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Research Article

Journal of Human Augmentation, Exoskeletons and Prosthetic Interfaces

Effect of Pomegranate (Molasses, White Peel and Red Peel) Extract on Healthy Liver and Hepatotoxicity Induced by Phenyl hydrazine in Male Rats

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Submitted: 08 January 2026 **Accepted:** 19 January 2026 **Published:** 26 January 2026

Citation: *Mohammed Ahmed Ammar. (2026). Effect of Pomegranate (Molasses, White Peel and Red Peel) Extract on Healthy Liver and Hepatotoxicity Induced by Phenyl hydrazine in Male Rats. J of Hum Augment Exoskelet Prosthet.Interfaces, 2(1), 01-10.*

Abstract

Pomegranates (Punica granatum L.) are said to provide various health advantages, according to accumulating research. The Liver tissue and antioxidant stress effect of pomegranate molasses, white and red peel extracts on male rats with phenylhydrazine (PHZ)-induced anaemia are highlighted in this article.

Phenylhydrazine Induced Anemia Resulted In

Decreasing of Direct Bilirubin, CAT, GPx, SOD, ALP, Accompanied by increasing of LDH, Total Bilirubin, Indirect Bilirubin, MDA, ALT, AST.

Regarding The Histopathology Study of Liver

PHZ exposed group showed a loss of the normal architecture with dilated, congested central vein and necrotic areas, dilated and congested blood sinusoids with pycnotic Kuppfer cells and hepatocytes with karyolytic nuclei. PHZ exposed group showed a severely-vacuolated hepatic environment with hydrobic degeneration apoptotic and degenerated hepatocytes, focal necrosis, dilated blood sinusoids with atrophied Kuppfer cells and dilated central vein.

Regarding of Molasses Pomegranate + PHZ; White Peel Pomegranate + PHZ and Red Peel Pomegranate + PHZ (Improvement Group)

There was an increase of Direct Bilirubin, CAT, GPx, SOD, ALP. Accompanied by decreasing of LDH, Total Bilirubin, Indirect Bilirubin, MDA, ALT, AST, ALP. Red peel pomegranate after PHZ (Red Peel + PHZ) exposed group showed a partial restoration of the normal histological pattern to a great extent with a central vein having a good profile and hepatocytes with healthy and intact nuclei. But some vacuolization and leucocytic infiltration is still evident. White peel pomegranate after PHZ (White Peel + PHZ) exposed group showed a regeneration in hepatocytes, a nearly normal blood sinusoids, but the central vein is still congested and surrounded with damaged cells. Molasses pomegranate after PHZ (Molasses + PHZ) exposed group showed most of hepatocytes and Kuppfer cells taking normal appearance but the hepatic environment is still vacuolated (V) and the central vein is congested. Conclusion: Molasses, White peel and Red peel Pomegranate have a strong antioxidant for protective liver tissue.

Keywords: Molasses Pomegranate, White Peel Pomegranate, Red Peel Pomegranate, Antioxidant Activities, Liver.

Introduction

Phenylhydrazine induces the destruction of red blood cells by oxidation stress and many joint changes at cellular levels resulting in hemolytic anemia. PHZ-induced toxic anemia offers a model for research into the pathogenesis of hemolytic anemia and the influence of anemia on other physiological processes or the course of associated diseases [1].

The effects of pomegranate molasses (PM) on cisplatin (CP)-induced oxidative stress in male albino rats. Results showed that the concentrations of liver function enzymes (ALP, ALT, AST) and serum total bilirubin were significantly ($P<0.05$) improved by PM treatment after their significant elevation by CP- injection [2].

Plant extracts could play an important role as an alternative to synthetic antioxidants in the oil industry. Pomegranate peel is considered a cheap, abundant, enriched source of functional components and a sustainable source for the extraction of polyphenolic and flavonoid compounds which have a remarkable antioxidant capacity [3].

Materials and Methods

Plant Material

Pomegranates were obtained from an indigenous market and peeled off then the seeds were squeezed to obtain the juice. 9 liters of pomegranate fresh juice were filtered to remove seeds and then subjected to lyophilization Freez dryer (Model SB4, England Chemlab, England) to give 770 gram of pomegranate molasses.

White Peel Pomegranate

Pomegranate white peel (fresh mesocarp) was cut into small piece, air dried for few days to give 235gm powder. The powdered drug was extracted with 80% aqueous ethyl alc (4×8L), the solvent was removed under reduced pressure to gives 155gm viscous residue and 27gm of viscous residue were added to 200ml distilled water.

Red Peel Pomegranate

Pomegranate red peel (leathery mesocarp) was cut into small piece, air dried for few days to give 202gm powder. The powdered drug was extracted with 80% aqueous ethyl alc (4×8L), the olvent was removed under reduced pressure to gives 155gm viscous residue then 17gm of viscous residue were added to 200ml distilled water.

Biological Study

Experimental animals

Rats used in this study were male Wistar 6-8 weeks old rats weighing 250-275 g (Zagazig University, Zagazig, Egypt). Each 4 rats were housed in clear polypropylene cages and provided free access to purified water and standard rodent pellets. Constant animal housing conditions were applied constituting alternating 12 hours light and dark, a temperature of 22 ± 3°C, relative humidity of 50-60 %, and adequate ventilation. The experimental design and animal handling procedures were as indicated by the guidelines of the Ethical Committee for Animal Handling- at Zagazig University (ZU-IACUC/2/F/26/2022).

Study Design

Animals were randomly divided into 8 experimental groups, each of 80 male rats.

Group 1 (C): control rats that received regular tap water and food pellets for 2 weeks.

Group 2 (C-M): control rats received molasses extract (40 mg/kg/day) for 2 weeks.

Group 3 (C-WPP): control rats received WPP extract (dose) for 2 weeks.

Group 4 (C-RPP): control rats received (dose) for 2 weeks.

Group 5 (PHZ): rats received i.p. injection of PHZ in saline in a dose 50 mg/kg/day at the last three days of the 2 weeks of the study.

Group 6 (PHZ-M): rats received molasses for 2 weeks and PHZ at the last three days of the 2 weeks.

Group 7 (PHZ-WPP): rats received WPP for 2 weeks and PHZ at the last three days of the 2 weeks.

Group 8 (PHZ-RPP): rats received RPP for 2 weeks and PHZ at the last three days of the 2 weeks.

Determination of Oxidative Stress Biomarkers

Serum malondialdehyde (MDA) level, catalase (CAT) activity and superoxide dismutase (SOD) activity was determined colorimetrically by using Biodiagnostic kits (Biodiagnostic®, Dokki, Giza, Egypt) according to the manufacturer's instructions. Glutathione peroxidase (GPx) activity was measured spectrophotometrically using the Glutathione Peroxidase Assay kit (Cayman Chemicals, Ann Arbor, MI, USA). Serum level of lactate dehydrogenase (LDH) as a biomarker for hemolytic anemia was assayed spectrophotometer using reagent kit purchased from Wiener laboratories S.A.I.C. ® (Rosario, Argentina) according to manufacturer instructions .

Assessment of Liver Function

Serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were assayed enzymatically using commercially available kits supplied by Biodiagnostic® (Dokki, Giza, Egypt). Serum total bilirubin and direct bilirubin were assayed by colorimetric methods using kits supplied by Bio Diagnostic Co., Egypt. Indirect bilirubin is calculated as follows: Indirect bilirubin = total bilirubin – direct bilirubin [4,5].

Histopathological Examination

Liver specimens that were fixed in 10% neutral buffered formalin were embedded in paraffin blocks. Paraffin-embedded tissue sections (5 µm thick) were cut, dewaxed in xylene, hydrated using graded ethanol, and stained with hematoxylin and eosin (H&E) dyes for histopathological examination. The slides were examined by light microscopy [6].

Drugs and Chemicals

The following drugs and chemicals were used in this study: ketamine (Sigma pharmaceutical industries, Menoufia, Egypt) and xylazine (Sigma-Aldrich, St. Louis, MO, USA) for rat's anesthesia [7].

Statistical Analysis

Values are expressed as mean ± standard error of the mean. Statistical comparisons were carried out using one-way ANOVA, followed by Tukey's Post hoc test using Prism 5® software (Graphpad, CA, USA). Probability levels less than 0.05 were considered statistically significant [8].

Results

Phenylhydrazine Induced Anemia Resulted in

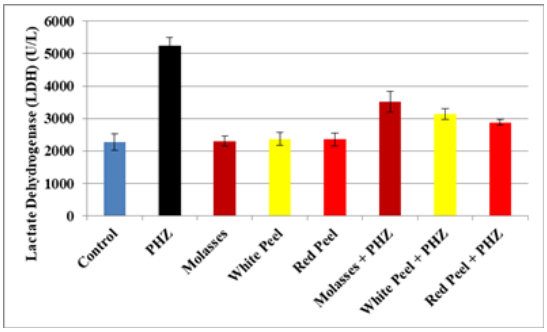
Decreasing of Direct Bilirubin, CAT, GPx, SOD, ALP, Accompanied by increasing of LDH, Total Bilirubin, Indirect Bilirubin, MDA, ALT, AST. As show in Tables (1, 2) and Figures (1, 2).

Regading of Molasses Pomegranate + PHZ,White Peel Pomegranate + PHZ and Red Peel Pomegranate + PHZ (Improvement Group)

There was an increase of Direct Bilirubin, CAT, GPx, SOD, ALP. Accompanied by decreasing of LDH, Total Bilirubin, Indirect Bilirubin, MDA, ALT, AST, ALP. As showing in Tables (1, 2) and Figures (1, 2).

Table 1: Effect on Antioxidant Enzymes Parameters

Groups	Lactate Dehydrogenase (LDH) (U/L)	Catalases (CAT) (U/L)	Glutathione Peroxidase (GPx) (mU/ml)	Superoxide Dismutase (SOD) (U/ml)	Malondialdehyde (MDA) (nmol/ml)
Control	2272±245.4	42.67±3.494	20.74±2.317	26.03±1.777	29.32±3.825
PHZ	5234±267.8	7.985±2.355	3.105±0.841	4.927±0.919	132.5±16.83
Molasses	2303±164.4	42.71±5.402	20.99±2.504	24.81±2.729	28.35±5.481
White Peel	2371±208.1	44.05±6.204	20.79±2.703	23.6±2.541	32.72±4.486
Red Peel	2350±207.8	47.17±4.282	21.9±2.839	23.48±2.167	26.03±7.96
Molasses+PHZ	3507.48±318.56	20.73±1.944	8.654±1.471	9.345±0.794	104.5±4.914
White Peel+PHZ	3127.58±164.3	30.22±1.692	12.25±1.438	13.79±0.871	79.25±6.319
Red Peel+PHZ	2878.56±83.9	36.01±4.316	16.32±2.736	19.62±2.091	55.52±8.918



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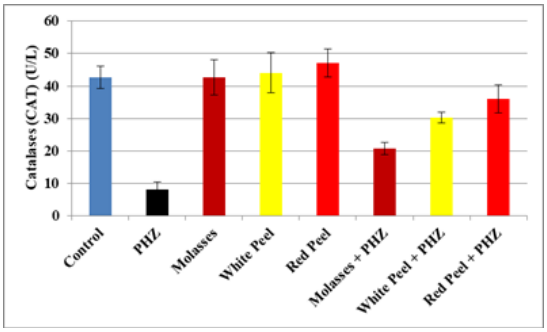

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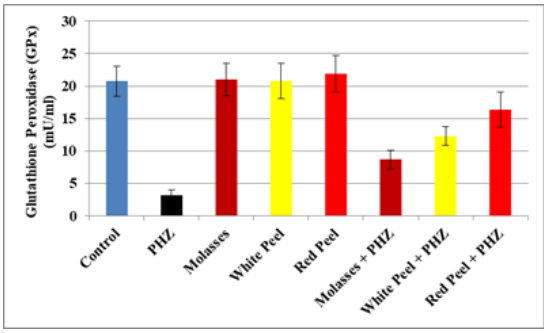

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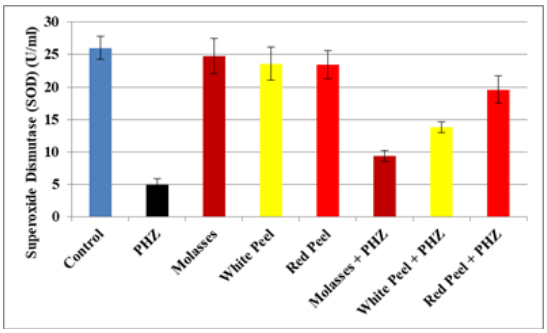

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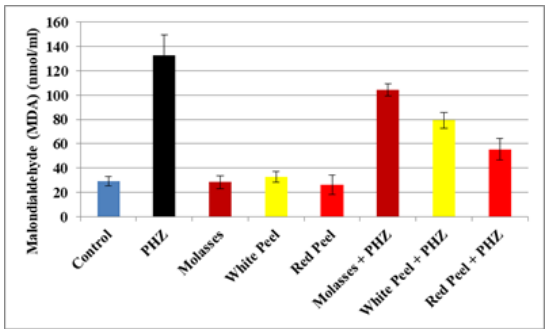

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Figure 1: Effect of oral administration of molasses extract, white peel pomegranate extract and red peel pomegranate extract to control or phenylhydrazine (PHZ) rats both at 25 mg/kg/day for 2 weeks on (A)Lactate Dehydrogenase (LDH) (U/L). (B)Catalases (CAT) (U/L). (C)Glutathione Peroxidase (GPx) (mU/ml).(D)Superoxide Dismutase (SOD) (U/ml). (E)Malondialdehyde (MDA) (nmol/ml).

Table 2: Effect on Liver Function Parameters

Groups	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	Indirect Bilirubin (mg/dl)	Alanine Transaminase (ALT) (U/L)	Aspartate Aminotransferase (AST) (U/L)	Alkaline Phosphatase (ALP) (U/L)
Control	0.78±0.062	0.3±0.031	0.47±0.065	11.72±0.92	22.58±1.568	59.17±10.26
PHZ	3.22±0.147	0.28±0.021	2.83±0.084	121.2±11.56	77.59±2.225	60.32±10.41
Molasses	0.77±0.084	0.26±0.064	0.51±0.06	12.23±2.7	24.01±1.563	62.48±15.01
White Peel	0.78±0.089	0.3±0.038	0.47±0.091	13±1.09	22.64±3.055	63.28±16.33
Red Peel	0.71±0.148	0.24±0.061	0.44±0.092	12.58±2.61	23.53±2.076	71.61±6.76
Molasses+PHZ	1.97±0.169	0.32±0.034	1.62±0.145	85.19±9.28	57.49±7.896	58.03±18.96
White Peel+PHZ	1.41±0.111	0.3±0.033	1.13±0.109	64.8±13.77	43.2±4.768	63.15±7.886
Red Peel+PHZ	0.99±0.12	0.29±0.035	0.69±0.127	45.8±9.74	29.53±4.424	69.32±8.28

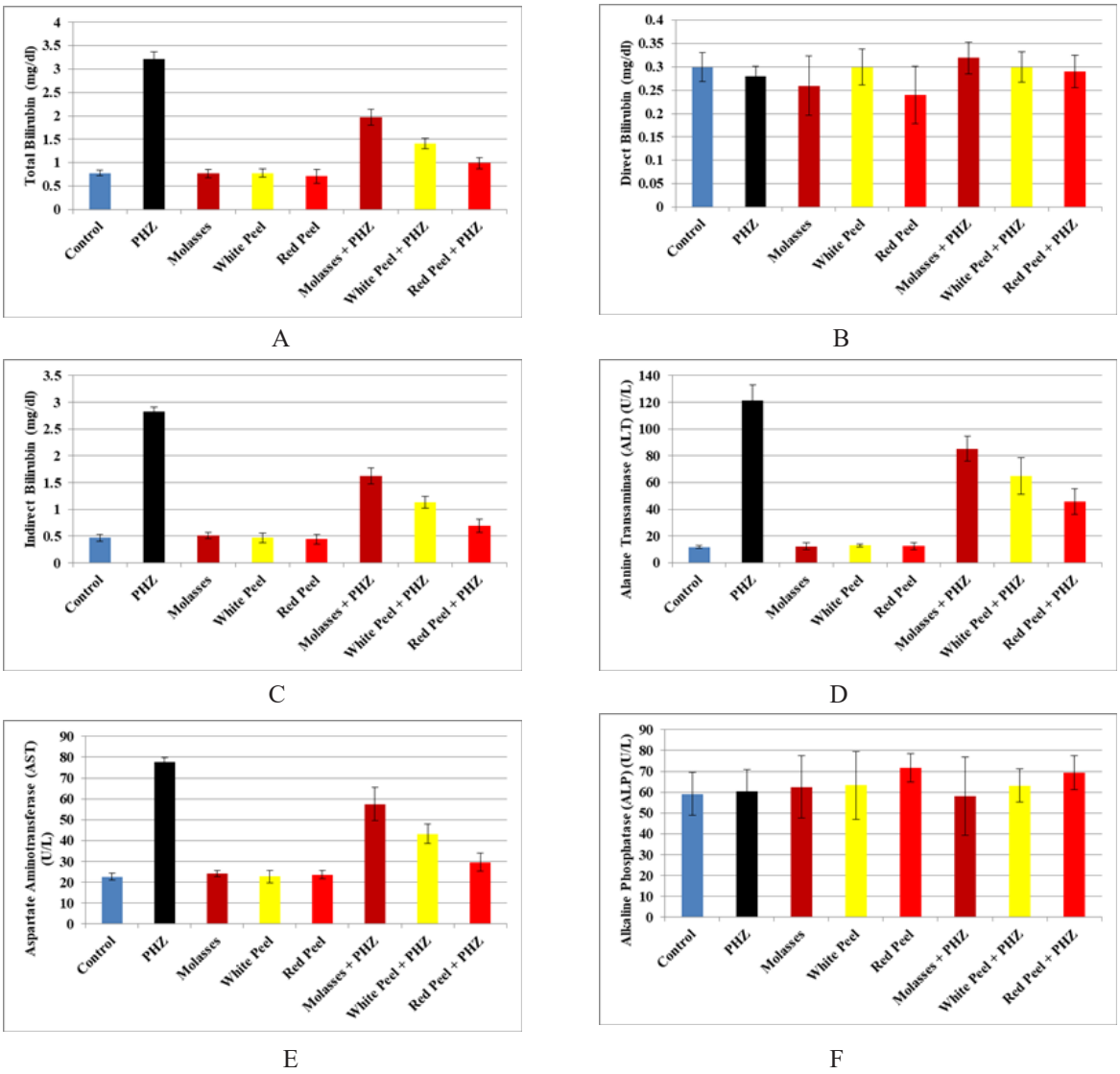

Figure 2: Effect of oral administration of molasses extract, white peel pomegranate extract and red peel pomegranate extract to control or phenylhydrazine (PHZ) rats both at 25 mg/kg/day for 2 weeks on (A)Total Bilirubin (mg/dl). (B)Direct Bilirubin (mg/dl). (C)Indirect Bilirubin (mg/dl). (D)Alanine Transaminase (ALT) (U/L). (E)Aspartate Aminotransferase (AST) (U/L). (F)Alkaline Phosphatase (ALP) (U/L).

Regarding the Histopathology Study of Liver

PHZ exposed group showed a loss of the normal architecture with dilated, congested central vein and necrotic areas, dilated and congested blood sinusoids with pycnotic Kuppfer cells and hepatocytes with karyolytic nuclei.PHZ exposed group showed a severely-vacuolated hepatic environment with hydrobic degeneration apoptotic and degenerated hepatocytes, focal necrosis, dilated blood sinusoids with atrophied Kuppfer cells and dilated central vein. Red peel pomegranate pure administered- rat exposed group showed a nearly normal histological architecture

with hepatocytes radiating from a central vein and having intact nuclei. White peel pomegranate pure administered- rat exposed group showed a hepatic parenchyma with normal histological pattern with normal hepatocytes and Kuppfer cells.

Molasses pomegranate pure administered- rat exposed group showed a hepatic cord with nearly normal histological pattern and mostly intact hepatocytes and central vein lined with pomegranate deposit. Red peel pomegranate after PHZ (Red Peel + PHZ) exposed group showed a partial restoration of the normal histological pattern to a great extent with a central vein having a good profile and hepatocytes with healthy and intact nuclei. But some vacuolization and leucocytic infiltration is still evident. White peel pomegranate after PHZ (White Peel + PHZ) exposed group showed a regeneration in hepatocytes, a nearly normal blood sinusoids, but the central vein is still congested and surrounded with damaged cells.Molasses pomegranate after PHZ (Molasses + PHZ) exposed group showed most of hepatocytes and Kuppfer cells taking normal appearance but the hepatic environment is still vacuolated (V) and the central vein is congested. As showing in Figure (3).

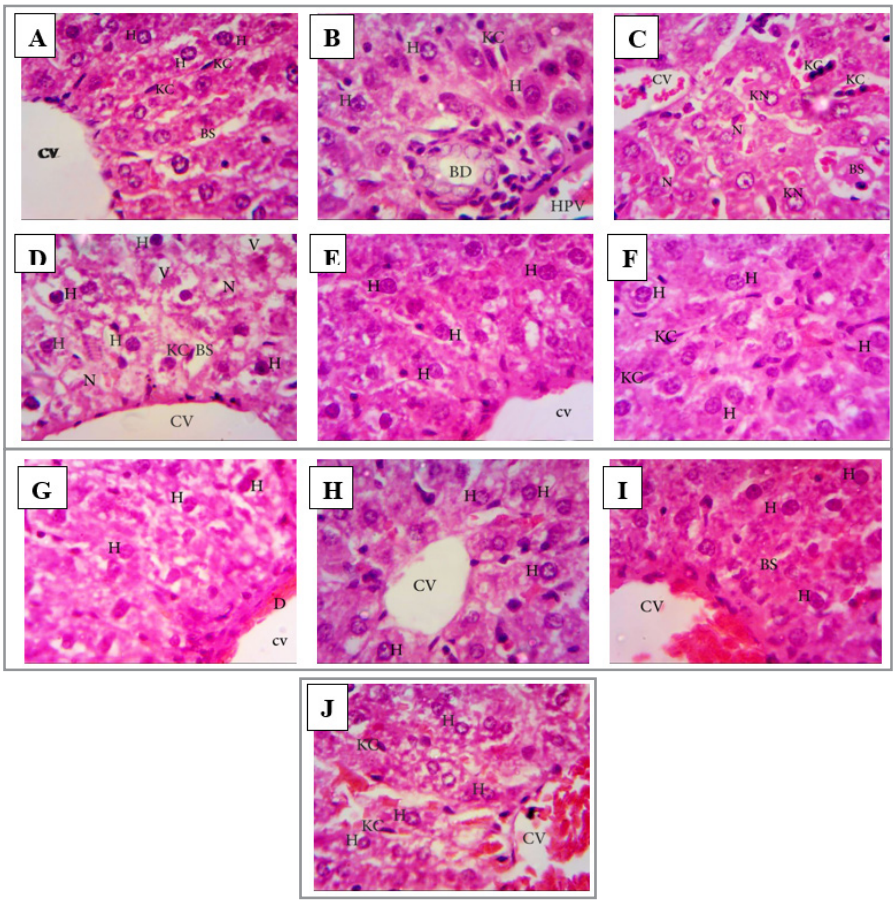

Figure 3: Photomicrographs (H & E) of Liver sections of (A):- Photomicrograph of liver section of control rat stained by H & E (X1000) showing a preserved architecture with central vein (CV), polygonal hepatocytes (H) arranged in hepatic strands with their rounded nuclei, Kuppfer cells (KC) and blood sinusoids (BS). (B): photomicrograph of liver section of control rat stained by H & E (X1000) showing a preserved architecture with hepatic portal vein (HPV), polygonal hepatocytes (H) with their rounded nuclei and prominent nucleoli, Kuppfer cells (KC) and bile ductile (BD) containing regular cuboidal cells. Figure (C): photomicrograph of liver section of a rat exposed to PHZ (1 mg) stained by H & E (X1000) showing a loss of the normal architecture with dilated, congested central vein (CV) and necrotic areas (N), dilated and congested blood sinusoids (BS) with pycnotic Kuppfer cells (KC) and hepatocytes with karyolytic nuclei (KN). (D): photomicrograph of liver section of a rat exposed to PHZ (1 mg) stained by H & E (X1000) showing a severely-vacuolated (V) hepatic environment with hydrobic degeneration apoptotic and degenerated hepatocytes (H), focal necrosis (N), dilated blood sinusoids (BS) with atrophied Kuppfer cells (KC) and dilated central vein (CV). (E): photomicrograph of liver section of a red peel pomegranate administered- rat stained by H & E (X1000) showing a nearly normal histological architecture with hepatocytes (H) radiating from a central vein (CV) and having intact nuclei. (F): photomicrograph of liver section of a white peel pomegranate administered- rat stained by H & E (X1000) showing a hepatic parenchyma with normal histological pattern with normal hepatocytes (H) and Kuppfer cells (KC). (G): photomicrograph of liver section of a molasses pomegranate administered- rat stained by H & E (X1000) showing a hepatic cord with nearly normal histological pattern and mostly intact hepatocytes (H) and central vein (CV) lined with pomegranate deposit (D). (H): photomicrograph of liver section of a rat treated with red peel pomegranate after PHZ (1 mg) (Red Peel + PHZ) stained by H & E (X1000) showing a partial restoration of the normal histological pattern to a great extent with a central vein (CV) having a good profile and hepatocytes with healthy and intact nuclei. But some vacuolization and leucocytic infiltration is still evident. (I): photomicrograph of liver section of a rat treated with white peel pomegranate after PHZ (1 mg) (White Peel + PHZ) stained by H & E (X1000) showing a regeneration in hepatocytes (H), a nearly normal blood sinusoids

(BS), but the central vein is still congested and surrounded with damaged cells (DC). (J): photomicrograph of liver section of a rat treated with molasses pomegranate after PHZ (1 mg) (Molasses + PHZ) stained by H & E(X1000) showing most of hepatocytes (H) and Kuppfer cells (KC) taking normal appearance but the hepatic environment is still vacuolated (V) and the central vein is congested.

Discussion

We found reticulocytes, bilirubin, LDH, fringe blood spread. G6PD and understanding with detailed that increment reticulocytes, bilirubin, LDH, decrease haptoglobin and fringe blood spread. G6PD insufficiency (diminished). We found molasses pomegranate, white peel, red peels are pharmacological pharmaceuticals and this can be in understanding with . Pomegranate is found to be related to different pharmacological exercises due to the nearness of a wide extend of bioactive compounds as portrayed in this audit [9, 10]. In line with our result in SOD levels are understanding with who expressed come about that, phenylhydrazine bunch: levels of RBC, Hb, Hct, Grass diminishes noteworthy and increment reticulocytes levels compared to control bunch. PHZ + TQ bunch: levels of RBC, Hb, Hct, Grass, reticulocytes expanded levels compared to PHZ bunch [11].

Our result in ALT, AST, bilirubin, MDA within the liver and kidney is in assention with. explored that, the inhibitory impacts of Derik pomegranate juice on CCl4-induced lipid peroxidation and its impact on plasma ALT, AST, ALB, and bilirubin. The organization of CCl4 essentially raised the serum level of the chemicals, such as ALT, AST, and bilirubin in rats. Pomegranate juice and ursodeoxycholic corrosive (UDCA) caused a diminish within the action of the ALT and AST. The level of egg whites (ALB) was moreover essentially decreased in CCl4-treated rats [12].

Phenylhydrazine actuates neonatal jaundice conditions since it increments unconjugated bilirubin levels without any noteworthy alter in liver work. Liver work was assessed by surveying serum ALT and AST since AST and ALT are touchy markers of liver cell harm . Within the display consider, had affirmed that phenylhydrazine did not increment AST and ALT levels within the serum of rats. Steady with the result, the liver histopathological perceptions moreover did not appear any hepatic harm due to phenylhydrazine organization. As hypothesized, typical action of the liver work chemicals and nonappearance of any liver harm after ABE organization shown the security profile of ABE. Presentation to oxidative push may result in over-the-top bilirubin generation that, when combined with decreased conjugation capacity, seriously worsens the potential for extraordinary hyperbilirubinemia [13-15].

In the show ponder we found in AST, ALT, LDH, SOD, GPx, CAT are assention with . In the display think about, we found in MCV, ALP, add up to bilirubin are in contradiction with [16]. In the display ponder, we found in RBCs, PCV, Hb, MCH, MCHC, Eosinophils, lymphocytes, EPO, total billirubin, indirect bilirubin is in understanding with . In the display consider we found in WBCs, platelet, press, neutrophils, monocytes are different with [17]. Within the show ponder, we found in AST, ALT, ALP are in assention with . In the show ponder, we found in MCH is different from detailed that a checked defensive impact of pomegranate seed oil (PSO) on the liver work that diminished AST, ALT, and ALP were moreover appeared [18-20].

Within the display consider, we found in LDH, MDA, SOD are in understanding with . detailed that drawn-out admissions of either pomegranate peel methanolic extricate (PPME) or pomegranate juice (PJ) may ensure against chlorpyrifos (CPF)-induced cardiotoxicity and reestablish cardiac capacities up to typical status. They concluded that PPME or PJ appears to offer a more prominent defensive impact against CPF-induced myocardial damage, likely through the synergism between their antioxidant and anti-apoptotic properties [21, 22].

Within the show think about, we found in masses pomegranate; white peel pomegranate, and red peel are great cancer prevention agents. Our comes about are in assention with . Reflected that both red peels and white peels had high antioxidant exercises and can be considered as a great cheap source of normal cancer prevention agents. Demonstrated the most noteworthy antioxidant action of pomegranate peel water extricate. The action of these squanders might not depend on the substance of phenols but depends on the quality and chemical structure of these phenols [23-24].

Considered that tactile assessment of pomegranate beverage indicated that the concentration of 1% of red peel refreshment was the foremost acknowledged in all traits having scores than white peel. It was cleared that the degree to which the panelists acknowledged the pomegranate peel refreshment, could be a great pointer of the plausibility of applying the generation of pomegranate red peel beverage [25].

Histopathology of Liver

In the current study, we discovered that the Pomegranate Molasses pure group has hepatic cords that are nearly normal. Pomegranate molasses (PM) has the strongest antioxidant properties in vitro when compared to pomegranate juice at a very low concentration, with polyphenols four times higher in molasses than in juice. According to, the levels of liver function parameters, specifically ALP, ALT, AST, and serum total bilirubin, were significantly higher in cisplatin-injected animals than in the control group. To assess liver dysfunction, the enzymatic activity of alanine (ALT) and aspartate (AST) aminotransferases, as well as alkaline phosphatase (ALP), was studied . When there is hepatopathy, hepatic enzymes are initially present in higher concentrations in the cytoplasm; these enzymes leak into the blood stream in proportion to the extent of liver damage. These findings could be attributed to pomegranate's antioxidant and antifibrotic properties, as well as its potential therapeutic value in protecting the liver from fibrosis and oxidative injury via oxidative stress suppression . Pomegranate enhances or maintains the activity of hepatic enzymes such as catalase, superoxide dismutase (SOD), and peroxidase, in addition to antioxidant effects and scavenging reactive oxygen species (ROS) [26-28].

According to, the antioxidant level in pomegranate juice was higher than that in grape juice. Green tea, cranberry, and orange According to, the level of serum MDA, which is a well-known marker of the degree of lipid peroxidation, was significantly higher in the model group. Hepatotoxicity not only causes lipid peroxidation but also inhibits the activities of tissue glutathione

peroxidase (GSH-px), glutathione s-transferase (GST), CAT, and SOD .On the other hand, demonstrated that PM significantly reduced MDA formation. In other words, the mechanism by which pomegranate molasses protects against lipid peroxidation may involve radical scavenging capability and the activation of antioxidant enzymes [29, 30].

We discovered that the PHZ group has a loss of normal architecture, with dilated, congested central veins and necrotic areas, dilated and congested blood sinusoids with pycnotic Kuppfer cells, and hepatocytes with karyolytic nuclei. Furthermore, PHZ have a severely vacuolated hepatic environment with hydrobic degeneration, apoptotic and degenerated hepatocytes, focal necrosis, dilated blood sinusoids with atrophied Kuppfer cells, and a dilated central vein. Furthermore, our findings in liver function (ALT, AST), LDH, and liver tissue are consistent with those of [31].

In this study, we discovered that pure Red peel pomegranate has a nearly normal histological architecture, with hepatocytes radiating from a central vein and intact nuclei. Furthermore, our findings in liver function (ALT, AST), LDH, and liver tissue are consistent with those of [32]. In the current study, we discovered that the (Red Peel Pomegranate + PHZ) group has a significant partial restoration of the normal histological pattern, with a central vein with a good profile and hepatocytes with healthy and intact nuclei. However, some vacuolization and leucocytic infiltration remain visible. In addition, our results in liver function (ALT, AST), LDH, and liver tissue are in the normal range. We discovered that the White peel pomegranate group has a hepatic parenchyma with a normal histological pattern, including normal hepatocytes and Kuppfer cells. Furthermore, our findings in liver function (ALT, AST), LDH, and liver tissue are consistent with those of [33]. In the current study, we discovered that the (White Peel Pomegranate + PHZ) group has hepatocyte regeneration and nearly normal blood sinusoids, but the central vein is still congested and surrounded by damaged cells. Furthermore, our findings in liver function (ALT, AST), LDH, and liver tissue are consistent with those of [34].

The effects of continuous administration of pomegranate peel extract (PP) on experimentally induced liver fibrosis in rats. Serum aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alanine aminotransferase (ALT) levels were measured to assess liver function and tissue damage. The serum levels of AST, LDH, ALT, and cytokines, which were elevated in liver fibrosis models, were found to be significantly reduced and brought back to near-normal levels after PP treatment. Similarly, the increase in hepatic collagen levels was reduced, which improved the structure and functions of the liver [35].

In the current study, we discovered that Molasses Pomegranate, White Peel Pomegranate, and Red Peel Pomegranate contain ellagic acid, which can be used to treat Kidney and Liver problems. Our findings are consistent with [36]. Pomegranate peel contains a high concentration of phenolic compounds such as anthocyanins, ellagic acid glycosides, free ellagic acid, ellagitannins, punicalagin, punicalin, and gallotannins. Pomegranate peel exhibited strong antimicrobial, preservative, and antioxidant activity, as well as the ability to improve kidney and liver function. In this study, we discovered that the Red peel pomegranate pure group had a nearly normal histological architecture, with hepatocytes radiating from a central vein and intact nuclei. Our findings are consistent with those of [37].

On the other hand,, it was found that Red peel pomegranate pure group decreased LDH, Total Bilirubin, Indirect Bilirubin, ALT, AST and increased ALP, Direct Bilirubin. Our findings are consistent with those of we discovered that the White peel pomegranate group had a hepatic parenchyma with a normal histological pattern, including normal hepatocytes and Kuppfer cells. Our findings are consistent with those of .In the current study, we discovered that White peel pomegranate pure group decreased LDH, Total Bilirubin, Indirect Bilirubin, ALT, AST and increased ALP, Direct Bilirubin. Our findings are consistent with those of [38].

Pomegranate peel extract treatment reduced liver and kidney coefficients (liver weight/body) insignificantly when compared to the control saline group. When compared to the saline group, pomegranate peel extract significantly reduced serum triglycerides, cholesterol, LDL, alkaline phosphatase (ALP), aspoartate aminotransferase (AST), and alanine aminotransferase (ALT) levels while increasing serum HDL levels in high lipid diet fed rats. A histopathological study found that pomegranate peel extract significantly reduced histopathological damage to the liver, including fatty changes in the hepatocye and sinusoid dilation [39].

The PHZ-exposed group showed a loss of normal architecture with dilated, congested central vein and necrotic areas, dilated and congested blood sinusoids with pycnotic Kuppfer cells, and hepatocytes with karyolytic nuclei, according to the findings of the current study. Furthermore, the PHZ-exposed group demonstrated a severely vacuolated hepatic environment with hydrobic degeneration, apoptotic and degenerated hepatocytes, focal necrosis, dilated blood sinusoids with atrophied Kuppfer cells, and dilated central vein. Our findings are consistent with [40, 41].

We discovered that the Red peel pomegranate pure exposed group had nearly normal histological architecture, with hepatocytes radiating from a central vein and intact nuclei. Our findings are consistent with we discovered that the White peel pomegranate pure exposed group had a hepatic parenchyma with a normal histological pattern, including normal hepatocytes and Kuppfer cells. Our findings are consistent with.In the current study, we discovered that the Molasses pomegranate pure exposed group had hepatic cords with nearly normal histological pattern and mostly intact hepatocytes, as well as a central vein lined with pomegranate deposit. Our findings are consistent with.

In the current study, we discovered that the (Red Peel Pomegranate + PHZ) exposed group showed a significant partial restoration of the normal histological pattern, with a central vein with a good profile and hepatocytes with healthy and intact nuclei. However, some vacuolization and leucocytic infiltration remain visible. Our findings are consistent with those of. In the current study, we discovered that the (White Peel Pomegranate + PHZ) exposed group showed hepatocyte regeneration and nearly normal blood sinusoids, but the central vein remained congested and surrounded by damaged cells. Our findings are consistent with [42].

In the current study, we discovered that the (Molasses Pomegranate + PHZ) exposed group had the majority of hepatocytes and Kuppfer cells appear normal, but the hepatic environment was still vacuolated and the central vein was congested. Our findings are consistent with. Increased aminotransferase levels are caused by leakage from damaged hepatic cells and are used as markers of liver injury. Discovered that abnormal aminotransferase activity was observed in rats injected with carbon tetrachloride (CCl4) and was reduced by administration of pomegranate peel extract (EPP) and pomegranate seed extract (PSE) (EPS). These findings show that EPP and EPS can improve hepatic steatosis in rats without causing hepatotoxicity.

The hepatoprotective effects of EPP and EPS were further demonstrated by a significant improvement in histopathological examination. Hyaluronic acid (HA), laminin (LN), and procollagen type III (PC III) proteins are important biomarkers of hepatic fibrogenesis . The level of hydroxyproline in the liver is an important index that reflects the amount of collagen and can thus be used to determine the extent of fibrosis . As a result, HA, LN, PC III, and hydroxyproline are important indicators of liver fibrosis. Demonstrated that EPP and EPS could significantly reduce HA, LN, and PC III in serum as well as hydroxyproline content in the liver, implying that EPP may be beneficial. The PHZ-exposed group showed a loss of normal architecture with dilated, congested central vein and necrotic areas, dilated and congested blood sinusoids with pycnotic Kuppfer cells, and hepatocytes with karyolytic nuclei, according to the findings of the current study. Furthermore, the PHZ-exposed group demonstrated a severely vacuolated hepatic environment with hydrobic degeneration, apoptotic and degenerated hepatocytes, focal necrosis, dilated blood sinusoids with atrophied Kuppfer cells, and dilated central vein. Our findings are consistent with [43].

In the current study, we discovered that the Red peel pomegranate pure exposed group had nearly normal histological architecture, with hepatocytes radiating from the liver. In the current study, we discovered that the (Red Peel Pomegranate + PHZ) exposed group showed a significant partial restoration of the normal histological pattern, with a central vein with a good profile and hepatocytes with healthy and intact nuclei. However, some vacuolization and leucocytic infiltration remain visible. Our findings are consistent with . In the current study, we discovered that the (White Peel Pomegranate + PHZ) exposed group showed hepatocyte regeneration and nearly normal blood sinusoids, but the central vein remained congested and surrounded by damaged cells. Our findings are consistent with.

In the current study, we discovered that the (Molasses Pomegranate + PHZ) exposed group had the majority of hepatocytes and Kuppfer cells appear normal, but the hepatic environment was still vacuolated and the central vein was congested. Our findings are consistent with discovered that administering 1000 ppm of lead via drinking water for 5 weeks resulted in a significant increase in serum AST and ALT activities, which could be due to increased permeability of the cell membrane or damage to the cell membrane of hepatocytes caused by lead intoxication. The findings of are consistent with those of serum ALP activity increased significantly in the lead acetate-treated group when compared to the control group. This could be due to lead's hazard effect on the liver, kidney, and bone, which results in ALP liberation. The histopathological findings of lead acetate-intoxicated rats revealed severe vacuolar degeneration in hepatocytes as well as sinusoidal congestion in the liver. Focal hepatic necrosis occurs primarily in portal areas, with congested blood vessels among necrotic hepatocytes. These modifications were similar to those stated by reported that the liver of lead-treated rats showed degenerative changes and focal necrosis of hepatocytes, which was consistent with the findings of lead toxicity caused hepatocyte swelling, vacuolization, focal necrosis, pyknotic nuclei, and central vein dilation. Serum AST, ALT, and ALP levels in rats treated with pomegranate peel aqueous extract for 5 weeks increased significantly. This finding by was consistent with the findings of, who reported that repeated overdoses of pomegranate peel extract resulted in a significant increase in serum AST, ALT, and ALP. On the other hand, discovered that while pomegranate had no significant effects on ALT or AST, it did cause a decrease in alkaline phosphatase when administered in the form of juice or peel extracts. In this context, 5 weeks of administration of Punica granatum peel extract to healthy female albino rats revealed the presence of apoptotic cells in the hepatic parenchyma. Cloudy swelling with condensation of chromatin materials in the nuclei's periphery and uneven nuclear membranes were observed. Several studies on the genotoxicity of P [44-46].

Granatum were conducted, and it was discovered that in-vitro use of an aqueous extract of P. granatum peel resulted in apoptosis in human cells . The results of P. granatum peel extract tested on brine shrimp assay by, which is the recommended cutoff point to detect cytotoxic. discovered no significant differences in snails after using different extraction methods and different parts of the P. granatum plant. These findings could be attributed to the toxic effect of P. granatum extract's alkaloid content . When compared to the serum of rats intoxicated with lead, most biochemical parameters in the serum of rats treated with both lead and P. granatum aqueous extract showed significant improvement. The livers of rats treated for 5 weeks with both lead acetate and P. granatum peel aqueous extract showed hydropic degeneration, small focal necrotic areas with hydropic degeneration, blood vessel congestion, and mononuclear cell infiltration [47-52].

Conclusion

Molasses, White peel and Red peel Pomegranate have a strong antioxidant for protective liver tissue.

Declaration of Competing

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of Interest

The authors have declared that no conflict of interests exist.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors Contribution

MA performed the experiments, RA and NH prepared the manuscript. NS and SM revised the manuscript. All authors discussed the results and commented on the manuscript.

Ethics Approval Statement

The animal study was reviewed and approved by the experimental design and animal handling procedures as indicated by the guidelines of the Ethical Committee for Animal Handling at Zagazig University (ZU-IACUC/2/F/26/2022).

Acknowledgment

We acknowledge initial support from Professor Abeer EL-Bayoumy from Department of physiologt, Faculty of Medicine, Zagazig University.

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