Taylor & Francis
Taylor & Francis Group

Immunological Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/timm20

The effects of grapes and their products on immune system: a review

Fatemeh Izadfar, Saba Belyani, Masomeh Pormohammadi, Simin Alizadeh, Mehrara Hashempor, Elaheh Emadi, Zohreh Sadat Sangsefidi, Mohammad Reza Jalilvand, Shima Abdollahi & Omid Toupchian

To cite this article: Fatemeh Izadfar, Saba Belyani, Masomeh Pormohammadi, Simin Alizadeh, Mehrara Hashempor, Elaheh Emadi, Zohreh Sadat Sangsefidi, Mohammad Reza Jalilvand, Shima Abdollahi & Omid Toupchian (09 May 2023): The effects of grapes and their products on immune system: a review, Immunological Medicine, DOI: 10.1080/25785826.2023.2207896

To link to this article: https://doi.org/10.1080/25785826.2023.2207896

Published online: 09 May 2023.

IMMUNOLOGICAL MEDICINE
https://doi.org/10.1080/25785826.2023.2207896

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

The effects of grapes and their products on immune system: a review

Fatemeh Izadfar[a], Saba Belyani[a], Masomeh Pormohammadi[a], Simin Alizadeh[a], Mehrara Hashempor[a], Elaheh Emadi[b], Zohreh Sadat Sangsefidi[a], Mohammad Reza Jalilvand[a], Shima Abdollahi[a] and Omid Toupchian[a]

[a]Department of Nutrition, School of Public Health, North Khorasan University of Medical SciencesBojnurd, Iran; [b]Department of Genetics, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences and Health ServicesYazd, Iran

ABSTRACT

Immune system plays a significant role in preventing and controlling diseases. Some studies reported the beneficial effects of grapes and their products on immunity. However, their results are controversial. This review aimed to discuss the effects of grapes and their products on immune system and their mechanisms of action. Although various in-vio and in-vitro studies and some human studies suggested that grapes and their products may help to improve the immune system's function, clinical trials in this area are limited and inconsistent.

In conclusions, although, consumption of grapes and their products may help to having a healthy immune syste, further studies particularly human studies are required to clarify the precise effects of them and their mechanisms regarding immune system.

ARTICLE HISTORY
Received 1 September 2022
Accepted 24 April 2023

KEYWORDS
Grape; grape products; immune system; immune function

1. Introduction

The immune system is the first-line defense against infectious agents and foreign invasions. This system is an interactive network of immune cells, humoral agents, and cytokines [1]. Immune cells are generated in the bone marrow. Some immune cells including neutrophils, other granulocytes, and B cells differentiate in the bone marrow, while T cells migrate to the thymus to differentiate (e.g., $\gamma\delta$ T cells, $CD8^+$ T cells). Moreover, monocytes move through the blood and differentiate into macrophages in the tissues [2]. Impaired immune system regulation can lead to severe inflammatory responses and diseases. In addition to the role of the immune system in disinfection and anti-neoplastic protection, recent studies have reported its impact in regulating systemic metabolic homeostasis [3–5]. Given that the immune system is involved in maintaining health and preventing disease, a better understanding of its regulatory and effective factors has great importance in preventing and improving diseases [6,7]. Nutrition and nutrients play a significant role in maintaining the immune system and its responses [8]. A diet rich in fruits and vegetables is effective in reducing inflammation and improving immune function due to its antioxidant compounds and other biologically active substances [9]. Moreover, some evidence showed that phytochemicals can have modulatory effects on the immune system [2,10]. Grapes (*Vitis vinifera*) and their products are among the possible nutritional effective factors on immune function [11]. Grapes and their products (e.g., fruits; grapes juice, fruits and seed extract, powder) contain beneficial compounds such as vitamins (e.g., vitamins E and C), phytochemicals (e.g., anthocyanins, flavan-3-ol monomers, proanthocyanidins, phenolic acids, resveratrol, and flavonols), and other compounds such as melatonin [11–15]. Red and purple grapes have the greatest phytochemicals with antioxidant properties in comparison to white grapes [15]. According to the literature, grapes and their products can be effective in preventing and reducing the risk of various diseases such as diabetes, obesity, cardiovascular diseases, and cancer [16–19]. Some in-vitro studies indicated the useful effects of grapes and their products on the immune system [20–22]. Moreover, the results of several studies on birds showed that the consumption of grapes products improved immunity [23–25]. Some research in mice also reported that intake of grapes or their products had some useful impacts on the immune system [26–28]. Human studies particularly clinical trials regarding

CONTACT Zohreh Sadat Sangsefidi sangsefidi.zsadat@gmail.com. Department of Nutrition, School of Public Health, North Khorasan University of Medical Sciences, Bojnurd, Iran; Elaheh Emadi elahehemadi@yahoo.com Department of Genetics, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

the effects of grapes and their products on the immune system are limited and controversial [7,29–33]. However, some of them reported some beneficial effects in this area. For instance, the results of a randomized clinical trial (RCT) among healthy individuals showed that consumption of grape juice increased the number of $\gamma\delta$ T cells and serum levels of vitamin C [7]. On the contrary, $\gamma\delta$ T cells number and serum antioxidant capacity decreased in the placebo group [7]. In another RCT study, in patients with allergic contact dermatitis to nickel demonstrated increased levels of interferon-γ (INF-γ), interleukin-4 (IL-4), IL-17, pentraxin 3, IL-10, and decreased nitric oxide (NO) levels in the group received grape polyphenols (GPP) versus the placebo group [29]. Moreover, a 9-week cross-over RCT among 24 obese subjects showed that intake of grape powder had immunomodulatory effects versus placebo [32]. Available review studies linking the effects of grapes and their products on immunity are limited and have some limitations; they reviewed a small number of studies over restricted grapes products using a finite number of possible mechanisms [19]. Given the results of some studies on the beneficial effects of grapes and their products on immunity, a limited number of review studies in this field, and limitations of the conducted review studies, the present review was carried out to fill this research gap. The aim was to discuss the effects of grapes and their products on the immune system and their possible mechanisms of action.

2. In-vitro and animal studies

Various in-vitro and animal studies reported beneficial impacts of grapes or their products on immunity. For example, in one study on peripheral blood mononuclear cells (PBMC) extracted from a group of obese individuals compared with healthy people, it was found that grape polyphenols increased IL-21 levels in the healthy group, while they reduced the release of IL-1? and IL-6 in the obese people [20]. Marzulli et al. 2012 also observed that fermented grape marc increased releasing the anti-inflammatory cytokines and the induction of FoxP3 (a biomarker of T regulatory cells) in human PBMC [21]. Another study on human PBMC also concluded that the grape products including red and white wines, as well as grape juice inhibited stimulation-induced effects of mitogens phytohaemagglutinin and concanavalin A such as neopterin production and tryptophan degradation following stimulation of macrophages by releasing IFN-γ [22].

Among animal studies, one study indicated that daily grapes intake (2.5 g/kg body weight) in mice reduced oxidative stress and changes in immune function due to chronic ethanol consumption [27]. So that, intake of grapes increased IL-4 concentration and reduced tumor necrosis factor alpha (TNF-α), INF-γ, transforming growth factor beta1 (TGF-β1), vascular endothelial growth factor A (VEGF-A) levels. These beneficial effects were attributed to polyphenols in grapes [27]. In another research on broilers, it was found that grape seed extract (GSE) supplementation increased glutathione levels versus the control group ($p < 0.01$) [25]. GSE intake also increased levels of specific antibodies against Newcastle disease virus in the intervention group ($p < 0.01$) [25]. Similarly, one research in broilers reported that the levels of glutathione peroxidase, humoral and cellular immune responses improved in the group with consuming GPP than the control group [24]. Although GPP supplementation had no significant effect on total antibody and IgG levels, IgM antibody levels were higher in the GPP group than in the control group [24]. Ao et al. 2020 also observed the advantageous effects of GSE supplementation on antioxidant activity and immune system function in ducks [34]. One study in mice examined the hepatoprotective effects of triterpenoids and total flavonoids of grapes against liver immunological damage by injection of lipopolysaccharide and bacillus Calmette [26]. Based on the findings of this study, medium and high doses of these compounds (150 or 300 mg/kg body weight) decreased IFN-γ and IL-2 levels but increased IL-4 and IL-10 levels. However, these substances had low effects on the ratio of Th1 ($CD4^+/CD8^+$, Th1 (IFN-γ, IL-2)/Th2 (IL-4, IL-10) in the groups with intake of low doses of these compounds (50 mg/kg body weight) [26]. The hepatoprotective effects of these compounds were attributed to their antioxidant properties and immune regulatory effects [26]. Moreover, several studies in mice demonstrated anti-tumor activities of grapes or their products by immunomodulatory effects such as increasing the activity of lymphocytes and lysosomal enzymes, as well as the phagocytic ability of macrophages [35,36]. Hao et al. 2015 reported that consuming 100 or 150 mg/kg of grape-seed proanthocyanidin (GSP) in the weaned piglets was related to increased serum levels of IgG, IgM, CD4, IL-2, total antioxidant capacity, glutathione peroxidase, and superoxide dismutase activity versus the control group [37]. However, serum levels of malondialdehyde decreased in the GSP groups versus the control group [37]. In the same regard, the results of an animal collagen-induced rheumatoid arthritis model indicated that GSP decreased Th1 cytokines as well as the inflammatory mediators including monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2), and intercellular adhesion molecule 1 (ICAM-1). In addition, GSP significantly increased up-regulated the number of proanthocyanin $CD4^{+}CD25^{+}Foxp3^{+}$ regulatory T (Treg) cells and induced Th17/Treg cells to rebalance [38].

3. Clinical trials

Few clinical trials were carried out on the effects of grapes and their products on the immune system and their findings are controversial [7,29–33]. For example, a single-blind cross-over RCT with four experimental treatments including 500 ml/day of red wine (RW) (12% ETOH v/v), dealcoholized red wine (DRW), and red grape juice (RGJ) among healthy males reported that intake of RW, DRW and RGJ for 2 weeks did not affect immune function [31]. Similarly, another cross-over study with the similar experimental treatments as above observed no significant effect on the immune system among healthy non-smoking men with moderate alcohol intake pattern [30]. Rowe et al. 2011 evaluated the effect of grape juice consumption on immunity among 85 healthy individuals in a double-blind RCT [7]. The participants were randomly assigned into two groups for receiving grape juice or the placebo (360 ml/day) for 9 weeks [7]. As a result, the group with consumption of the grape juice had more $\gamma\delta$ cells and higher levels of vitamin C compared with the placebo group. Moreover, a decrease in serum antioxidant activity, a decrease in $\gamma\delta$ T cell proliferation, and an increase in DNA strand breakage were observed in the placebo group [7]. In the RCT by Magrone et al. 2021; 25 patients with nickel-allergic contact dermatitis were randomly divided into two groups for intake of 300 mg of grape seed-derived polyphenol supplement or a placebo for three months [29]. According to the results, the levels of interferon-γ, IL-4, IL-17, pentraxin 3, and NO decreased in the grape polyphenol group, while an increase was observed in IL-10 levels in this group. However, no change was found in the placebo group [29]. In the same regard, the findings of one RCT in 28 runners demonstrated an increased total antioxidant capacity level without significant impact on the immune system following consumption of purple grape juice (10 mL/kg/min for 28 days) versus an isocaloric, isoglycemic and isovolumetric control beverage [33]. Zunino et al. 2013 in a 9-week double-blind, cross-over study among 24 obese subjects observed no difference in producing T-cell cytokines including interferon-γ, TNF-α, IL-4, IL-10, and IL-8 in the cells activated with lipopolysaccharide (LPS) or anti-CD3/CD28 antibodies between their intervention groups [grape powder equivalent to 92 g grape powder (the equivalent of approximately 4 servings of fresh grapes) versus placebo/day]. Nevertheless, producing IL-1β and IL-6 was increased in LPS-activated cells in the grape powder group versus the placebo group [32].

Some differences between various studies could be because of differences in sample size, characteristics of participants, trial duration, type of grapes products and their dosage, type of phytochemicals and amount of them in grapes products. The number of clinical trials in this field is limited. Furthermore, the sample size and duration of clinical trials are not enough large. Therefore, available evidence based on clinical trials is not very sufficient for conclusive and precise judgment yet.

Some beneficial effects of grapes and their products on immunity have been attributed to their phytochemicals such as anthocyanins, flavan-3-ol monomers, proanthocyanidins, phenolic acids, resveratrol, flavonols, and melatonin [19,39–41]. Some mechanisms related to the immunological effects of phytochemicals were presented as follows: increasing the activity of lymphocytes and lysosomal enzymes, the phagocytic ability of macrophages, the levels of immune function markers (such the number of $\gamma\delta$ T cells), and the antioxidant status. Moreover, these beneficial components had regulatory impacts on intestinal mucosal immunity and anti-allergic effects [19,39–41]. Another possible mechanism might be their anti-inflammatory effects *via* modulating transcription of inflammatory agents. Furthermore, they exhibited modifier effects on cell morphology, ligand-receptor interactions, signaling pathways, and foam-cell formation [19,40,41].

4. Conclusion

According to available evidence, the results of human studies especially clinical trials regarding the effect of grapes and their products on the immune system are limited and controversial. However, intake of grapes and their products may help to protect and promote immune system function due to having beneficial compounds such as different phytochemicals. Furthermore, more studies especially clinical trials are needed to clarify their exact effects of them and their mechanisms regarding the immune system.

Acknowledgements

We appreciate the Department of Nutrition and Public Health, School of Public Health, North Khorasan University of Medical Sciences, Bojnurd, Iran.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

No funding was received for this study.

ORCID

Zohreh Sadat Sangsefidi http://orcid.org/0000-0001-8185-4558

References

[1] Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;357(9270):1777–1789.

[2] Percival SS. Nutrition and immunity: balancing diet and immune function. Nutrition Today. 2011;46(1):12–17.

[3] Ganeshan K, Chawla A. Metabolic regulation of immune responses. Annu Rev Immunol. 2014;32:609–634.

[4] Sattler S. The role of the immune system beyond the fight against infection. Adv Exp Med Biol. 2017;1003:3–14.

[5] Zmora N, Bashiardes S, Levy M, et al. The role of the immune system in metabolic health and disease. Cell Metab. 2017;25(3):506–521.

[6] Hedges JF, Lubick KJ, Jutila MA. Gamma delta T cells respond directly to pathogen-associated molecular patterns. J Immunol. 2005;174(10):6045–6053.

[7] Rowe CA, Nantz MP, Nieves C, et al. Regular consumption of concord grape juice benefits human immunity. J Med Food. 2011;14(1–2):69–78.

[8] Iglesias J, Pazos M, Torres JL, et al. Antioxidant mechanism of grape procyanidins in muscle tissues: redox interactions with endogenous ascorbic acid and α-tocopherol. Food Chem. 2012;134(4):1767–1774.

[9] Hosseini B, Berthon BS, Saedisomeolia A, et al. Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: a systematic literature review and meta-analysis. Am J Clin Nutr. 2018;108(1):136–155.

[10] Neyestani TR. *Polyphenols and immunity*., In Wild-Type Food in Health Promotion and Disease Prevention. 2008. Humana Press. Springer. p. 413–434.

[11] Iriti M, Faoro F. Bioactivity of grape chemicals for human health. Nat Prod Commun. 2009;4(5):1934578X0900400.

[12] Sangsefidi ZS, Hasanizadeh S, Hosseinzadeh M. Effect of purified anthocyanins or anthocyanin-rich extracts on C-reactive protein levels: a systematic review and meta-analysis of randomised clinical trials. Br J Nutr. 2018;120(12):1406–1414.

[13] Sangsefidi ZS, Mozaffari-Khosravi H, Sarkhosh-Khorasani S, et al. The effect of anthocyanins supplementation on liver enzymes: a systematic review and meta-analysis of randomized clinical trials. Food Sci Nutr. 2021;9(7):3954–3970.

[14] Sarkhosh-Khorasani S, Sangsefidi ZS, Hosseinzadeh M. The effect of grape products containing polyphenols on oxidative stress: a systematic review and meta-analysis of randomized clinical trials. Nutr J. 2021;20(1):1–18.

[15] Vislocky LM, Fernandez ML. Grapes and grape products: their role in health. Nutrition Today. 2013;48(1):47–51.

[16] Jeandet P, Bessis R, Gautheron B. The production of resveratrol (3,5,4'-trihydroxystilbene) by grape berries in different developmental stages. Am J Enol Vitic. 1991;42(1):41–46.

[17] Marzulli G, Magrone T, Vonghia L, et al. Immunomodulating and anti-allergic effects of Negroamaro and Koshu Vitis vinifera fermented grape marc (FGM). Curr Pharm Des. 2014;20(6):864–868.

[18] Williamson G, Carughi A. Polyphenol content and health benefits of raisins. Nutr Res. 2010;30(8):511–519.

[19] Percival SS. Grape consumption supports immunity in animals and humans. J Nutr. 2009;139(9):1801s–1805s.

[20] Magrone T, Jirillo E, Spagnoletta A, et al. Immune profile of obese people and in vitro effects of red grape polyphenols on peripheral blood mononuclear cells. Oxid Med Cell Longevity. 2017;2017:1–11.

[21] Marzulli G, Magrone T, Kawaguchi K, et al. Fermented grape marc (FGM): immunomodulating properties and its potential exploitation in the treatment of neurodegenerative diseases. Curr Pharm Des. 2012;18(1):43–50.

[22] Neurauter G, Wirleitner B, Schroecksnadel K, et al. Wine and grape juice modulate interferon-y-induced neopterin production and tryptophan degradation in human PBMC. Pteridines. 2004;15(1):1–9.

[23] Iqbal Z, Kamran Z, Sultan JI, et al. Replacement effect of vitamin E with grape polyphenols on antioxidant status, immune, and organs histopathological responses in broilers from 1-to 35-d age. J Appl Poult Res. 2015;24(2):127–134.

[24] Ebrahimzadeh SK, Navidshad B, Farhoomand P, et al. Effects of grape pomace and vitamin E on performance, antioxidant status, immune response, gut morphology and histopathological responses in broiler chickens. SA J An Sci. 2018;48(2):324–336.

[25] Farahat MH, Abdallah FM, Ali HA, et al. Effect of dietary supplementation of grape seed extract on the growth performance, lipid profile, antioxidant status and immune response of broiler chickens. Animal. 2017;11(5):771–777.

[26] Liu T, Zhao J, Ma L, et al. Hepatoprotective effects of total triterpenoids and total flavonoids from *Vitis vinifera* L against Immunological Liver Injury in Mice. Evid Based Complement Alternat Med. 2012;2012:969386.

[27] Mukherjee S, Das SK, Vasudevan DM. Dietary grapes (*Vitis vinifera*) feeding attenuates ethanol-induced oxidative stress in blood and modulates immune functions in mice. Indian J Biochem Biophys. 2012;49(5):379–385.

[28] Katiyar SK. Dietary proanthocyanidins inhibit UV radiation-induced skin tumor development through functional activation of the immune system. Mol Nutr Food Res. 2016;60(6):1374–1382.

[29] Magrone T, Jirillo E, Magrone M, et al. Red grape polyphenol oral administration improves immune response in women affected by nickel-mediated allergic contact dermatitis. Endocr Metab Immune Disord Drug Targets. 2021;21(2):374–384.

[30] Watzl B, Bub A, Briviba K, et al. Acute intake of moderate amounts of red wine or alcohol has no effect on the immune system of healthy men. Eur J Nutr. 2002;41(6):264–270.

[31] Watzl B, Bub A, Pretzer G, et al. Daily moderate amounts of red wine or alcohol have no effect on the immune system of healthy men. Eur J Clin Nutr. 2004;58(1):40–45.

[32] Zunino SJ, Peerson JM, Freytag TL, et al. Dietary grape powder increases IL-1β and IL-6 production by lipopolysaccharide-activated monocytes and reduces plasma concentrations of large LDL and large LDL-cholesterol particles in obese humans. Br J Nutr. 2014;112(3):369–380.

[33] Toscano LT, Tavares RL, Toscano LT, et al. Potential ergogenic activity of grape juice in runners. Appl Physiol Nutr Metab. 2015;40(9):899–906.

[34] Ao X, Kim I. Effects of grape seed extract on performance, immunity, antioxidant capacity, and meat quality in Pekin ducks. Poult Sci. 2020;99(4):2078–2086.

[35] Sharma SD, Katiyar SK. Dietary grape-seed proanthocyanidin inhibition of ultraviolet B-induced immune suppression is associated with induction of IL-12. Carcinogenesis. 2006;27(1):95–102.

[36] Tong H, Song X, Sun X, et al. Immunomodulatory and antitumor activities of grape seed proanthocyanidins. J Agric Food Chem. 2011;59(21):11543–11547.

[37] Hao R, Li Q, Zhao J, et al. Effects of grape seed procyanidins on growth performance, immune function and antioxidant capacity in weaned piglets. Livest Sci. 2015;178:237–242.

[38] Ahmad SF, Zoheir KMA, Abdel-Hamied HE, et al. Grape seed proanthocyanidin extract has potent anti-arthritic effects on collagen-induced arthritis by modifying the T cell balance. Int Immunopharmacol. 2013;17(1):79–87.

[39] Ding S, Jiang H, Fang J. Regulation of immune function by polyphenols. J immunol res. 2018;2018:1–8.

[40] Malaguarnera L. Influence of resveratrol on the immune response. Nutrients. 2019;11(5):946.

[41] Peluso I, Miglio C, Morabito G, et al. Flavonoids and immune function in human: a systematic review. Crit Rev Food Sci Nutr. 2015;55(3):383–395.