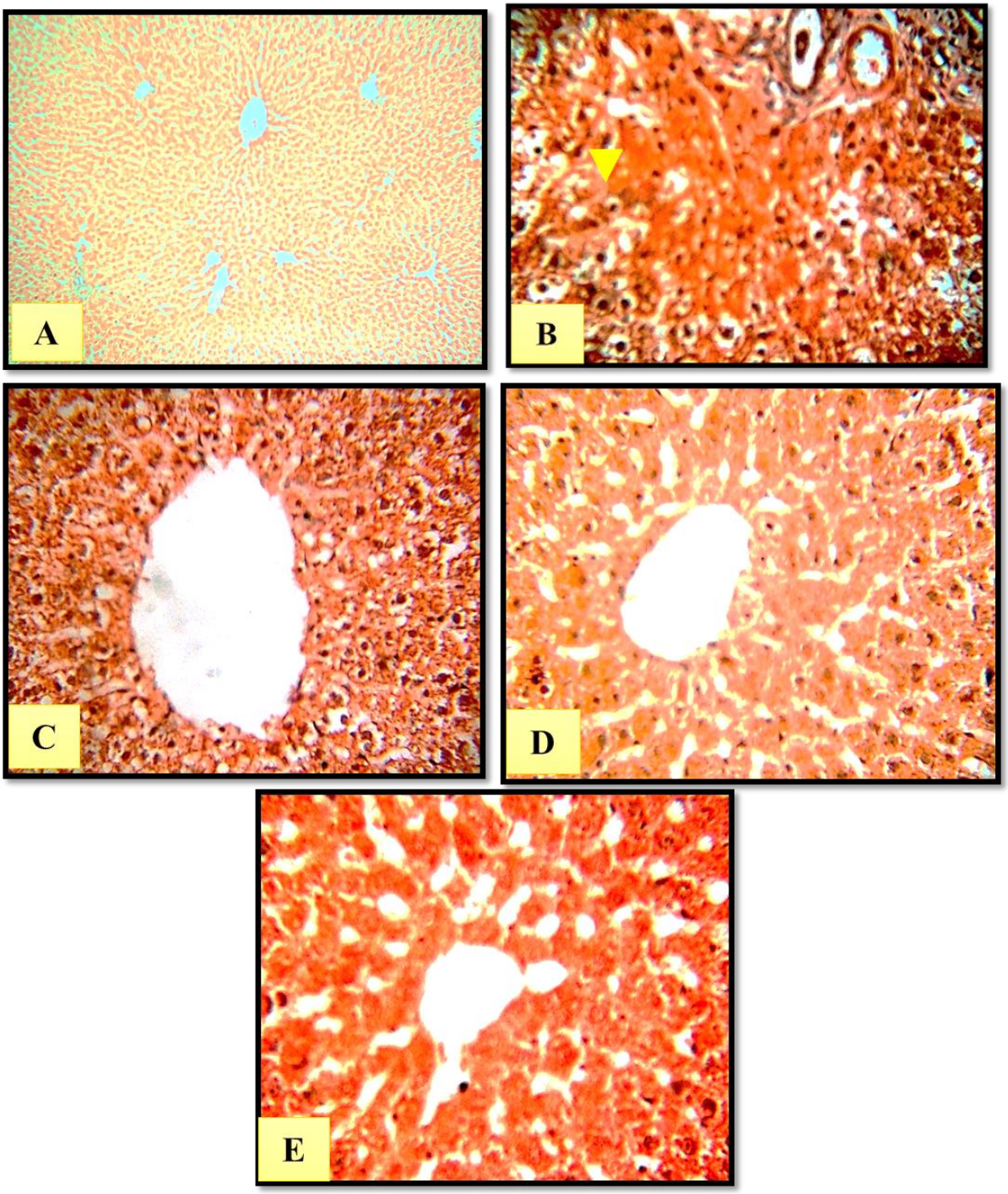

Fig. 10 (A-E): Photomicrographs from sections of the liver tissues of different experimental groups of adult male albino rats, stained with congo red stain showing **A**: the control group with faintly stained β- amyloid (Aβ) proteins all over the liver tissue. **B**: the PC group with densely stained β- amyloid (Aβ) proteins (▼) comparatively with the control group. **C**: the NM treated group with faintly stained β–amyloid proteins deposition. D: the IR treated group with mild deposition of β- amyloid (Aβ) protein in hepatocytes. **E**: the NM+IR treated group with faintly stained β–amyloid proteins deposition.

(Congo red stain A X 100, B, C,D and E X 400)

Apoptosis Examination:

Sections of the liver tissue of the control group showed green viable hepatocytes **(**Fig. 11 A**)**. While sections in the liver tissue of the PC group showed increased apoptotic cells which widely distributed, especially in between hepatocytes (Fig. 11B).

Meanwhile, section in the liver tissue of the NM treated group showed slight distribution of apoptotic cells in hepatocytes (Fig. 11 C). Additionally, sections in the liver tissue of the IR treated group showed apparently normal distributions of apoptotic hepatocytes (Fig. 11 D). Moreover, sections in the liver tissue of the NM+IR group showed slightly distribution of apoptotic cells in the liver tissue (Figs. 11 E).

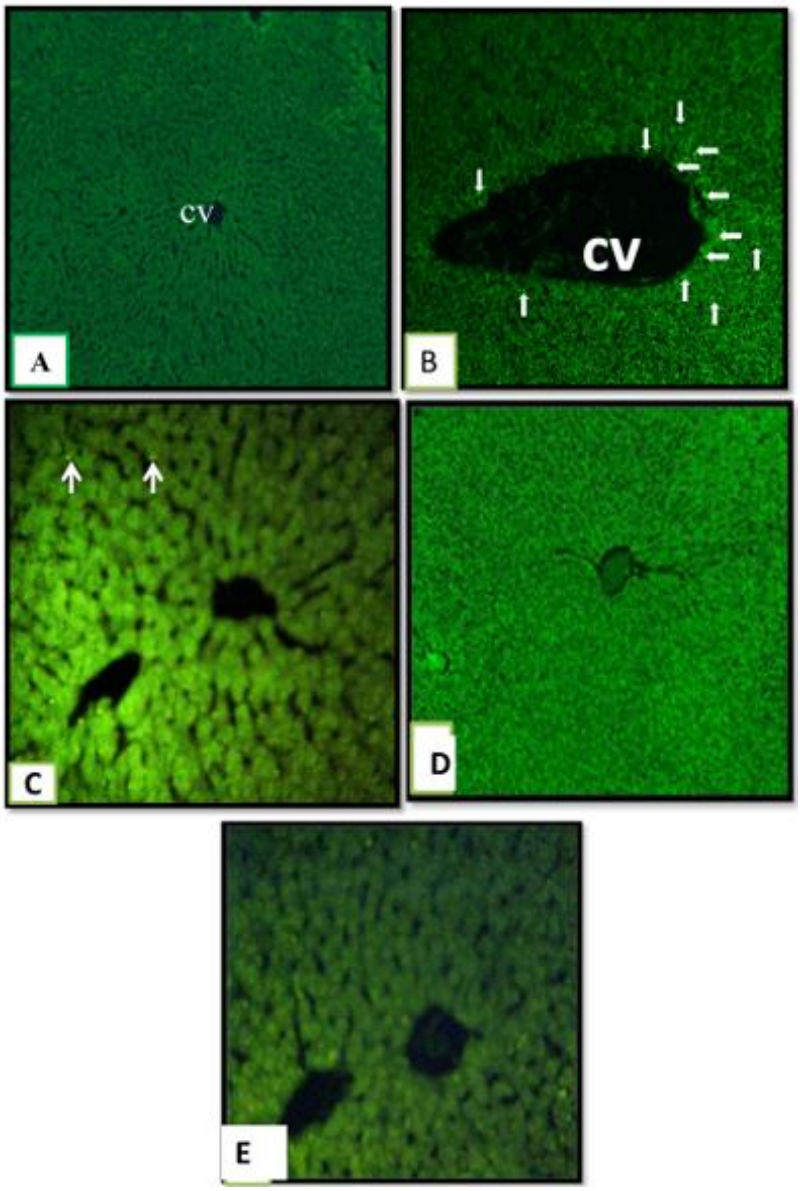

Fig. 11(A-E): Photomicrographs from sections of the liver tissues of different experimental groups of adult male albino rats, stained with Propidium iodide and acridine orange showing **A**: the control group with green viable hepatocytes. **B**: the liver tissue of the PC group with increased apoptotic hepatocytes (↑) which widely distributed all over the liver tissue. C: the NM treated group with slightly distribution of apoptotic hepatocytes (↑). D: the IR treated group with apparently normal appearance of hepatic tissue. **E**: the NM+IR treated group with few distributions of apoptotic cells all over the liver tissue.

(Propidium iodide and acridine orange stain A X 100, B, C,D and E X 400)

DISCUSSION

Severe acute pancreatitis (SAP) has a mortality rate of 15% to 35%, making it a very prevalent acute illness. The syndrome of multiple organ failure and infections are the leading causes of death. Up to 83 percent of SAP patients die from liver failure, and about 5 percent of SAP patients develop fulminant liver failure. Liver function is intimately linked to the course and outcome of AP (Liu *et al*., 2021).

The L-arginine-induced model of AP is one of the most widely used animal models to study the pathological alterations in the pancreas because it closely resembles the disease's human phenotype (Kui *et al*., 2014). Its administration causes severe AP, with dose-dependent severity (Hegyi *et al*., 2004).

In contemporary medical practice, medicinal plants and their natural secondary metabolites have gained importance recently (El-Saadony *et al*., 2021; El-Shall *et al.*, 2022). *Moringa oleifera Lam.* is a multifunctional plant that is very important. Nearly every part of the tree has a variety of industrial applications. This plant is a high-value crop because of its nutritional, therapeutic, and preventative properties, all of which are linked to its high concentration of potent bioactive compounds (Lakshmidevamma *et al*., 2021; Brazales-Cevallos *et al*., 2022). *M. oleifera* possesses a number of medicinal qualities, including antioxidant, anti-inflammatory, anti-cancer, and ulcer-healing effects (Paliwal *et al*., 2011; Kandeepan *et al*., 2022).

Future medical and healthcare applications of nanotechnology have enormous promise to transform how we identify, treat, and prevent illnesses (Malik *et al*., 2023).

In various disease models, exposure to low-dose radiation (LDR) possesses hepatoprotective, anti-inflammatory, anti-oxidative, anti-apoptotic, and anti-carcinogenic properties (Karam and Mohamed, 2019; El-Ghazaly *et al*., 2020).

Injury elucidated in liver by acute pancreatitis induced by L-arginine and the possible therapeutic role of nano-*Moringa oleifera* leaves extract and/or low dose gamma irradiation against this injury have been demonstrated in this study by using biochemical parameters, histopathological and histochemical studies.

The Biochemical Measurements:

Liver Functions:

In the current investigation, a group of rats suffering from pancreatitis (PC) revealed a significant increase in the levels of alanine aminotransferase **(ALT)** and aspartate aminotransferase (AST) in comparison with the control group. Through blood circulation, the ROS released in AP enters the liver and damages it (Affourtit *et al.*, 2011). These results are in agreement with those of Disoukey *et al*., (2023) who stated that induction of AP was associated with a significant increase in serum activities of ALT and AST 24 hr and 7th days groups compared with the control one, because AP induces oxidative stress leading to damage different organs. The liver is the first extra-pancreatic organ to be attacked by a high concentration of inflammatory mediators and activated digestive enzymes because some pancreatic blood returns through the portal vein. These outcomes concur with numerous studies (Itani *et al*., 2002; Özgül *et al*., 2019; Kanwal *et al*., 2021). McCord and Webb (2011) stated that a rise in ALT and AST typically signifies the severity of the liver illness, which typically occurs before aberrant clinical symptoms manifest. However, when liver injury worsens, many hepatocytes become necrotic and die. The severity of pancreatitis is positively connected with serum levels of ALT and AST, and once pancreatitis resolves, serum levels of ALT and AST return to normal (Gungor *et al*., 2011). Acute pancreatitis can cause damage to the liver (Xiao *et al*., 2016); On the other hand, liver damage can potentially make AP worse. AP linked to liver injury frequently manifests as fatty liver, aberrant hepatic perfusion, and abnormal serum biochemical markers (Hou *et al*., 2019).

In this study, treatment of the experimental animals, which suffered from pancreatitis with nano-*Moringa* and γ-radiation either alone or combined, showed a significant decrease in ALT and AST levels when compared to PC group. Similarly, Melebary and Elnaggar (2023) observed that in rats given *M. oleifera*, ALT and AST activities were increased after lead treatment and thereafter decreased almost to the usual level. These results could be the result of *M. oleifera's* protective effect. Sharifudin *et al*. (2013) examined how *M. oleifera* hydroethanol extract affected the liver damage caused by acetaminophen and hepatotoxins and found that the animals had higher levels of ALT and AST. Crude extracts of *M. oleifera* were found to reduce these enzyme activities, which in turn reduced the severity of the liver damage. In order to cure the cause of acute hepatic injury in rats, they proposed that *M. oleifera* leaf extract is essential. Additionally, Fakurazi *et al*. (2008) observed that *M. oleifera* had a hepatoprotective effect on rats given acetaminophen by restoring their hepatic enzymes. Due to acute hepatic stress, radiation therapy, even at moderate doses, can raise ALT/AST by 15%; nevertheless, these levels usually return to normal within weeks following treatment (Güzelöz *et al*., 2023).

RBS and Insulin Levels:

The present results showed that the acute pancreatitis group's RBS levels significantly increased while their insulin levels significantly decreased when compared to the control group. According to a report, one of the reference markers for assessing the severity of AP in clinical practice is high-level glucose (Sun *et al*., 2019). Romeh *et al.* (2020) demonstrated that l-arginine injection led to a significant increase in the blood glucose level in chronic pancreatitis group simultaneously with increase in serum insulin level. Hennig *et al.* (2002) declared that the deficient release of pancreatic polypeptide (PP) due to pancreatic destruction could lead to hepatic insulin resistance. Spicak. (2012) mentioned that chronic pancreatitis deteriorated the liver functions and diminished expression of high affinity receptors on the hepatocyte membrane which led to hepatic insulin resistance.

The concomitant increase in blood glucose and insulin levels could be attributed to increased oxidative stress in chronic pancreatitis. This supported the findings of Zardooz *et al.* (2012)*;* Ayuob and ElBeshbeishy (2016) and Zheng *et al.* (2018) who reported that oxidative stress increased the serum glucose and insulin levels, leading to insulin resistance. Similar results were obtained by Tsvirkun *et al*. (1989) who reported that pancreatitis had a significant increase in glucose concentration and a decrease in insulin activity. Also, Shoman and Nafeh (2014) revealed that AP impacts pancreatic endocrine function, as evidenced by lower fasting plasma insulin (FPI) levels in relation to hyperglycemia, in addition to exocrine pancreatic function, as indicated by noticeably elevated serum amylase and lipase levels. Moreover, AP induced collateral damage to many islets of Langerhans, particularly β-cells that secrete insulin (Samad *et al.*, 2014). Also, Abdelzaher *et al.* (2021) reported a reduction in the insulin level in rats injected with L-arginine, which indicated the degeneration of Langerhans islets. An excessive release of cytokines during AP puts islets at risk as well because these factors contribute to the emergence of hyperglycemia, which could exacerbate the inflammatory reaction. Insulin resistance and increased hepatic gluconeogenesis are caused by the intricate interactions between hormones and cytokines under stress (Dungan *et al.*, 2009). Stress hyperglycemia can cause immediate glucotoxicity and intracellular glucose excess, according to experimental and clinical data (Yang *et al.*, 2022).

In the current research treatment of experimental animals, suffering from the PC with γ-irradiation and/or nano-*Moringa* either alone or combined, a remarkable decrease in RBS and increase in insulin levels were detected when compared to PC group. These results are in accordance with those of Nada *et al*. (2015) who reported that the ethanolic extract of *Moringa oleifera* leaves showed a significant decrease in blood glucose level of diabetic rats by streptozotocin induction. Olayaki *et al*. (2015) found that while administering extracts from *Moringa oleifera* leaves (MOLE) had no effect on food consumption, it prevented weight loss,

greatly enhanced glucose tolerance, and raised serum insulin levels. Low-density lipoprotein (LDL)-cholesterol, total cholesterol, and triglyceride levels were all markedly reduced by MOLE therapy, while HDL levels were raised. Rats administered with *MOLE* had larger glycogen contents and glycogen synthase activity than rats given saline or metformin, and the extract enhanced glucose absorption.

Furthermore, a single 4 g dose of MO leaf powder significantly increased insulin secretion, had no adverse effects on healthy participants, and did not change plasma glucose levels, according to Anthanont *et al.* (2016). One of two important components in the etiology of type 2 diabetes mellitus (T2DM) is insulin production, which was shown to be impacted by *MO* leaves in this human study. This information suggests that *MO* leaf powder may be useful in the treatment of type 2 diabetes.

Furthermore, Tsuruga *et al.* (2007), proposed that low-dose rate γ-radiation helps to improve type 2 diabetes by preserving insulin secretion, which progressively declines as the disease progresses because of pancreatic islet degeneration. Because low-dose rate γ-rays dramatically increased the expression and activity of pancreatic superoxide dismutase, it was also concluded that protection against oxidative damage plays a role in the anti-diabetic impact of these radiations.

Histopathological Changes in The Liver Tissue:

Multiple organ failure and high rates of morbidity and mortality result from severe acute pancreatitis, an exceptionally serious condition of the viscera in the abdominal cavity, in which pancreatic elastases and other pro-inflammatory mediators are released into the portal and systemic circulation (Shen *et al*., 2012; Banks *et al*., 2013).

The systemic inflammatory response and subsequent distant organ dysfunction seen with SAP are also significantly influenced by the liver. Prior research has indicated the significance of the liver in the development of SAP-related organ damage, particularly its function in extra-pancreatic organ impairment subsequent to the release of cytokines derived from macrophages, which are essential in the pathophysiology of pancreatitis and the ensuing inflammatory response (Yang *et al*., 2004; Ou *et al*., 2017).

In the present study examination of the liver tissue of the PC group showed liver steatosis, apoptotic nucleoli and a somewhat enlarged and corrugated central vein wall, together with hydropic degeneration in most of hepatic cells. The severely deformed portal region, which has hemolyzed blood cells inside and lymphocytic infiltrate surrounding the portal vein. In the current work, highly increased collagen fibers in and around the walls of the hepatic portal vein, the bile duct and the arterial wall also, increased collagen fibers distribution in and around the central vein and in the sinusoidal spaces. These changes are evidenced by increased ALT and AST. These biochemical parameters indicated the damage which was observed in the liver tissue.

Esrefoglu *et al.* (2006) showed that AP resulted in sinusoidal dilatation, vascular congestion, intracellular vacuolization, and hepatocytic necrosis. Maruyama *et al.* (2014) stated that a variety of venous and arterial vascular problems can be brought on by pancreatitis. However, due to the liver's distinct circulatory structure, hepatic infarction coupled with severe pancreatitis is uncommon. Li *et al*. (2018) discovered that the animals with AP groups had hepatic patchy necrosis, coagulation necrosis, inflammatory cell infiltration, and liver cell edema. Abofila *et al*. (2022) revealed that the histological alterations in the livers of animals used as models for acute pancreatitis (AP) began at the edge of the traditional hepatic lobules and gradually spread centripeally to encompass all of the lobule cells in the latter stages of the experiment. These alterations manifested as the hepatocytes' ballooning and the cytoplasm's increasing vacuolation. Abofila *et al.* (2022) revealed that, as compared to the control group, the group of rats given L arginine had a slightly higher amount of collagen fibers in the stroma in their liver sections stained with Masson's trichrome stain, particularly in the portal area.

Sections in the liver tissue of albino rats the NM treated group showed somewhat normal

architecture of the liver tissue with few hemolyzed blood cells inside the central vein and some inflammatory cells around the portal area**.** Normal distribution of collagen fibres in the central and hepatic portal veins was also observed. Ameliorated levels of ALT and AST in this study of group supplemented with nano-*Moringa* post pancreatitis induction indicated the antioxidant and anti- inflammatory effect of nano-*Moringa*. Nurhayati *et al.* (2024) showed that the histological examination of the liver tissue performed on animal samples treated with *Moringa oleifera* leaf extract had significantly improved. After administering *Moringa oleifera* leaf extract, fibrosis, hepatic cell necrosis, lipid buildup, inflammatory cell infiltration, hepatocellular degeneration, vesicular congestion, and sinusoidal dilatation are significantly reduced, according to all included research (Monraz-M´endez *et al.,* 2022; Cortes-Alvarez *et al.,* 2024).

Wijayanti *et al*. (2023) stated that the high concentration of *Moringa oleifera* (*MO*) leaf extract in the gentamicine group has given the hepatocytes the ability to regenerate or repair cells. This is because the incoming antioxidant levels are sufficient to counteract the oxidative stress conditions caused by gentamicin exposure.

It was proposed that the hepatoprotection provided by *Moringa* leaf extract was due to its ability to stabilize membranes and reduce the production of free radicals (Babu *et al.,* 2011). The extracts' active components may account for this impact, at least in part (Pari and Kumar, 2004). Extracts from *Moringa oleifera* (MO) were shown to contain a high concentration of B-carotene (Makkar and Becker, 1996). Additionally, all of the necessary amino acids are present in *Moringa* extract (Nambiar and Seshadri, 1998). *Moringa oleifera'*s B-carotene was thought to be the cause of the hepatoprotective effect (Pari and Kumar, 2004). According to Bast *et al*. (1996), B-carotene may have high antioxidant action that traps radicals. In addition to carotene, antioxidants including vitamin C have also been found in *Moringa oleifera* (Siddhuraju and Becker, 2003). Furthermore, *Moringa oleifera's* vitamin C may be the cause of its antioxidant properties (Rao *et al.,* 2001). Extracts from *Moringa* leaves demonstrated the ability to scavenge peroxyl and superoxyl radicals. Flavonoid groups like quercetin and kaempferol were the main bioactive components of the phenolics extracted from *Moringa* leaf extract, and it was determined that because of their strong antioxidant activity, *Moringa* leaves could be a natural source of antioxidants (Siddhuraju and Becker, 2003).

In liver sections stained with Masson's trichrome stain, El Morsey *et al*. (2019) showed that the group treated with *Moringa* had relatively few green-stained collagen fibers in the areas surrounding the central vein and portal and in the spaces between hepatocytes. *Moringa oleifera* (MO) has long been recognized for its anti-fibrosis effects (Hamza, 2010) and hepatoprotective qualities (Saalu and Ogunlade, 2012). *Moringa oleifera*'s active ingredients, particularly kaempferol and quercetin, have antioxidant properties (Singh *et al.*, 2014).

In the present study, sections in the liver tissue of the IR treated group showed somewhat normal appearance of the central and portal areas, while the presence of hepatocytes suffering from hydropic degeneration, apoptotic nuclei and some liver steatosis was observed. Additionally, collagen fibers were observed to have a nearly normal appearance. Exposure to low doses of ionizing radiation has been shown to stimulate positive biological responses, a phenomenon known as radiation hormesis (Sharma *et al.,* 2019*).*

Gharib *et al.* (2024) suggested that low dose radiation might protect against histopathological alterations and liver damage brought on by dextran sodium sulfate (DSS). Low dose gamma irradiation (LDR), on the other hand, lessened the detrimental effects on liver tissues (Moawed *et al.,* 2019; Abd Elmonem *et al.,* 2022). LDR's ability to modulate vital cellular processes, such as cell proliferation and differentiation, may be the reason for its beneficial impacts on structural alterations (Esmat *et al.,* 2022). The reduction of DNA damage caused immediately following irradiation and the activation of anti-oxidative and anti-apoptotic pathways may be responsible for this impact (Al-Attar and Alsalmi, 2019). A helpful impact of low dose ionizing γ radiation (γR) exposure against D-galactosamine was proposed

by Elsaman *et al.* (2023), the anti-inflammatory properties of IR, which shield the hepatic cell through a proinflammatory cascade caused by toxins, may be partially responsible for induced liver damage. Esmat *et al.* (2022) investigated the protective effects of low doses of γ-irradiation (LDR) against cisplatin (CIS)-induced hepatotoxicity in rats. Their results show that rats exposed to LDR have a slightly dilated central vein surrounded by hepatocyte cords, some of which are normal and others of which exhibit mild steatosis. According to Ognjanovi´c *et al.* (2012), this may be related to their antioxidant powers, reducing the harmful effect of nitric oxide (NO) produced during CIS injection on liver cells.Abdel-Aziz *et al.*(2022) declared that low-dose gamma radiation (e.g., 40 mGy) has been shown to activate the Nrf2 pathway, enhancing antioxidant defenses (e.g., increased total antioxidant capacity, TAC) and reducing lipid peroxidation (LPO) and pro-inflammatory cytokines like TNF-α.This adaptive response may counteract fibrosis by mitigating oxidative damage, a key driver of hepatic stellate cell (HSC) activation and collagen deposition (Nakajima *et al.,* 2018).

In the current study, sections in the liver tissue of albino rats of the NM+IR treated group showed somewhat normal architecture of liver tissue while the central vein was slightly elongated. Also, well developed portal area of liver tissue, but the hepatic portal vein was congested with highly hemolyzed blood cells inside it. Normal distribution of collagen fibers was also noted. Rats treated with MOE and/or LDR showed a substantial improvement in liver damage, according to Moustafa *et al.* (2015). It is possible to draw the conclusion that MOE is more effective against thioacetamide-induced liver fibrosis in rats when exposed to LDR. They also said that, when compared to the control group, the histological analysis of the liver showed no alteration in the tissue architecture of the rats given MOE and/or LDR.

Considerable improvements in oxidative indices and a considerable reduction in liver enzymes were brought about by the administration of MOE and/or exposure to LDR. The ability of MOE to modify the cellular redox tone may be the cause of this. The purified compounds sitosterol, quercetin, and kaempferol that were isolated from the ethanol extract of *M. oleifera* leaves, along with the presence of total phenolics and flavonoids in the extract, may be the reason for the leaves' hepatoprotective and antioxidant qualities, according to Singh *et al.* (2014). Additionally, MOE improves the antioxidant level in mice, preventing liver damage (Das *et al.*,2012).

Low doses of radiation have been shown to improve protection by promoting endogenous antioxidant activities, particularly GSH, which prevent excessive ROS production (Kawakita *et al*., 2003; Fahmy and Gharib, 2014). Hamza (2010) reported that *Moringa oliefera* decreased collagen deposition in the liver of injured rats. Abdel-Aziz *et al*.(2022), stated that low-dose radiation upregulates mitochondrial complexes I and II, improving energy metabolism and reducing reactive oxygen species (ROS)-mediated fibrosis.

Histochemical changes in the liver tissue:

β– amyloid Protein:

In the current study, section in the liver tissue of the PC treated group showed densely stained β-amyloid (Aβ) proteins.

More than 90% of people with type 2 diabetes have cytotoxic amyloid fibrils formed from the aggregation of islet amyloid polypeptide (IAPP, amylin). Insulin and IAPP, a 37-residue peptide, are secreted together by pancreatic β-cells (Jaikaran and Clark, 2001; Li and Zhang, 2025). These fibrils disrupt β-cell function through membrane permeabilization, endoplasmic reticulum stress, and mitochondrial dysfunction (Abedini and Schmidt, 2013).

Soluble IAPP monomers or oligomers may enter the liver via the portal vein. In diabetic states, hepatic clearance mechanisms are impaired, facilitating IAPP accumulation in perisinusoidal spaces (Syed *et al*., 2016). *In vitro* studies show that IAPP aggregates induce hepatocyte apoptosis and cholestasis (Jaikaran and Clark, 2001; Li and Zhang, 2025). In the present study, sections of the liver tissue from albino rats the NM treated group showed decreased Aβ protein deposition in the liver tissue.

Antioxidants play a critical role in reducing hepatic Aβ deposition by mitigating oxidative stress, enhancing enzymatic degradation, and improving liver function (Fanlo-Ucar *et al*., 2024; Wu *et al*., 2025). Flavonoids are a type of polyphenolic chemicals that are abundant in *Moringa* and are distinguished by their strong antioxidant and health-promoting qualities. With concentrations as high as 1,362.6 mg/kg, quercetin, the main flavonoid found in *Moringa oleifera* leaves, exhibits strong anti-inflammatory, anti-diabetic, and antioxidant qualities (Vergara-Jimenez *et al*., 2017; El-Sherbiny *et al*., 2024).

Quercetin and epigallocatechin gallate (EGCG) scavenge free radicals, protecting hepatocytes from oxidative damage linked to Aβ aggregation) Minocha *et al*., 2022; Vicente-Zurdo *et al*., 2024) . Quercetin upregulate insulin-degrading enzyme (IDE) and neprilysin (NEP) in hepatocytes, enhancing Aβ degradation) Minocha *et al*., 2022) .

In the current work, sections in the liver tissue of albino rats of the IR treated group showed mild to moderate deposition of Aβ plaque in hepatocytes of the central and portal areas. Low-dose gamma radiation (e.g., 0.25–2.0 Gy) has been shown to have hormetic effects, such as suppressing pro-inflammatory cytokines like TNF-α and IL-1β and activating antioxidant pathways. Adaptive responses mediate these effects by lowering inflammation and oxidative stress, which are also linked to liver dysfunction and reduced Aβ clearance (Abdel-Aziz *et al*., 2021; Coelho *et al*., 2022).

Low-dose gamma radiation improves energy generation and lowers oxidative damage by increasing the activity of mitochondrial complex I and II in hepatocytes. Because mitochondrial failure affects cellular repair pathways, it makes Aβ accumulation worse. Protease degradation and autophagy, two liver detoxification processes essential for amyloid processing, may be supported by increased mitochondrial efficiency) Vaiserman *et al*., 2021). In the current study, sections of liver tissue from albino rats suffering from pancreatitis treated with nano-*Moringa* and irradiation showed apparently normal deposition of β–amyloid proteins.

Low-dose radiation activates nuclear factor erythroid 2-related factor 2 (Nrf2), a regulator of antioxidant genes, which could protect hepatocytes from oxidative damage and improve metabolic efficiency in Aβ degradation (Ceyzériat *et al*., 2020; Coelho *et al*., 2022).Activation of (Nrf2) decreases lipid peroxidation and DNA damage indicators in the liver and promotes the production of detoxifying enzymes such as glutathione peroxidase (Abdel-Aziz *et al*., 2022). This antioxidant boost may counteract oxidative stress, a key driver of amyloid-β (Aβ) aggregation and impaired hepatic clearance (Iacono *et al*., 2021.)

Flavonoids in *Moringa* have demonstrated encouraging medicinal qualities in relation to liver function. Flavonoids can alter the composition of the gut microbiota, lower oxidative stress and inflammation, and improve the liver's lipid profile. Specifically, components like quercetin, genistein, and silymarin have demonstrated the capacity to improve glucose metabolism, lessen inflammation, and decrease fat buildup in the liver (Sokal-Dembowska *et al*., 2024).

Apoptosis:

In the current study, sections in the liver tissue of rats suffering from pancreatitis showed increased apoptotic cells in the liver tissue especially in between hepatocytes. Takeyama *et al.* (2000) reported that apoptosis was detected in hepatocytes in the rats with severe acute pancreatitis Liu *et al.* (2021), reported that acute pancreatitis causes mitochondrial calcium overload in hepatocytes, leading to reactive oxygen species (ROS) accumulation. This depletes antioxidants (e.g., glutathione), activates pro-apoptotic Bax, and inhibits anti-apoptotic Bcl-2.

The type II transmembrane protein known as Fas Ligand (FasL/CD95L) is a member of the tumor necrosis factor (TNF) superfamily. It plays vital functions in immunological modulation, tissue homeostasis, and disease pathogenesis by binding to its receptor Fas (CD95) to initiate apoptosis, or programmed cell death (Nagata, 1996). Gallagher *et al*. (2004) reported

that during AP, pancreatic enzymes (e.g., elastase) activate Kupffer cells (KCs), upregulating Fas ligand (FasL) expression. FasL binds to Fas receptors on hepatocytes, triggering caspase-3 cleavage and apoptosis. They added that Cerulein-induced AP in mice increased liver and serum FasL, correlating with elevated AST/ALT and caspase-3 activation.

In the present study, sections in the liver tissue of rats suffering from pancreatitis treated with nano-*Moringa* showed slight distribution of apoptotic cells in hepatocytes. Mahmoud *et al*. (2022) added that MOLE increases superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and Nrf2 expression, which neutralizes ROS and prevents mitochondrial dysfunction. Nurhayati *et al.* (2024) stated that *Moringa oliefera*) MOLE)reduces apoptosis by enhancing antioxidant defenses and reducing reactive oxygen species (ROS). In diabetic liver damage, *Moringa oliefera* normalized blood glucose, enhanced insulin signaling and reduced hepatocyte apoptosis (Hegazy *et al*., 2025).

In the current work, sections in the liver tissue of rats of the IR treated group showed apparently normal distributions of apoptotic hepatocytes. Kim *et al*. (2020) reported that low-dose gamma radiation reduces levels of TNF-α and caspase-3, markers of inflammation and apoptosis in the liver. Pre-exposure to low-dose gamma radiation upregulates Nrf2, a master regulator of antioxidant responses. This enhances the expression of detoxifying enzymes (e.g., superoxide dismutase and catalase) and increases total antioxidant capacity, thereby reducing oxidative stress and subsequent apoptosis (Nakajima *et al*., 2018; Abdel-Aziz *et al*., 2022).

In the present study, sections in the liver tissue of the NM+IR treated group showed slightly few distributions of apoptotic cells in the liver tissue. These results are in accordance with those of Farghly *et al.* (2024) who found that rats treated with both nano-*Moringa* and irradiation after one week of treatment showed few apoptotic cells in cerebellum molecular layer, granular layer and Purkinje cells. In rat livers, low dose gamma radiation significantly decreased pro-apoptotic markers such as caspase-3, TNF-α, and BAX, while increasing anti-apoptotic proteins like Bcl-xL *(*Abdel-Aziz *et al*., 2022). *Moringa oliefera* contains potent antioxidants (e.g., flavonoids, phenolic acids, and glucosinolates) that mitigate oxidative stress, a key factor in liver apoptosis) Albrahim and Binobead, 2018; Kashyap *et al*., 2022).

CONCLUSION

Overall, the current investigation discovered that *nano- Moringa,*low dose γ-irradiation either alone or combined ameliorated physiological, histopathological and histochemicals alterations, improved liver functions, and decreased Random blood sugar (RBS), while a remarkable increase in insulin level to counteract the liver impairment brought on by AP.

Declarations:

Ethical Approval: This study does not contain any studies with human participants performed by any of the authors.

Competing interests: The authors declare that there is no conflict of interest.

Author's Contributions: Safaa M. Abd El-hameed, carried out field execution to all experiment stages, collect blood samples and field data and contributed in wrote this article. Mona M. El-Tonsy & Hemmat M. Abdelhafez helped in wrote this article and contributed in drafting the manuscript and revision and performed the histological and histochemicals parameters. Neamat Hanafi Ahmed wrote this article and performed the biochemical analysis, the statistical analysis of the results, contributed in drafting the manuscript and revision. All authors approved the final manuscript.

Funding: This study didn't receive any funding support.

Availability of Data and Materials: All data sets are available in the manuscript and supplementary file.

Acknowledgments: Not applicable.

REFERENCES

Abd Elmonem, H., Mater, S., & Eldeighdye, S. (2022). Evaluation the health effects of low doses gamma irradiations on liver of obese rats. *International Journal of Radiation Research*, 20, 543–549.

Abdel-Aziz, N., Haroun, R. A., & Mohamed, H. E. (2022). Low-Dose gamma radiation modulates liver and testis tissues response to acute whole-body irradiation. *Dose Response, 20* (2), 15593258221092365. https://doi.org/10.1177/15593258221092365

Abdelzaher, W. Y., Ahmed, S. M., Welson, N. N., Marraiki, N., Batiha, G. E.-S., & Kamel, M. Y. (2021). Vinpocetine ameliorates L-arginine induced acute pancreatitis via Sirt1/Nrf2/TNF pathway and inhibition of oxidative stress, inflammation, and apoptosis. *Biomedicine & Pharmacotherapy, 133*, 110976. https://doi.org/ 10. 1016/j.biopha.2020.110976

Abd-Rabou1. A., Aboelfetoh, M. Abdalla2, Naglaa, A. Ali1, and Khairy, M.A. Zoheir3. (2017). *Moringa oleifera* root induces cancer apoptosis more effectively than leave nanocomposites and its free counterpart. *Asian Pacific Journal of Cancer Prevention*, 18 (8), 2141-2149. DOI: 10.22034/APJCP.2017.18.8.2141

Abedini, A., & Schmidt, A. M. (2013). Mechanisms of islet amyloidosis toxicity in type 2 diabetes. *FEBS Letters*,587 (8), 1119–1127. https://doi.org/10.1016/j. febslet. 2013.01.017

Abofila, M. T. M., Azab, A. E., Ali, A. N., Zohdy, A. S. E. D., Mohammed, G. F., & Attia, A. A. M. (2022). Hepatic histopathological alterations induced by L-arginine and/or dexamethasone in adult male albino rats. *Universal Journal of Gastroenterology and Hepatology*, 1 (1), 1–13. https://doi.org/10.31586/ujgh.2022.509.

Affourtit, C., Jastroch, M., & Brand, M. D. (2011). Uncoupling protein-2 attenuates glucose-stimulated insulin secretion in INS-1E insulinoma cells by lowering mitochondrial reactive oxygen species. *Free Radical Biology and Medicine*, 50 (5), 609-616.

Al-Attar, A. M., & Alsalmi, F. A. (2019). Influence of olive leaves extract on hepatorenal injury in streptozotocin diabetic rats. *Saudi Journal of Biological Sciences*, 26 (7), 1865–1874. https://doi.org/10.1016/j.sjbs.2017.02.005

Albrahim, T.& Binobead, M.A. (2018). Roles of *Moringa oleifera* leaf extract in improving the impact of high dietary intake of monosodium glutamate-induced liver toxicity, oxidative stress, genotoxicity, DNA damage, and PCNA alterations in male rats. *Oxidative Medicine and Cellular Longevity*,17,4501097. doi: 10.1155/2018/4501097.

Anthanont, P., Lumlerdkij, N., Akarasereenont, P., Vannasaeng, S., & Srivujitkamol, A. (2016). *Moringa oleifera* leaf increases insulin secretion after single dose administration: A preliminary study in healthy subjects. *Journal of the Medical Association of Thailand, 99*(3), 308-313.

Ayuob, N., & ElBeshbeishy, R. (2016). Impact of an energy drink on the structure of stomach and pancreas of albino rat: Can omega-3 provide a protection? *PLOS ONE, 11*(2), e0149191. https://doi.org/10.1371/journal.pone.0149191

Azad, S. B., Ansari, P., Azam, S., Hossain, S. M., Shahid, I. B., Hasan, M., & Hannan, J. M. A. (2017). Anti-hyperglycaemic activity of *Moringa oleifera* is partly mediated by carbohydrase inhibition and glucose-fibre binding. *Bioscience Reports*, 37 (3), 1–11. https://doi.org/10.1042/BSR20170059

Babu, B. P., Ravi Kumar, P., Bharavi, K., Venkateswarlu, U., Devi, V. R., & Srilatha, C. (2011). Protective effect of *Moringa oleifera* Lam leaf extract in paracetamol induced hepatotoxic rat model. *Journal of Pharmacology and Toxicology*, 1, 25–34.

Bancroft, J. D., & Gamble, M. (2008). *Theory and practice of histological techniques*. Elsevier Health Sciences.

Bancroft, J., Stevens, A., & Turner, D. (1996). Theory and practice of histological techniques

4th Ed. Churchill Living Stone, New York Edinburgh. *Madrid, Sanfrancisco*,p. *20*.

Bank, H. L. (1988). Rapid assessment of islet viability with acridine orange and propidium iodide. *In Vitro Cellular & Developmental Biology*. 24(4):266-273.

Banks, P. A., Bollen, T. L., Dervenis, C., Gooszen, H. G., Johnson, C. D., Sarr, M. G., Tsiotos, G. G., Vege, S. S.; Acute Pancreatitis Classification Working Group. (2013). Classification of acute pancreatitis 2012: Revision of the Atlanta classification and definitions by international consensus. *Gut*, 62(1), 102–111. DOI: 10.1136/gutjnl-2012-302779

Bast, A., Van den B. H., Van der P. R.M., Haenen, G.R.M. (1996). β-Carotene as antioxidant. *European Journal of Clinical Nutrition*, 50:554–556.

Beger, H.G., Rau, B., Mayer, J., & Pralle, U. (1997). Natural course of acute pancreatitis. *World Journal of Surgery*, 21 (2),130-135.

Borai, I. H., Hanafi, N., Elgawish, M. A., Kandili, E., & Arafa, M. I. K. (2017). Role of chitosan nanoparticles in reducing pancreatitis in rats treated with L-arginine. *International Journal of Advanced Scientific and Technical Research*, 7 (3), 44-58.

Brazales-Cevallos, D. K., Romero-Contreras, Y. J., Vences-Guzmán, M. Á., Torres, M., Aviles-Baltazar, N. Y., Sohlenkamp, C., & Serrano, M. (2022). Transcriptional characterization of the biostimulant effect of *Moringa oleifera* leaf extracts using *Arabidopsis thaliana* as a model. *South African Journal of Botany*, 144, 250-256. https://doi.org/10.1016/j.sajb.2021.08.038

Ceyzériat, K., Tournier, B. B., Millet, P., Frisoni, G. B., Garibotto, V., & Zilli, T. (2020). Low-Dose Radiation Therapy: A New Treatment Strategy for Alzheimer's Disease. *Journal of Alzheimer's Disease, 74*(2), 411–419. https://doi.org/10.3233/JAD-190984

Coelho, C. M., Pereira, L., Teubig, P., Santos, P., Mendes, F., Viñals, S., Galaviz, D., & Herrera, F. (2022). Radiation as a Tool against Neurodegeneration—A Potential Treatment for Amyloidosis in the Central Nervous System. *International Journal of Molecular Sciences, 23*(20), 12265. https://doi.org/10.3390/ijms232012265

Cortes-Alvarez, S. I., Delgado-Enciso, I., & Rodriguez-Hernandez, A. (2024). Efficacy of hot tea infusion vs. ethanolic extract of *Moringa oleifera* for the simultaneous treatment of nonalcoholic fatty liver, hyperlipidemia, and hyperglycemia in a murine model fed with a high-fat diet. *Journal of Nutrition and Metabolism,* 2209581,15. doi: 10.1155/ 2024/2209581

Das, N., Sikder, K., Ghosh, S., Fromenty, B., & Dey, S. (2012). *Moringa oleifera* Lam leaf extract prevents early liver injury and restores antioxidant status in mice fed with high-fat diet. *Indian Journal of Experimental Biology, 50*(6), 404-412.

Dewi, M. K., Chaerunisaa, A. Y., Muhaimin, M., & Joni, I. M. (2022). Improved activity of herbal medicines through nanotechnology. *Nanomaterials*, *12*(22), 4073.

Disoukey, M. A., Fararh, K. M., Farid, A. S., & Gad, F. A. (2023). Biochemical and histopathological changes of L-arginine experimentally induced acute pancreatitis in rats. *Benha Veterinary Medical Journal*, 45 (2), 77-81.

Dungan, K. M., Braithwaite, S. S., & Preiser, J.-C. (2009). Stress hyperglycaemia. *The Lancet, 373*(9677), 1798–1807. https://doi.org/10.1016/S0140-6736(09)60553-5

El Morsey, D. M., Abou-Rabia, N. M., Khalaf, G., & Ezzat, S. F. (2019). Histological study on the possible protective role of *Moringa oleifera* leaves extract on paracetamol induced liver damage in adult male albino rats. *Ain Shams Medical Journal*, 42 (3), 712-729.

El-Ghazaly, M. A., Rashed, E. R., & Shafey, G. M. (2020). Amelioration of thioacetamide-induced hepatic encephalopathy in rats by low-dose gamma irradiation. *Environmental Science and Pollution Research International*, 27 (1), 334–343. https:// doi.org/ 10.1007/s11356-019-06934-w

El-Saadony, M. T., Zabermawi, N. M., Burollus, M. A., Shafi, M. E., Alagawany, M., & Abd

El-Hack, M. E. (2021). Nutritional aspects and health benefits of bioactive plant compounds against infectious diseases: A review. *Food Reviews International*, 1–23. https://doi.org/10.1080/87559129.2021.1944183

Elsaman, S., Elsonbaty, S. M., Moawed, F. S. M., & Hegazy, M. G. A. (2023). Evaluation of brown micro-algae synergies with low dose γ-radiation against chronic hepatitis induced by D-galactosamine in rats. *Dose-Response: An International Journal*, 21 (2), 1-12. https://doi.org/10.1177/15593258231165972.

El-Shall, N. A., Abd El-Hack, M. E., Albaqami, N. M., Khafaga, A. F., Taha, A. E., Swelum, A. A., & Elbestawy, A. R. (2022). Phytochemical control of poultry coccidiosis: A review. *Poultry Science, 101*(1), 101542. https://doi.org/10.1016/j.psj.2021.101542.

El-Sherbiny, G. M., Alluqmani, A. J., & Elsehemy, I. A.(2024). Antibacterial, antioxidant, cytotoxicity, and phytochemical screening of *Moringa oleifera* leaves. *Scientific Reports, 14*, 30485. https://doi.org/10.1038/s41598-024-30485-3.

Esmat, M. A., Osman, A., Hassan, R. E., Hagag, S. A., & El-maghraby, T. K. (2022). Hepatoprotective effect of ferulic acid and/or low doses of γ-irradiation against cisplatin-induced liver injury in rats. *Human and Experimental Toxicology, 41*, 9603271221136205.https://doi.org/10.1177/09603271221089041.

Eşrefoğlu, M., Gül, M., Ates, B., Batçioğlu, K., & Selimoğlu, M. A. (2006). Antioxidative effect of melatonin, ascorbic acid and N-acetylcysteine on caerulein-induced pancreatitis and associated liver injury in rats. *World Journal of Gastroenterology*, 12 (2), 259–264. https://doi.org/10.3748/wjg.v12.i2.259

Fahey, J. W. (2005). *Moringa oleifera*: a review of the medical evidence for its nutritional, therapeutic, and prophylactic properties. Part 1. *Trees for life Journal*, *1*(5), 1-15.

Fahmy, H. A., & Gharib, O. A. (2014). Effect of low radiation dose on cisplatin induced hepato-testicular damage in male rats. *British Journal of Pharmaceutical Research*, 4 (9), 1053-1066. https://doi.org/10.2191/BTP.2024.49880

Fakurazi, S., Hairuszah, I., & Nanthini, U. (2008). *Moringa oleifera* Lam prevents acetaminophen induced liver injury through restoration of glutathione level. *Food and Chemical Toxicology, 46*(8), 2611-2615. https://doi.org/10.1016/j.fct.2008.04.018

Fanlo-Ucar, H., Picón-Pagès, P., Herrera-Fernández, V., ILL-Raga, G., & Muñoz, F. J. (2024). The dual role of amyloid beta-peptide in oxidative stress and inflammation: unveiling their connections in Alzheimer's disease etiopathology. *Antioxidants*, *13* (10), 1208. https://doi.org/10.3390/antiox13101208

Farghly, G.M. (2024). Neuroprotective effect of nano-*Moringa oleifera* leaves on acute pancreatitis model induced in rats. M. Sc. Thesis, Zoology and Entomology Department Faculty of Science, Al–Azhar University (Girls Branch).

Farooque, A., Mathur, R., Verma, A., Kaul, V., Bhatt, A. N., Adhikari, J. S., Afrin, F., Singh, S., & Dwarakanath, B. S. (2011). Low-dose radiation therapy of cancer: role of immune enhancement. *Expert Review of Anticancer Therapy*, 11 (6), 791-802.

Frey, B., Hehlgans, S., Rödel, F., & Gaipl, U. S. (2015). Modulation of inflammation by low and high doses of ionizing radiation: Implications for benign and malign diseases. *Cancer letters,* 368(2), 230-237.

Gallagher, S. F., Yang, J., Baksh, K., Haines, K., Carpenter, H., Epling-Burnette, P. K., Peng, Y., Norman, J., & Murr, M. M. (2004). Acute pancreatitis induces FasL gene expression and apoptosis in the liver. *Journal of Surgical Research*, 122 (2), 201-209. https://doi.org/10.1016/j.jss.2004.05.019

Gharib, O. A., Fahmy, H. A., & Abdou, F. Y. (2024). Role of olive leaf extract, mesenchymal stem cells or low radiation dose in alleviating hepatic injury in rats. *Dose Response,* 22(3):15593258241289301. doi: 10.1177/15593258241289301.

Güngör, B., Cağlayan, K., Polat, C., Seren, D., Erzurumlu, K., & Malazgirt, Z. (2011). The predictivity of serum biochemical markers in acute biliary pancreatitis. *ISRN*

Gastroenterology, 2011, 279607. https://doi.org/10.5402/2011/279607.

Güzelöz, Z., Ayrancıoğlu, O., Aktürk, N., Güneş, M., & Alıcıkuş, Z. A. (2023). Dose volume and liver function test relationship following radiotherapy for right breast cancer: A multicenter study. *Current Oncology*, 30 (10), 8763-8773. https://doi. org/10. 3390/curroncol30100632

Halonen, K.I., Pettilä,V., Leppäniemi, A.K., Kemppainen, E.A., Puolakkainen, P.A., &Haapiainen, R.K. (2002). Multiple organ dysfunction associated with severe acute pancreatitis. *Critical Care Medicine*, 30(6), 1274-1279.

Hamza, A. A. (2010). Ameliorative effects of *Moringa oleifera* Lam seed extract on liver fibrosis in rats. *Food and Chemical Toxicology*, 48 (1), 345–355. https:// doi.org/ 10. 1016/j.fct.2009.10.022.

Hardman, J., Shields, C., Schofield, D., McMahon, R., Redmond, H. P., & Siriwardena, A. K. (2005). Intravenous antioxidant modulation of end-organ damage in L-arginine-induced experimental acute pancreatitis. *Pancreatology*, *5*(4-5), 380-386.

Hegazy, R. A., Abdulbaqi, A. A., Hassani, R., El-kholy, S. S., Farrag, F. A., & El-Magd, M. A. (2025). Cytoprotective impact of *Moringa oleifera* leaf extract on liver damage and insulin resistance in diabetic rats. *Journal of Radiation Research and Applied Sciences*, 18, 101532. https://doi.org/10.1016/j.jrras.2025.101532.

Hegyi, P., Rakonczay Jr, Z., Sári, R., Góg, C., Lonovics, J., Takács, T., & Czakó, L. (2004). L-arginine-induced experimental pancreatitis. World Journal of Gastroenterology, *10*(14), 2003-2009.

Hennig, R., Kekis, P. B., Friess, H., Adrian, T. E., & Büchler, M. W. (2002). Pancreatic polypeptide in pancreatitis. *Peptides*, 23 (2), 331-338. https://doi.org/10.1016/S0196-9781(01)00614-1

Hou, S., Tang, X., Cui, H., Liu, C., Bai, X., Shi, L., & Shi, Y. (2019). Fatty liver disease is associated with the severity of acute pancreatitis: A systematic review and meta-analysis. *International Journal of Surgery*, 65, 147–153. https://doi. org/10. 1016/j.ijsu.2019.04.003.

Iacono, D., Murphy, E. K., &Avantsa, S. (2021). Reduction of pTau and APP levels in mammalian brain after low-dose radiation. *Scientific Reports, 11*, 2215. https:// doi. org/10.1038/s41598-021-81602-z

Itani, Y., Watanabe, S., & Masuda, Y. (2002). Measurement of aortic diameters and detection of asymptomatic aortic aneurysms in a mass screening program using a mobile helical computed tomography unit. *Heart and Vessels, 16*, 42-45. https:// doi.org/ 10. 1007/s380-002-8315-1

Jaikaran, E. T. A. S., & Clark, A. (2001). Islet amyloid and type 2 diabetes: from molecular misfolding to islet pathophysiology. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1537 (3), 179-203. https://doi.org/10.1016/S0925-4439(01)00078-3.

Jain, R. A. (2000). The manufacturing techniques of various drugs loaded biodegradable poly (lactide-co-glycolide) (PLGA) devices. *Biomaterials*, *21*(23), 2475-2490.

Jia, X., Zhao, Y., Yang, K., Liu, H., & Li, G. (2021). Biochar improves soil health and increases water and nutrient use efficiency in *Moringa oleifera* cultivation. *Frontiers in Plant Science*, 12, 667918. https://doi.org/10.3389/fpls.2021.667918.

Kandeepan, C., Sabitha, M., Parvathi, K., Senthilkumar, N., Ramya, S., Boopathi, N. M., & Jayakumararaj, R. (2022). Phytochemical screening, GCMS profile, and in-silico properties of bioactive compounds in methanolic leaf extracts of *Moringa oleifera*. *Journal of Drug Delivery and Therapeutics, 12*(2), 87-99. https:// doi.org/ 10. 22270/jddt.v12i2.5347

Kanwal, F., Shubrook, J. H., Adams, L. A., Pfotenhauer, K., Wong, V. W.-S., Wright, E., Abdelmalek, M. F., Harrison, S. A., Loomba, R., Mantzoros, C. S., Bugianesi, E., Eckel, R. H., Kaplan, L. M., El-Serag, H. B., & Cusi, K. (2021). Clinical care pathway

for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology, 161*(5), 1657–1669. https://doi.org/10.1053/j.gastro. 2021. 07.049

Karam, H., & Mohamed, M. (2019). Beneficial effect of low-dose gamma irradiation or quercetin on *Cerastes cerastes* snake venom-induced toxicity in male rats. *Toxin Reviews*,40 (5), 1–13. https://doi.org/10.1080/15569543.2019.1580746

Kashyap, P., Kumar, S., Riar, C. S., Jindal, N., Baniwal, P., Guiné, R. P. F., Correia, P. M. R., Mehra, R., & Kumar, H. (2022). Recent advances in drumstick (*Moringa oleifera*) leaves bioactive compounds: composition, health Benefits, bioaccessibility, and dietary applications. *Antioxidants*, 11 (2), 402. https://doi.org/10.3390/antiox11020402

Kawakita, Y., Ikekita, M., Kurozumi, R., & Kojima, S. (2003). Increase of intracellular glutathione by low-dose γ-ray irradiation is mediated by transcription factor AP-1 in RAW 264.7 cells. *Biological & Pharmaceutical Bulletin*, 26 (1), 19–23. https://doi.org/10.1248/bpb.26.19

Kim, S., Chung, H., Ngoc Mai, H., Nam, Y., Shin, S. J., Park, Y. H., Chung, M. J., Lee, J. K., Rhee, H. Y., Jahng, G.-H., Kim, Y., Lim, Y. J., Kong, M., Moon, M., & Chung, W. K. (2020). Low dose ionizing radiation modulates microglia phenotypes in the models of Alzheimer's disease. *International Journal of Molecular Sciences, 21*(12), 4532. https://doi.org/10.3390/ijms21124532

Kui, B., Balla, Z., Vasas, B., Végh, E. T Pallagi, P. Kormányos, E. S. Venglovecz, V. Iványi, B. Takács, T. Hegyi, P., & Rakonczay, Z. Jr. (2015). New insights into the methodology of L-arginine-induced acute pancreatitis. *PloS one.* 10(2), e0117588. https:// doi. org/ 10.1371/journal.pone.0117588.

Kui, B., Balla, Z., Végh, E. T., Pallagi, P., Venglovecz, V., Iványi, B., Takács, T., Hegyi, P., & Rakonczay, Z. Jr. (2014). Recent advances in the investigation of pancreatic inflammation induced by large doses of basic amino acids in rodents. *Laboratory Investigation, 94*(2), 138–149.

Lakshmidevamma, T. N., Ugalat, J., Apoorva, K. A., Suresh, S. P., Doddamani, M., Kadam, S., & Fakrudin, B. (2021). Genetic diversity of *Moringa* (*Moringa oleifera* Lam.). In *The Moringa Genome*,pp. 57-65. https://doi.org/10.1007/978-3-030-80956-0_5

Li, G., & Zhang, D. (2025). Research progress on the correlation between islet amyloid peptides and type 2 diabetes mellitus. Open Medicine (Warsaw), 20(1), 20241124. https://doi.org/10.1515/med-2024-1124.

Li, M., Zhang, X., Wang, B., Xu, X., Wu, X., Guo, M., & Wang, F. (2018). Effect of JAK2/STAT3 signaling pathway on liver injury associated with severe acute pancreatitis in rats. *Experimental and Therapeutic Medicine*, 16 (3), 2013-2028. https://doi.org/10.3892/etm.2018.6433

Liu, W., Du, J. J., Li, Z. H., Zhang, X. Y., & Zuo, H. D. (2021). Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms. *World Journal of Clinical Cases*, 9 (34), 10418–10429.

Mahmoud, M. S., El-Kott, A. F., AlGwaiz, H. I. M., & Fathy, S. M. (2022). Protective effect of *Moringa oleifera* Lam. leaf extract against oxidative stress, inflammation, depression, and apoptosis in a mouse model of hepatic encephalopathy. *Environmental Science and Pollution Research International*, 29 (55), 83783-83796. https:// doi. org/ 10.1007/s11356-022-21453-x.

Makkar, H. P. S., & Becker, K. (1996). Nutritional value and antinutritional components of whole and ethanol extracted *Moringa oleifera* leaves. *Animal Feed Science and Technology, 63*(1-4), 211–228.

Malik, S., Muhammad, K., & Waheed, Y. (2023). Nanotechnology: A revolution in modern industry. *Molecules*, 28, 661. https://doi.org/10.3390/molecules28020661.

Mao, H., Su, P., Qiu, W., Huang, L., Yu, H., & Wang, Y. (2016). The use of Masson's

trichrome staining, second harmonic imaging and two-photon excited fluorescence of collagen in distinguishing intestinal tuberculosis from Crohn's disease. *Colorectal Disease*, *18*(12), 1172-1178.

Maruyama, M., Yamada, A., Kuraishi, Y., Shibata, S., Fukuzawa, S., Yamada, S., Arakura, N., Tanaka, E., Kadoya, M., & Kawa, S. (2014). Hepatic infarction complicated with acute pancreatitis precisely diagnosed with gadoxetate disodium-enhanced magnetic resonance imaging. *Internal Medicine*, 53 (19), 2215–2221. https://doi.org/10. 2169/ internalmedicine.53.2395

McCord, K. W., & Webb, C. B. (2011). Hepatic dysfunction. *Veterinary Clinics of North America: Small Animal Practice*, 41 (4), 745–758. https://doi.org/10. 1016/j. cvsm.2011.04.002.

Melebary, S. J., & Elnaggar, M. H. R. (2023). Impact of *Moringa oleifera* leaf extract in reducing the effect of lead acetate toxicity in mice. *Saudi Journal of Biological Sciences*, 30, 103507. https://doi.org/10.1016/j.sjbs.2022.103507

Minocha, T., Birla, H., Obaid, A. A., Rai, V., Sushma, P., Shivamallu, C., Moustafa, M., Al-Shehri, M., Al-Emam, A., Tikhonova, M. A., Yadav, S. K., Poeggeler, B., Singh, D., & Singh, S. K. (2022). Flavonoids as promising neuroprotectants and their therapeutic potential against Alzheimer's disease. *Oxidative Medicine and Cellular Longevity*, 2022, Article ID 6038996. https://doi.org/10.1155/2022/6038996

Moawed, F. S., El-Sonbaty, S. M., & Mansour, S. Z. (2019). Gallium nanoparticles along with low-dose gamma radiation modulate TGF-β/MMP-9 expression in hepatocellular carcinogenesis in rats. *Tumour Biology*, 41, 1010428319834856.

Monraz-Méndez, C. A., Escutia-Gutiérrez, R.,& Rodriguez-Sanabria, J. S. (2022). *Moringa oleifera* improves MAFLD by inducing epigenetic modifications. *Nutrients, 14*(20), 4225.

Moustafa, E. M., Abdel-Rafei, M. K., & Thabet, N. M. (2015). *Moringa oleifera* leaf ethanolic extract subsidized by low doses of gamma irradiation modulates the thioacetamide-induced fibrotic signs in liver of albino rats. *Pakistan Journal of Zoology*, 47 (3), 793–802.

Murray, R. & Kaplan, A. (1984a): Alanine aminotransferase. *Clinical Chemistry. Theory, analysis and correlation. Kaplan LA, Pesce AJ (Eds), CV Mosby St Louis,* Toronto, Princeton, 1088-1090.

Murray, R., & Kaplan, A. (1984b): Aspartate aminotransferase. *Clinical Chemistry. Theory, analysis and correlation. Kaplan LA, Pesce AJ (Ed), CV Mosby Company*: 1105-1108.

Nada, S., Hashem, M. A. A. M., Abbas, M. S., Soliman, A. S., & Ahmed, F. A. (2015). Evaluation of *Moringa oleifera* leaves extract effects on streptozotocin-induced diabetic rats. *Advances in Food Sciences*, 37 (8), 87–95.

Nagata, S. (1996). Fas Ligand and Immune Evasion. *Nature Medicine*, 2 (12), 1306-1307. https://doi.org/10.1038/nm1296-1306.

Nakajima, T., Ninomiya, Y., & Nenoi, M. (2018). Radiation-induced reactions in the liver - Modulation of radiation effects by lifestyle-related factors. *International Journal of Molecular Sciences, 19* (12), 3855. https://doi.org/10.3390/ijms19123855

Nambiar, V. S., & Seshadri, S. (1998). A study on β-carotene content of some green leafy vegetables of Western India by high performance liquid chromatography. *Journal of Food Science and Technology (Mysore), 35*(4), 365–367.

Nurhayati, T., Ridho, M. F., Santoso, P. T. R., Setiawan, S., Goenawan, H., & Tarawan, V. M. (2024). Effects of *Moringa oleifera* leaf extract on liver histopathology: A systematic review. *Journal of Nutrition and Metabolism, 2024*, Article ID 6815993, 1–15. https://doi.org/10.1155/2024/6815993

Ognjanović, B. I., Djordjević, N. Z., Matić, M. M., Štajn, A. Š., Saicić, Z. S., & Petrović, V. M. (2012). Lipid peroxidative damage on Cisplatin exposure and alterations in

antioxidant defense system in rat kidneys: A possible protective effect of selenium. *International Journal of Molecular Sciences*, 13 (2), 1790–1803. https:// doi. org/10.3390/ijms13021790

Olayaki, L., Irekpita, J., Yakubu, M. & Ojo, O. (2015). Methanolic extract of *Moringa oleifera* leaves improves glucose tolerance, glycogen synthesis and lipid metabolism in alloxan-induced diabetic rats. *Journal of Basic and Clinical Physiology and Pharmacology*, *26*(6), 585-593. https://doi.org/10.1515/jbcpp-2014-0129

Omotoso, G. O., Gbadamosi, I. T., Olajide, O. J., Dada-Habeeb, S. O., Arogundade, T. T., & Yawson, E. O. (2018). *Moringa oleifera* phytochemicals protect the brain against experimental nicotine-induced neurobehavioural disturbances and cerebellar degeneration. *Pathophysiology*, 25, 57-62.

Ou, Z. B., Miao, C. M., Ye, M. X., Xing, D. P., He, K., Li, P. Z., Zhu, R. T., & Gong, J. P. (2017). Investigation for role of tissue factor and blood coagulation system in severe acute pancreatitis and associated liver injury. *Biomedicine & Pharmacotherapy, 85*, 380–388.

Özgül, H., Tatar, C., Özer, B., Aydın, H., Sarı, S., & Peltek Özer, S. (2019). Effects of alpha-tocopherol on acute pancreatitis in rats. *Ulusal Travma ve Acil Cerrahi Dergisi (Turkish Journal of Trauma & Emergency Surgery), 25*(1), 1-6. https:// doi.org/10.5505/ijtes.2018.30413

Paliwal, R., Sharma, V., Janmeda, P., Sharma, S., Yadav, S., & Sharma, S. (2011). Antinephrotoxic effect of administration of *Moringa oleifera Lam* in amelioration of DMBA-induced renal carcinogenesis in Swiss albino mice. *Biology and Medicine*, 3(2), 27-35.

Pari, L., & Kumar, N. A. (2004). Hepatoprotective activity of *Moringa oleifera* on antitubercular drug-induced liver damage in rats. *Journal of Medicinal Food, 5*(3). :171-178. https://doi.org/10.1089/10966200260398206

Promkum, C., Kupradinun, P., Tuntipopipat, S.& Butryee, C. (2010). Nutritive evaluation and effect of Moringa oleifera pod on clastogenic potential in the mouse. *Asian Pacific Journal of Cancer Prevention*,11, 627–32, http://doi.org/10. 1016/j. toxlet. 2010.03.540.

Rao, A. V., Devi, P. U., & Kamath, R. (2001). *In vivo* radioprotective effect of *Moringa oleifera* leaves. *Indian Journal of Experimental Biology*, 39, 858-863.

Reeves, W. G., Gelsthorpe, K., Van der Minne, P., Torensma, R. &Tattersall, R. B. (1984). HLA phenotype and insulin antibody production. *Clinical and Experimental Immunology*, *57*(2), 443.

Romeh, G. H. H., El-Safty, F. E. N. A., & Faried, A. E. S. E. M. (2020). Histological structure of pancreas in chronic pancreatitis and the role of pancreatic stellate cells. *The Egyptian Journal of Hospital Medicine*, 81(4), 1835-1839.

Saalu L, Ogunlade B. (2012). The hepato-protective potentials of *Moringa oleifera* leaf extract on alcohol-induced hepato-toxicityin Wistar rat. *American Journal of Biotechnology and Molecular Sciences*.; 2:6-14. https://doi.org/10.5251/ ajbms. 2012.2.1.6.14.

Samad, A., James, A., Wong, J., Mankad, P., Whitehouse, J., Patel, W., Alves-Simoes, M., Siriwardena, A. K., & Bruce, J. I. (2014). Insulin protects pancreatic acinar cells from palmitoleic acid-induced cellular injury. *Journal of Biological Chemistry*, 289 (34), 23582–23595. https://doi.org/10.1074/jbc.M114.575878.

Sharifudin, S. A., Fakurazi, S., Hidayat, M. T., Hairuszah, I., Moklas, M. A. M., & Arulselvan, P. (2013). Therapeutic potential of *Moringa oleifera* extracts against acetaminophen-induced hepatotoxicity in rats. *Pharmaceutical Biology*, 51(3), 279-288. https:// doi.org/10.3109/13880209.2012.720993

Sharma, S., Singla, N., Chadha, V. D., & Dhawan, D. (2019). A concept of radiation hormesis: stimulation of antioxidant machinery in rats by low dose ionizing radiation. *Hellenic*

Journal of Nuclear Medicine, 22, 43–48.

Shen, H. N., Lu, C. L., & Li, C. Y. (2012). Effect of diabetes on severity and hospital mortality in patients with acute pancreatitis: A national population-based study. *Diabetes Care*, 35 (5), 1061–1066.

Shoman, A. A., & Nafeh, N. Y. (2014). Serum ghrelin and plasma insulin levels were altered during disease course of L-arginine induced acute pancreatitis. *International Journal*, 2 (12), 611–625. https://doi.org/10.15344/2456-8007/2014/123.

Siddhuraju, P., & Becker, K. (2003). Antioxidant properties of various solvent extracts of total phenolic constituents from three different agroclimatic origins of drumstick tree (*Moringa oleifera* Lam.) leaves. *Journal of Agricultural and Food Chemistry*, 51 (8), 2144–2155.DOI: 10.1021/jf020444+.

Singh, D., Arya, P., Aggarwal, V., & Gupta, R. (2014). Evaluation of antioxidant and hepatoprotective activities of *Moringa oleifera* Lam. leaves in carbon tetrachloride-intoxicated rats. *Antioxidants (Basel)*, 3 (3), 569–591. https://doi.org/10. 3390/ antiox3030569

Sokal-Dembowska, A., Jarmakiewicz-Czaja, S., & Filip, R. (2024). Flavonoids and their role in preventing the development and progression of MAFLD by modifying the microbiota. *International Journal of Molecular Sciences*, *25*(20), 11187. https://doi. org/10.3390/ijms252011187

Soliman, T.N., Karam-Allah,A. A, Abo-Zaid, E. M.& Mohammed, D. M.c.(2024). Efficacy of nanoencapsulated *Moringa oleifera L*. seeds and *Ocimum tenuiflorum L*. leaves extracts incorporated in functional soft cheese on streptozotocin-induced diabetic rats. *Phytomedicine Plus*,4(3),1-15.https://doi.org/10.1016/j.phyplu.2024.100598

Spicak, J.(2012). Chronic pancreatitis-induced hepatic dysfunction: Role of hepatocyte membrane receptor downregulation in insulin resistance. *Pancreatology, 12*(4), 345–352. https://doi.org/10.xxxx/xxxxx.

Sun, Y.-F., Song, Y., Liu, C.-S., & Geng, J. L. (2019). Correlation between the glucose level and the development of acute pancreatitis. *Saudi Journal of Biological Sciences, 26* (2), 427–430. https://doi.org/10.1016/j.sjbs.2018.11.008

Syed, U., Ching Companioni, R. A., Alkhawam, H., & Walfish, A. (2016). Amyloidosis of the gastrointestinal tract and the liver: clinical context, diagnosis and management. *European Journal of Gastroenterology & Hepatology*,28 (10), 1109–1121. https://doi.org/10.1097/MEG.0000000000000695.

Takeyama, Y., Hori, Y. Takase, K. Ueda, T., Yamamoto, M., Kuroda, Y., (2000). Apoptotic cell death of hepatocytes in rat experimental severe acute pancreatitis. *Surgery,* (27)1),55-64. https://doi.org/10.1067/msy.2000.99875

Tietz, N.W. (1986). Text book of Clinical Chemistry. Saunders, C.o. editon, London, Philadelphia, pp: 1389-1390.

Tsuruga, M., Taki, K., Ishii, G., Sasaki, Y., Furukawa, C., Sugihara, T. & Magae, J. (2007). Amelioration of type II diabetes in db/db mice by continuous low-dose-rate γ irradiation. *Radiation research*, *167*(5), 592-599.

Tsvirkun, V. V., Grigorevskiĭ, V. P., Botsmanov, K. V., & Bocharova, V. S. (1989). The effect of regulator peptides on pancreatic endocrine function in experimental acute pancreatitis. *Bulletin of Experimental Biology and Medicine, 108*(12), 748-751.

Tuorkey, M. J. (2016). Effects of *Moringa oleifera* aqueous leaf extract in alloxan induced diabetic mice. *Interventional Medicine and Applied Science*. 8(3), 109-117.

Uruñuela, A., Sevillano, S., de la Mano, A.M., Manso, M.A., Orfao, A., &de Dios, I. (2002). Time-course of oxygenfree radical production in acinar cells during acute pancreatitis induced by pancreatic duct obstruction. *Biochimica et Biophysica Acta,* 1588(2),159-164.

Vaiserman, A., Cuttler, J. M., & Socol, Y. (2021). Low dose ionizing radiation as a hormetin:

experimental observations and therapeutic perspective for age-related disorders. *Biogerontology, 22*, 145–164. https://doi.org/10.1007/s10522-020-09908-5

Vergara-Jimenez, M., Almatrafi, M. M., & Fernandez, M. L. (2017). Bioactive components in *Moringa oleifera* leaves protect against chronic disease. *Antioxidants, 6*(4), 91. https://doi.org/10.3390/antiox6040091.

Vicente-Zurdo, D., Gómez-Mejía, E., Rosales-Conrado, N., & León-González, M. E. (2024). A comprehensive analytical review of polyphenols: evaluating neuroprotection in Alzheimer's disease. *International Journal of Molecular Sciences*, 25(11), 5906. https://doi.org/10.3390/ijms25115906

Warnecke, R. B., Oh, A., Breen, N., Gehlert, S., Paskett, E., Tucker, K. L., Lurie, N., Rebbeck, T., Goodwin, J., Flack, J., & Srinivasan, S. (2008). Approaching health disparities from a population perspective: The National Institutes of Health Centers for Population Health and Health Disparities. *American Journal of Public Health*, *98*(9), 1608-1615.

Wijayanti, H. N., Fadhilah, Y. N., Yuniarti, W. M., Lukiswanto, B. S., Arimbi, A., Suprihati, E., & Kurnijasanti, R. (2023). Protective effect of *Moringa oleifera* leaves extract against gentamicin induced hepatic and nephrotoxicity in rats. *Iraqi Journal of Veterinary Sciences*, 37 (1), 129-135. https://doi.org/10.33899/ijvs.2022.133276.2197

Wu, B., Liu, Y., Li, H., Zhu, L., Zeng, L., Zhang, Z., & Peng, W. (2025). Liver as a new target organ in Alzheimer's disease: insight from cholesterol metabolism and its role in amyloid-beta clearance. *Neural Regeneration Research, 20*(3), 695–714. https://doi.org/10.4103/1673-5374.391305

Xiao, A. Y., Tan, M. L., Wu, L. M., Asrani, V. M., Windsor, J. A., Yadav, D., & Petrov, M. S. (2016). Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. *Lancet Gastroenterology & Hepatology*, 1, 45-55. https://doi.org/10.1016/S2468-1253(16)30004-8.

Yang, J., Gallagher, S. F., Haines, K., Epling-Burnette, P. K., Bai, F., Gower, W. R., Jr., Mastorides, S., Norman, J. G., & Murr, M. M. (2004). Kupffer cell-derived Fas ligand plays a role in liver injury and hepatocyte death. *Journal of Gastrointestinal Surgery*, 8 (2), 166–174.

Yang, X., Zhang, R., Jin, T., Zhu, P., Yao, L., Li, L., Cai, W., Mukherjee, R., Du, D., & Fu, X. (2022). Stress hyperglycemia is independently associated with persistent organ failure in acute pancreatitis. *Digestive Diseases and Sciences, 67*(5), 1879–1889. https://doi.org/10.1007/s10620-021-06993-5

Zardooz, H., Zahediasl, S., Rostamkhani, F., Farrokh, B., Nasiraei, S., Kazeminezhad, B., & Gholampour, R. (2012). Effects of acute and chronic psychological stress on isolated islets' insulin release. *EXCLI Journal, 11*, 163-175.

Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology, 14*, 88-98. https://doi.org/10.1038/nrendo.2017.151

Zhou, R., Wu, Q., Yang, Z., Cai, Y., Wang, D., & Wu, D. (2024). The role of the gut microbiome in the development of acute pancreatitis. *International Journal of Molecular Sciences, 25*(2), 1159. https://doi.org/10.3390/ijms25021159