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Original Article

The Effect of Whole Pomegranate Juice (*Punica Granatum*) on Nutritional and Immunological Status of Hospitalized Covid-19 Patients

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ABSTRACT

Background: Pomegranate juice may favorably affect nutritional and immunological status. This study set out to explore the nutritional-immunological effects of pomegranate juice on hospitalized COVID-19 patients.

Methods: We conducted this study as an exploratory randomized clinical trial recruiting 48 COVID-19 patients. Subjects were randomly allocated to intervention and placebo groups. Intervention participants received 500 mL of whole pomegranate juice as a complementary therapy, and control patients received the same amount of placebo for 2 weeks. Controlling nutritional status (CONUT), prognostic nutritional index (PNI) and albumin to globulin ratio (AGR) scores were measured at baseline and the end of the trial.

Results: Forty three patients completed the study. Cholesterol level significantly decreased ($p<0.0001$), and albumin ($p<0.0001$), total protein ($p=0.03$) and lymphocytes ($p=0.04$) levels significantly increased in the pomegranate juice group. However, the result remained insignificant regarding CONUT, PNI and AGR.

Conclusion: Our intervention showed that pomegranate juice had no significant effect on nutritional-immunological indicators, including CONUT, PNI and AGR scores. However, it did significantly reduced cholesterol level and increased albumin, total protein and lymphocyte levels. Further studies are needed to determine the long-term effects of pomegranate juice consumption on nutritional-immunological indicators and overall health outcomes.

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Introduction

SARS-COV-2 infected cases were initially detected in China in 2019. This highly contagious virus which belongs to coronaviruses, spread worldwide and has turned into a global pandemic (1). Like other areas of the world, Iran was not an exception and has been tremendously affected by the outbreak (2). The appearance of different viral variants with higher transmissibility and disease severity, despite the effectiveness of different vaccines, makes the situation even more complicated and leads the pandemic to be continued (3). Although some patients may be asymptomatic, others experience a wide range of disease severity and symptoms (4). As the COVID-19 pandemic continues to ravage much of the world, researchers are constantly on the lookout for ways to improve the immunological status of patients infected by the virus. One such avenue of exploration is the role of nutritional strategies in boosting the immunity of COVID-19 patients (5).

Researchers hypothesize that the immunomodulatory effects of bioactive food components could be particularly beneficial to patients with severe or critical symptoms. By improving their nutritional and immunological status, these patients may be more likely to mount an effective immune response against infections, reducing the severity and duration of their illness, and improving their chances of recovery (6). Nutrient-derived antigens which are recognized by enteroendocrine cells can interact with B and T cells and play a major role in activating Gut-Associated Lymphoid tissue (7). Consequently, immune-boosting nutrients and appropriate nutritional strategies are strongly advised (8).

The pomegranate (*Punica granatum*) is a fleshy berry fruit originating from the Middle East and belongs to the Punicaceae family (9). This fruit is a well-known source of anthocyanins, polyphenols, alkaloids, terpenoids, and antiviral components, including catechins, ellagitannins, punicalagin, vitamins, organic and phenolic acids in its entire parts (10-12). Besides inhibiting nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways and subsequently suppressing most potent inflammatory processes (13), pomegranate juice exerts its antiviral activity through attachment to the virion envelope and preventing virus binding to the host cells (14). Researchers also demonstrated that some components of pomegranate peel extract exhibit potential benefits against SARS-CoV-2 via inhibiting interaction between virus spikes and angiotensin-converting enzyme 2 (ACE2) (14, 15), which has been recognized as the first receptor for the SARS-CoV-2 (16).

Based on our assumption, pomegranate juice may favorably affect nutritional and immunological status. We have tested this theory by measuring controlling nutritional status (CONUT) score, prognostic nutritional index (PNI) and albumin to globulin ratio (AGR) before and after consumption of whole pomegranate juice in hospitalized covid-19 patients. The CONUT score is recognized as an independent risk factor for predicting clinical outcomes and mortality in COVID-19 subjects (17) and is mainly based on total cholesterol and albumin levels and total lymphocyte count (17) and is widely used for timely diagnosis and management of detrimental nutritional status (18). Polyphenols regulate the fecal excretion of cholesterol and bile acids through modulating cholesterol 7α-hydroxylase (CYP7A1), which is known as the rate-limiting step in cholesterol metabolism (19) and reduce the intestinal absorption of cholesterol (20). Hypoalbuminemia is a remarkable finding in these patients, who can adversely affect clinical outcomes. It appears mainly due to capillary leakage due to hypoxemia and oxidative stress (21). We hypothesized that certain polyphenolic compounds might alleviate hypoalbuminemia by improving vascular resistance and lymphatic drainage and this study was undertaken to determine the effect of whole pomegranate juice on nutritional and immunological status of hospitalized Covid-19 patients.

Materials and Methods

This study was conducted in February 2021 as a randomized, placebo-controlled, double-blind clinical trial. It involved patients with COVID-19 who were hospitalized in Shahid Jalil Hospital located in Yasuj which is situated in the Kohgiluyeh and Boyer Ahmad province in the southwest region of Iran. The study received approval from the Ethics Committee of Yasuj University of Medical Sciences. (IR.YUMS.REC.1399.181), and was recorded at the Iranian registry of clinical trials (IRCT20150711023153N2) on 28/02/2021. The study protocol was published in the Trial journal (22). After obtaining the informed written consent form and explanation of the study goals to the patients and their companions for the study, 48 individuals who were at least 18 years old and had received a COVID-19 diagnosis via RT-PCR were randomly assigned to participate. We also defined several exclusion criteria, including pregnancy or lactation, IgA<61 mg/dL.

Patients with any types of coagulopathies, severe congestive heart failure, or who have participated in any other clinical trials within the past month, were not eligible for enrollment in the present study. Other contraindications prescribed by the specialists, transfer out of intensive care unit (ICU), unwillingness to continue participation in the study, or any other relevant conditions may also disqualify a patient from participation. The patients were divided into two groups of pomegranate juice (PJ, n=24) and placebo (n=24), after which they were randomly assigned using a block random sampling method based on gender and age. This was done using random allocation software to ensure the allocation was blind to both the researchers and participants. The PJ group received 250 mL of natural whole pomegranate juice twice a day, and the control group received the same amount of placebo with the same color and taste as natural juice for 14 days. In the case of patients discharged earlier than scheduled, they were followed up after being discharged. The preparation of pomegranate juice and placebo was fully described elsewhere (23).

A demographic questionnaire for the medical records was provided. Height, weight, and waist-to-hip ratio (WHR) were measured, and body mass index (BMI) was calculated by dividing weight (kg)/ by Height^2 (cm). Analysis of primary outcomes was already published (23). As for secondary outcomes, we measured total cholesterol, albumin and total protein levels. Globulin level was determined by subtracting the albumin level from the total protein level. All variables were measured at baseline and by the end of week 2. If a patient refused to continue the study, blood samples were taken on the same day.

Assessment of nutritional status and immunological condition was conducted using the CONUT, PNI and AGR scores (24). CONUT score categorized patients within a two-step process. The first step evaluated nutritional status mainly based on serum albumin, total cholesterol and total lymphocyte levels. The second and final step was evaluating nutritional risk according to the information in Table 1. PNI calculation and categorization were defined as 10×serum albumin (g/dL)+0.005×total lymphocyte count (per mm3). PNI<35 was considered to be high, 35≤PNI<38 as middle, and PNI≥38 as low (low=worse) (24, 25).

A seven-day 24-hour dietary recall was conducted to evaluate nutrient intake and eating patterns (including the weekend day).

Dietary intakes were then entered into the Nutritionist IV program for additional analysis. SPSS software (SPSS, Inc., Version 26, Chicago, IL, USA) and GraphPad Prism 9.4.1 were used to analyze the data. The distribution of variables was examined using the Shapiro-Wilk test to determine normality. Standard quantitative variables were reported as mean±standard deviation. Non-normal quantitative variables were reported as median IQR, and qualitative variables were reported as number (percentage). To compare the mean of variables between the two groups, independent T-test and Mann-Whitney test were used. Paired T-test or Wilcoxon test was performed to analyze the group means. Regarding ordinal categorical variables, Chi-Square and Wilcoxon signed rank tests were applied for between-groups and within-group analysis, respectively. A *p* value <0.05 was considered statistically significant.

Results

A total of 43 patients (23 males and 20 females) with an average age of 58.6 for placebo and 56 for intervention groups completed the study. During the intervention, 5 subjects (3 patients in intervention and 2 patients in placebo) failed to complete the study due to personal reasons and unwillingness to continue participation (Figure 1). As presented in Table 2, the analysis between groups showed that cholesterol level significantly decreased (*p*<0.0001), while albumin (*p*<0.0001), total protein (*p*=0.03) and lymphocytes (*p*=0.04) levels significantly increased in the PJ group. Globulin showed a significant increase in the group receiving a placebo (*p*=0.04). Information about dietary patterns and nutritional intake was not shown here (23). CONUT and PNI did not indicate any significant changes in either of the groups. AGR significantly increased in the intervention group (*p*=0.39), but the changes were insignificant (*p*=0.004). More information was demonstrated in Table 3.

Table 1: Controlling nutritional status (CONUT) scoring system.

Parameter	Normal	Light	Moderate	Severe
Serum Albumin (g/dL)	≥3.5	3.0-3.49	2.5-2.9	<2.5
Score	0	2	4	6
Total lymphocytes count (%)	>1600	1200-1599	800-1199	<800
Score	0	1	2	3
Cholesterol (mg/dL)	>180	140-180	100-139	<100
Score	0	1	2	3
Total score	0-1	2-4	5-8	9-12

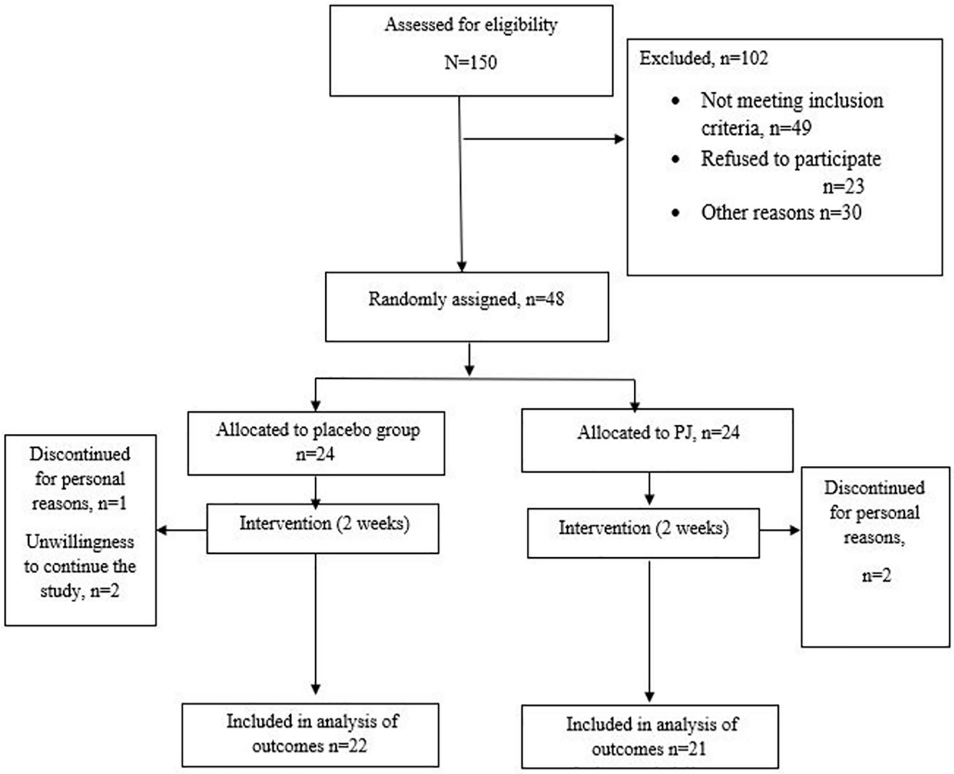

Figure 1: Participants, Recruitment and Randomization.

Table 2: Biochemical information from baseline to the end of intervention.

Variable	Intervention (n=21)	Placebo (n=22)	Mean difference	95 % CI	*P* value[a]
Cholesterol (mg/dL)					
Baseline	183.50±51.65	170.45±51.80	13.02	-18.85 to 44.89	0.41
Week-2	148.50±36.31	163.10±51.60	-14.61	-42.21 to 12.98	0.29
Change	-23.00 (-49.00 to -15.00)	-1.50 (-16.75 to 3.25)	-27.63	7.67 to -43.35	<0.0001
P value[c]	<0.0001	0.03			
Albumin (g/dL)					
Baseline	4.21 (3.88 to 4.62)	3.94 (3.74 to 4.24)	0.24	-0.09 to 0.57	0.08
Week-2	4.81 (4.45 to 5.05)	3.99 (3.78 to 4.20)	0.73	0.39 to 1.06	<0.0001
Change	0.42 (0.17 to 0.68)	0.02 (-.0.07 to 0.22)	0.49	0.22 to 0.75	<0.0001
P value[c]	<0.0001	0.34			
Total protein (g/dL)					
Baseline	6.85 (6.51 to 7.27)	6.56 (5.98 to 6.94)	0.25	-0.17 to 0.68	0.11
Week-2	7.11 (6.95 to 7.72)	6.88 (6.01 to 7.09)	0.49	-0.17 to 0.67	0.01
Change	0.43±0.34	-0.11±0.45	0.24	0.02 to 0.44	0.03
P value[c]	<0.0001	0.02			
Globulin (g/dL)					
Baseline	2.62±0.36	2.60±0.41	0.01	-0.23 to 0.25	0.92
Week-2	2.50±0.60	2.74±0.50	-0.24	-0.57 to 0.09	0.15
Change	0.19±0.33	0.14±0.32	-0.25	-0.49 to -0.01	0.04
P value[c]	0.263	0.06			
Lymphocyte (%)					
Baseline	13.66±8.42	14.09±18.29	-0.42	-5.57 to 4.72	0.86
Week-2	25.80±12.62	19.18±11.02	6.62	-0.66 to 13.91	0.07
Change	12.14±13.42	5.09±8.43	7.05	0.17 to 13.92	0.04
P value	0.001	0.01			

Data presented as mean±SD and median (IQR).

Table 3: Nutritional-Immunological indicators from baseline to the end of trial.

Variable			Intervention (n=21)	Placebo (n=22)	*P* value
CONUT	Baseline	Normal	8 (18.6)	4 (9.3)	0.41
		Light	11 (25.6)	15 (34.9)	
		Moderate	2 (4.7)	3 (7)	
		Severe	0	0	
	Week-2	Normal	10 (23.3)	5 (11.6)	0.34
		Light	10 (23.3)	15 (34.9)	
		Moderate	1 (2.3)	2 (4.7)	
		Severe	0	0	
P value			0.25	0.15	
PNI	Baseline	Low	17 (39.5)	16 (37.2)	1.00
		Middle	3 (7)	4 (9.3)	
		High	1 (2.3)	2 (4.7)	
	Week-2	Low	20 (46.5)	18 (41.9)	0.47
		Middle	1 (2.3)	3 (7)	
		High	0	1 (2.3)	
P value			0.10	0.18	
AGR					
Baseline			1.67 (1.43 to 1.79)	1.55 (1.35 to 1.70)	0.38
Week-2			1.84 (1.51 to 2.54)	1.47 (1.32 to 1.64)	0.004
Change			0.06 (-0.25 to 0.34)	0.04 (-0.02 to 0.36)	0.39
P value			0.004	0.35	

Data presented as number (percent) and median (IQR). Controlling nutritional status (CONUT), prognostic nutritional index (PNI), albumin to globulin ratio (AGR).

Discussion

In COVID-19 as a cytokine storm syndrome has occurred in critical patients associated with inflammatory mediators, systemic inflammation, and multiple organ failure (26). In our study, we used whole pomegranate juice, which incorporated seed oil and juice, to facilitate meals and the incorporation of bioactive compounds, including cyaniding, delphinidin, and pelargonidin (27). These compounds are flavonoids with different properties in preventing inflammatory, cardiovascular, and other diseases. This fruit can inhibit inflammatory mediators, such as cyclooxygenase and lipoxygenase (28). Balachandar *et al.* suggested that its antiviral property is due to an active compound called punicalagin (29). Other hydrolyzable punicalin tannins can help establish H-bonds with the crucial catalytic residues of pocket spatial position, inhibiting this virus's duplication and life cycle (30).

All in all, our intervention showed no significant effect on CONUT, PNI and AGR scores. However, contrary to our findings apple polyphenols exhibited promising effects on AGR in liver injury models (31). One explanation to the neutral effects of our intervention on AGR is that in our study both albumin and globulin increased, so the ratio remained approximately the same. Regarding CONUT and PNI, almost every single parameter of these scores illustrated significant changes. However, since the scoring criteria encompass a wide range, a more remarkable change is needed to affect the whole score. As mentioned previously, we did observe a significant reduction in cholesterol level in the PJ group. This finding is consistent with previous studies which have reported the hypolipidemic effects of pomegranate juice (32).

In another study conducted on high-cholesterol diet-fed rats, the administration of seed extract of two pomegranate types had favorable effects on total cholesterol and other components of the lipid profile (33). On the contrary, an uncertain effect was observed on TG and cholesterol levels after administrating pomegranate seed powder to diabetic patients (34). The observed reduction in cholesterol level may be attributed to the presence of polyphenols and other bioactive compounds in pomegranate juice, which have been shown to inhibit oxidized LDL uptake by macrophages and reduce cholesterol synthesis and promote cholesterol excretion (10-12). Our study also showed a significant increase in albumin and total protein levels and lymphocyte count in the group receiving pomegranate juice. This finding suggests that pomegranate juice may have a positive impact on the immune system and overall health status of individuals. The increase in albumin and total protein may be attributed to the antioxidant and anti-inflammatory properties of pomegranate juice, which have been shown to protect against oxidative stress and capillary leakage (28).

The increase in lymphocyte count could be related to the immunomodulatory effects of pomegranate juice, which have been demonstrated in both *in vitro* and *in vivo* studies. Different types of polyphenol receptors are expressed by various immune cells. Polyphenols binding to these receptors could potentially activate immune-related responses (35-37). Wu *et al.* reported that administration of 200 mg/kg/d and 400 mg/kg/d to immunosuppressed mice could get back the proliferation rate of lymphocytes to normal. (35). Polyphenols could also prevent lymphocytes from oxidative damage (36). As researchers indicated, some of these immunoregulatory effects of pomegranate could be linked to polysaccharides which could upregulate immunoglobulin production of mucosal tissue and inhibit pathogen invasion (37).

The literature reflected that pomegranate efficacy in the antiviral treatment could be strengthened through a synergic effect with other compounds such as zinc (38), which decreased the action of SARS 3CL-protease (being the only cysteine protease found in coronaviruses and essential for replication of the virus) (39) and chebulagic acid which reduced virus-induced plaque formation in Vero-E6 monolayer at noncytotoxic concentrations, by allosterically regulating of viral 3-chymotrypsin-like cysteine protease (3CLpro) targeting the enzymatic activity (40).

Conclusion

Maintaining overall good nutritional status through a balanced and varied diet, along with other measures such as adequate sleep, exercise, and stress management is crucial in supporting the immune system and promoting overall health. Consequently, while the role of pomegranate juice in boosting the nutritional-immunological status of COVID-19 patients warrants further investigation, it should be viewed as part of a broader strategy to support immune function and promote overall health.

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Authors' Contribution

MH: Conceptualization, formal analysis, and writing the original draft, writing, review and editing; BP: Conceptualization, methodology and resources; MY: Investigation and resources; MR: Visualization; SM: Investigation; MS: Investigation; BS: Investigation; JS: Writing, review and editing; MA: Writing, review and editing; AP: Supervision.

Conflict of Interest

None declared.

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