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The effects of pomegranate juice consumption on the treatment of nonalcoholic fatty liver disease

Maryam Noori [1], **Azita Hekmatdoost** [1*]

[1] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*] **Corresponding author:** Azita Hekmatdoost, Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran. **Email:** a_hekmat2000@yahoo.com

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Abstract

Background: While it is well-known that pomegranate has beneficial effects on risk factors associated with nonalcoholic fatty liver disease (NAFLD), no study has evaluated its effects in treating this disease.

Objectives: The objective of this study was to assess the effects of regular pomegranate juice (PJ) consumption on the treatment of NAFLD using an experimental disease model.

Methods: Sprague-Dawley rats were fed a high-fat diet for seven weeks to induce NAFLD. Subsequently, they were treated with either the same high-fat diet (HF), or high-fat diet supplemented with 60±5 cc of PJ (HF+PJ), or a standard chow diet (control), or chow diet supplemented with 60±5 cc of PJ (control+PJ) ad libitum for four weeks. Serum levels of fasting glucose, triglycerides, cholesterol, liver enzymes, insulin, and hepatic pro-inflammatory gene expression were measured. Hepatic histology was assessed using H&E staining.

Results: Animals fed a high-fat diet showed significantly higher food intake and weight gain compared to other groups; however, animals on the high-fat diet supplemented with PJ did not consume significantly different amounts of food compared to the other groups. Animals on the standard chow diet or chow diet supplemented with PJ had significantly lower plasma levels of hepatic enzymes, lipid profiles, glycemic indices, hepatic TNF-α gene expression, and hepatic steatosis compared to those fed the HF diet.

Conclusion: Our findings suggest that regular consumption of PJ can mitigate the risk factors associated with NAFLD when combined with a healthy diet. Further studies utilizing various doses of PJ are recommended to determine if there is an optimal dosage that yields promising effects.

Keywords: Pomegranate, Nonalcoholic Fatty Liver Disease, Treatment, Body Weight, Experimental Model.

Introduction

With the increasing prevalence of obesity, Nonalcoholic Fatty Liver Disease (NAFLD) has become a rapidly growing health concern, making it the most common liver disease worldwide.[1] NAFLD is closely linked to metabolic syndrome characteristics such as hyperglycemia, central obesity, and dyslipidemia.[2] Therefore, the role of diet is crucial in both the development and treatment of NAFLD.[3] While recent studies have highlighted the beneficial effects of diet and certain dietary supplements in managing NAFLD, there is still no consensus on the optimal therapeutic approaches for this disease, leading to ongoing exploration of natural remedies.[3-10]

Pomegranate has been shown to possess anti-inflammatory, antioxidant, hypoglycemic, and hypolipidemic properties.[11-13] Additionally, research has indicated that pomegranate consumption can influence gut microbiota composition.[14] These combined properties make pomegranate a promising candidate for combating NAFLD and its associated risk factors.

Objectives

The aim of this study was to investigate the impact of orally administering pomegranate juice (PJ) on hepatic

and serum markers of NAFLD using an experimental disease model.

Methods

Animals and Diets

Twenty-four male Sprague-Dawley rats weighing 120-150 grams were obtained from the Pasteur Institute in Karaj, Iran. The rats were individually housed in wire bar-floor cages and allowed a one-week acclimatization period in a standard environment set at 22°C, 50% humidity, and 12-hour light/dark cycles with ad libitum access to food and water. Initially, all animals were fed a standard laboratory chow diet from the Pasteur Institute in Iran for the first week. Subsequently, they were switched to a high-fat, high-sugar diet for seven weeks to induce NAFLD.[15] A subset of animals was sacrificed to confirm the induction of NAFLD, as previously described.[16] Following the induction phase, a four-week treatment period was initiated. Body weights (BW) in grams were recorded upon arrival and every two weeks thereafter, while food intakes were monitored twice a week. During the treatment phase, the rats were randomly assigned to one of four groups: the first group received a standard chow diet (control group) with 10% of energy derived from fat, 30% from protein, and 60% from carbohydrates; the second group received a high-fat, high-sugar diet (HF group) with 59% of energy derived from fat, 30% from carbohydrates, and 11% from protein; the third group received the high-fat, high-sugar diet along with daily consumption of 60±5 cc of pomegranate juice (HF+PJ group) with energy distribution of 59% fat, 31% carbohydrates, and 10% protein; and the fourth group received the chow diet supplemented with pomegranate juice (control + PJ) with energy distribution of 10% fat, 62% carbohydrates, and 28% protein. All groups had ad libitum access to their respective diets. The pomegranate juice was provided by Sanich Company in Tehran, Iran, and analyzed using colorimetric assays. The phenolic content was determined using the Folin-Ciocalteau reagent with Gallic acid as a standard,[17] the total flavonoid content was measured by the aluminum chloride colorimetric assay using Catechin as a standard,[18] and the total antioxidant capacity (TAC) was assessed based on the inhibition percentage of ABTS compared to a bovine serum albumin (BSA) standard curve.[19] The nutritional composition of pomegranate juice per 100 ml included 195 mg of total polyphenols, 35 mg of total flavonoids, 0.7 mmol of TAC, 50 kcal of energy, 10 g of sugar, and 0.5 g of protein. The diets were prepared weekly, vacuum-packed (500 g), and stored at -20°C. Packs taken for use were thawed in the refrigerator at 4°C and offered daily at the beginning of the dark phase, with any remaining food weighed and removed after 48 hours.

After an eleven-week feeding period, the animals were euthanized in an overnight fasting state by exsanguination under light pentobarbital anesthesia. All animal procedures were conducted in accordance with the guidelines of the National Nutrition and Food Technology Research Institute (NNFTRI). The study protocol was approved by the NNFTRI ethics committee with ethics code NNFTRI 1393-568.

Tissue and Blood Preparation

Blood samples were collected in heparinized tubes, centrifuged at 3500 rpm for 15 minutes at 6°C to obtain plasma. Fasted plasma glucose levels were immediately measured, and the remaining samples were stored at -80°C for subsequent biochemical analysis. Following blood sampling, the livers were excised, washed with cold physiological saline (0.9%), and dried. One lobe of each liver tissue was preserved in a 10% buffered formalin solution for histopathological examination. Other liver samples (200 mg) were placed in a liquid nitrogen tank and stored at -80°C for gene expression evaluation.[20-23]

RNA Extraction and Quantitative RT-PCR

Total RNA was purified using RNeasy Plus Mini Kits (Qiagen) following the manufacturer's instructions, and cDNA was synthesized with Superscript II reverse transcriptase (Invitrogen). Quantitative real-time PCR was conducted using the Bio-Rad Laboratories MJ mini Opticon Real-Time PCR System with IQ SYBR Green Supermix (Bio-Rad).

The PCR mix included 2 µl of cDNA, 1 µl of the appropriate forward and reverse primers, and 2 µl of SYBR Green PCR Master mix in a total volume of 25 µl. The PCR protocol consisted of 50 cycles of denaturation at 94°C for 30 s, annealing at the melting temperature (Tm) for 30 s, and extension at 72°C for 60 s. Primer sequences, sources, and optimal PCR annealing temperatures for each target gene were as follows:

- TNF-a: sense (5'-ATGAGCACAGAAAGCATGATG-3'), antisense (5'-TACAGGCTTGTCACTCGAATT-3')
-TGF-b1: sense (5'-CACGATCATGTTGGACAACTGCTCC-3'), antisense (5'-CTTCAGCTCCACAGAGAAGAACTGC-3')
-GAPDH: sense (5'-TGAAGGTCGGAGTCAACGGATTTGGT-3'), antisense (5'-CATGTGGGCCATGAGGTCCACCAC-3')

Primer specificity was confirmed by agarose gel electrophoresis for product size and melt curve analysis for PCR product specificity.

Biochemical Assessments

Plasma concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured at 340 nm using optimized UV methods. Insulin concentrations were determined using a rat insulin radioimmunoassay kit at 4°C (Linco Research Inc, St. Charles, MO). Plasma glucose and triglycerides (TG) were measured calorimetrically, while gamma glutamyltransferase (GGT) and alkaline phosphatase (ALP) were assessed photometrically. Total cholesterol, HDL, and LDL cholesterol levels were enzymatically examined using a commercial kit (Parsazmoon, Iran).

Histopathology

Liver sections from different lobes were processed through ethyl alcohol and xylene series, embedded in paraffin blocks, stained with Hematoxylin Eosin and Masson's Trichome, and viewed under light microscopy with a Nikon E 200. The grading for hepatic steatosis was defined as follows: grade 0 indicated no fat present, grade 1 represented steatosis occupying less than 33% of the hepatic parenchyma, grade 2 corresponded to 34–66% involvement, and grade 3 indicated more than 66% of the hepatic parenchyma affected. In terms of inflammatory cell infiltration, the grading system is as follows: Grade 0 indicates no infiltration, Grade 1 signifies 1-2 foci per field, Grade 2 denotes 3-4 foci per field, and Grade 3 indicates more than 4 foci per field. For ballooning, the categorization includes minimal, mild, and marked levels.[23,24]

Statistical analysis

Results are presented as median (interquartile range) and analyzed using nonparametric tests including Mann Whitney, Kruskal Wallis, and chi-square tests. A significance level of $P<0.05$ was considered for all analyses, conducted using GraphPad Prism Software Version 5.00 (GraphPad Software, San Diego, CA) or SPSS 20.0 software (Chicago, IL, USA).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval (code: IR.RUMS.REC.1396.119) was obtained.

Results

Weight gain was measured and compared among the four groups at the beginning, second, and fourth weeks of the treatment phase [Figure 1]. Statistically significant differences in weight gain were observed among the four groups ($P<0.05$). Specifically, the HF group exhibited significantly higher weight gain compared to the other three groups ($P<0.05$). Additionally, the HF+PJ group showed greater weight gain than the control and control+PJ groups ($P<0.05$), while no other significant differences were observed among the groups.

Food intake among the different groups during the study is illustrated in Figure 2. The HF group had significantly higher food intake compared to the control and control+PJ groups ($p<0.05$), with no other significant differences noted in food intake among the groups.

Plasma levels of hepatic enzymes, glycemic parameters, and lipid profiles in the four groups at the end of the study are presented in Table 1. The HF group exhibited significantly higher plasma levels of AST ($P=0.05$), TG ($P=0.01$), glucose ($P=0.02$), cholesterol ($P=0.04$), and ALP ($P=0.004$) compared to the control group. Addition of PJ to the control group led to a decrease in ALT compared to the HF group ($P=0.02$). The control and control+PJ groups were similar, except for TG levels, which were lower in the control+PJ group compared to the control group ($P=0.02$). Adding PJ to the HF diet did not result in significant changes compared to the HF diet.

Hepatic TNF-α gene expression in different study groups is depicted in Figure 3. There was no significant decrease in hepatic TNF-α gene expression in the HF+PJ group compared to the HF group. Treatment with chow or chow+PJ significantly reduced hepatic TNF-α gene expression ($P<0.05$).

Table 2 and Figure 4 show that only hepatic steatosis decreased in chow-fed groups, with no significant differences observed among the four groups in other hepatologic indices (ballooning, lobular inflammation, and portal inflammation) after four weeks of treatment.

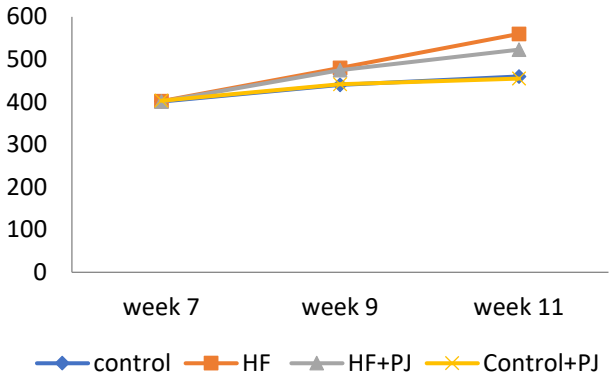

Figure 1. Animal weights in different groups during the study. Weight gain was statistically different among the four groups ($P < 0.05$). Weight gain was significantly higher in the HF group compared to the other three groups ($P < 0.05$). The HF + PJ group showed more weight gain than the Control and Control + PJ groups ($P < 0.05$). PJ: pomegranate juice

Table 1. Serum Levels of Hepatic Enzymes, Lipid, and Glycemic Profiles in Different Groups at the End of the Study

	HF group (median (IQR))	HF + PJ group (median (IQR))	Control group (median (IQR))	Control + PJ group (median (IQR))
ALT(IU/L)	58 (45-72) [b,c]	64 (48-78) [c]	50 (28-64) [a,b,c]	44(30-53) [a]
AST(IU/L)	35 (25-52) [b]	26(17-32) [a,b,c]	21 (15-33) [a,c]	25 (18-31) [c]
GGT (IU/L)	4.1 (3.6-4.9) [a]	3.1(2.1-4.2) [a]	3 (2.7-3.2) [a]	3.1 (2.5-3.4) [a]
Glucose (mg/dl)	195(162-217) [b]	165 (136-190) [a,b,c]	151(134-170) [a,c]	134 (120-151) [c]
Insulin (pmol/l)	467 (402-512)[a]	443 (392-506)[a]	189(176-219)[b]	180 (165-202)[b]
TG (mg/dl)	136 (117-146) [a]	125 (114-150) [a,b]	101 (88-121) [b,c]	82(71-92) [c]
Cholesterol (mg/dl)	127 (110-139)[a]	121 (116-137) [a]	110 (98-117) [b]	105 (96-119) [b]
HDL-c (mg/dl)	45 (35-53) [a]	37 (29-43) [a]	41 (36-52) [a]	50 (43-56) [a]
LDL-c (mg/dl)	56 (36-75) [a,b]	62 (51-81) [b]	45 (34-53) [a,b]	40 (33-52) [a]

*Kruskal–Wallis test, [a,b] In every row different scripts show significant difference.

Table 2. Histopathological Characteristics of HF, Control, HF + PJ, and Control + PJ Groups (n=6 in each group)

	Group	Stage	
		Low	High
Steatosis	Control	6 (100)	0
N (%)	HF	2(33.3%)	4 (66.7%)
	HF + PJ	3 (50)	3 (50)
	Control+PJ	6 (100)	0
Ballooning	Control	4(66.7)	2 (33.3)
N (%)	HF	1 (16.7)	5 (83.3)
	HF + PJ	4 (66.7)	2 (33.3)
	Control+PJ	4(66.7)	2 (33.3)
Lobular inflammation	Control	5 (83.3)	1 (16.7)
N (%)	HF	3 (50)	3 (50)
	HF + PJ	4 (66.7)	2 (33.3)
	Control+PJ	5 (83.3)	1 (16.7)
Portal inflammation	Control	4 (66.7)	2 (33.3)
N (%)	HF	3 (50)	3 (50)
	HF + PJ	3 (50)	3 (50)
	Control+PJ	5 (83.3)	1 (16.7)

Low = 0 or 1 stage, High = 2 or 3 stage, PJ: pomegranate juice, HF: high fat

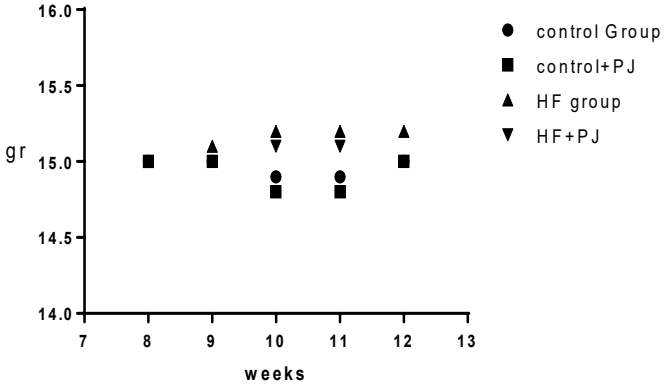

Figure 2. Food intakes in different groups during the study. Food intake did not differ significantly among the four groups. However, food intake was significantly higher in the HF group compared to the Control and Control + PJ groups ($P < 0.05$). No other significant differences were observed in food intake among the different groups.

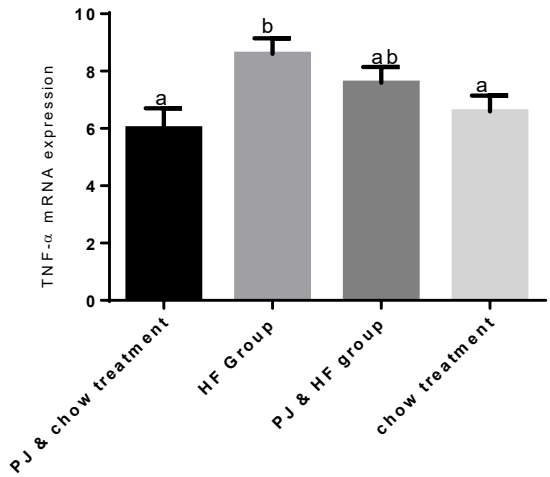

Figure 3. Hepatic TNF-α mRNA expression comparison among the four groups. Different scripts indicate a significant difference. HF: high fat diet; PJ: pomegranate juice

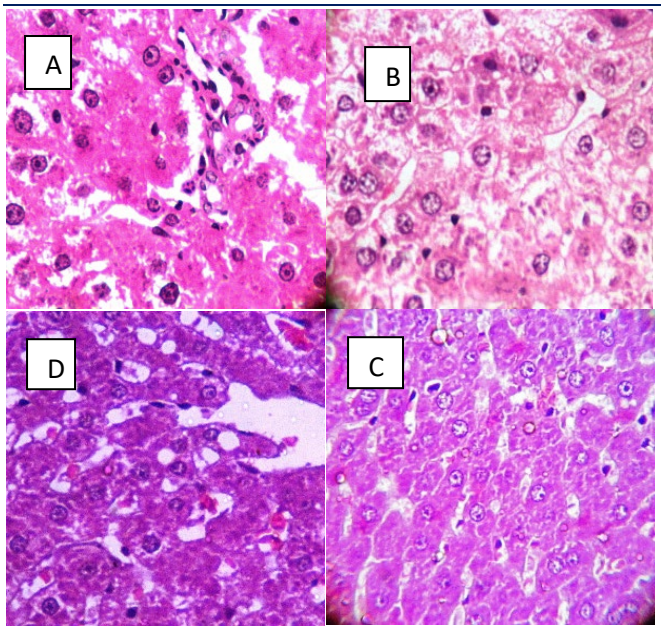

Figure 4. Hepatic pathology in rats: (A) Fed Control + PJ ×400, (B) Fed High-Fat, High-Sugar Diets Ad Libitum ×400, (C) Fed Chow Diet Ad Libitum ×400, and (D) Fed High-Fat, High-Sugar Diets + PJ ×400. Liver samples were stained with hematoxylin and eosin.

Discussion

Our study findings demonstrate that regular PJ consumption can mitigate the risk factors associated with NAFLD, particularly when combined with a healthy diet. Previous research has highlighted the beneficial effects of a healthy diet in improving NAFLD conditions.[3] Additionally, dietary supplements with antioxidant, anti-inflammatory, and insulin-sensitizing properties have shown promise in enhancing these effects. [25-27] While the antioxidant and anti-inflammatory properties of pomegranate have been documented in prior studies,[28-31] our results suggest that PJ alone may not significantly enhance the beneficial effects of a healthy diet on NAFLD. This discrepancy could be attributed to the potentially lower antioxidant properties of PJ compared to other supplements or the dosage of PJ utilized in our study, which may not have been sufficient to amplify the effects of a healthy diet. Therefore, further investigations utilizing varying PJ dosages are warranted to determine the optimal therapeutic dose.

While there is a lack of studies specifically evaluating the effects of PJ on NAFLD, existing research has explored the impact of PJ in other contexts characterized by high oxidative stress, such as diabetes and intense exercise.[29,30, 32-34] Despite variations in PJ dosages across these studies, all collectively suggest that PJ can effectively reduce oxidative stress, with lower dosages potentially yielding more pronounced benefits than higher doses. For instance, Fuster et al. reported that a daily consumption of 100cc of PJ was more effective than a 200cc dosage in reducing oxidative stress in endurance athletes.[32]

This study holds several strengths, including being the first to investigate the effects of PJ on NAFLD characteristics. By utilizing an animal model of the disease, we were able to evaluate hepatic histology and simulate the real-life condition of NAFLD in humans using a high-fat diet. Furthermore, the use of an animal model ensured that study animals consumed all provided PJ doses consistently.

However, this study also had limitations, such as the inability to assess various factors involved in NAFLD pathogenesis and explore different PJ dosages due to budget constraints.

Conclusions

The current findings suggest that regular consumption of PJ may help alleviate NAFLD risk factors when combined with a healthy diet. Further research employing diverse PJ dosages is recommended to identify an optimal dose that may offer promising effects in managing NAFLD.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Nonalcoholic Fatty Liver Disease: NAFLD;
Pomegranate juice: PJ; High-fat diet: HF;
Body weights: BW; Total antioxidant capacity: TAC;
Bovine serum albumin: BSA; Triglycerides: TG;
National Nutrition and Food Technology Research Institute: NNFTRI;
Alanine aminotransferase: ALT;
Aspartate aminotransferase: AST;
Gamma glutamyltransferase: GGT;
Alkaline phosphatase: ALP.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval (code: IR.KaUMS.REC.1396.119) was obtained (April 2023). The present study did not interfere with the process of diagnosis and treatment of patients and all participants signed an informed consent form.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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