

Review Article

Possible Beneficial Effects of Fresh Pomegranate Juice in SARS-CoV-2 Infection Conditions

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Rather than the prophylactic vaccination, any effective synthetic, natural, or nutritional therapy or regimen that may cure or remedy, albeit partially, the complications of SARS-CoV-2 should be highly acknowledged. Here, we reviewed and discussed possible beneficial biological effects of pomegranate juice in such diseased condition of viral infection based on the current published evidence (direct and indirect) and owing to the robust evidence that fresh pomegranate juice is highly rich with unique bioactive compounds that are approved in various occasions to be effective in several chronic diseased conditions. All related references that serve our aim are accessed through available electronic databases, particularly PubMed and Scopus. In summary, there is accepted evidence that pomegranate juice may be beneficial in SARS-CoV-2 infection conditions, especially for patients with the clinical history of chronic diseases such as hypertension, cardiovascular disease, diabetes, and cancer. However, the interventional studies that directly probe and confirm the effectiveness of fresh pomegranate juice in the management of SARS-CoV-2 infection are mandatory.

1. Introduction

Since December 2019, the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases reached more than 250 million with more than 5 million deaths worldwide [1]. Still, this number is increasing every day [1]. Other than the used prophylactic vaccines, to date, the potential therapy to manage SARS-CoV-2 infection conditions is still an ongoing global challenge with a very limited specific pharmacological therapy which has been identified to be potentially effective in such diseased circumstances, especially with the evident vaccine breakthrough infections with different variants of SARS-CoV-2, making this pandemic the worst for this generation since the Spanish flu of 1918 [2].

Therefore, any approved natural product or even food regimen that may cure or reduce, albeit partially, the complications of SARS-CoV-2 infection should be highly acknowledged. One such possible example that could be helpful in the management of this unique diseased situations is fresh pomegranate juice.

In actual fact, our attention to review fresh pomegranate juice in ameliorating SARS-CoV-2 infection conditions was not random, but it is due to several published reports that correlate the severity and mortality rate of coronavirus disease 19 (COVID-19) with the clinical history of the infected patients [3–6]. It has been shown that patients with COVID-19 and with the clinical history of chronic diseases/conditions such as coronary heart disease [7], hypertension [8], cancer [9, 10], and diabetes were found to develop more serious and critical cases, and hence markedly increase rates of death among these people [6, 11, 12]. In addition, in general, a number of research studies have revealed a valuable benefit of pomegranate juice in management of viral infection, including influenza [13–15].

In effect, the potential health benefits of pomegranate juice is due to its antihypertensive [16], antiatherogenic [17], anti-inflammatory [18, 19], anticancer [20], and antidiabetic effects [21]. Such imperative biological activities of pomegranate juice are due to its unique chemical composition, which includes a wide range and powerful dietary

phytochemicals such as flavonoids (e.g., quercetin, phloridzin, and catechin) [22, 23] and polyphenols (e.g., anthocyanins, tannins, gallic acid, ferulic acid, coumaric acids, and chlorogenic acid) [24]. Also, here, it is worth mentioning that these substantial phytochemicals have let pomegranate juice to exhibit a very strong antioxidant activity that is greater than the renowned antioxidants, for example, from red wine or green tea [25].

2. Pomegranate Juice against Viral Infection

Studies have revealed the effectiveness of pomegranate juice or its bioactive compounds against different types of viruses, for example, pomegranate juice was found to inactivate human immunodeficiency virus (HIV) may be by blocking the HIV virus binding to the cluster of 4 (CD4), which is a glycoprotein present on the surface of several types of white blood cells such as T helper cells and monocytes [13]. The same study suggested that at least one of the bioactive compounds in pomegranate juice bound tightly, or irreversibly, to the CD4 binding-site on envelope glycoprotein GP120 [13]. In addition, an experimental study showed that punicalagin, a polyphenol in pomegranate juice, has been identified to have a potential virucidal activity against herpes simplex virus in epithelial Vero host cells [26]. Moreover, another experimental study on the effect of pomegranate juice on the infectivity of foodborne viral surrogates showed that 20 minutes incubation with pomegranate juice powder at approximately 4 or 8 mg·mL⁻¹ resulted in titer reductions of 0.79, 3.12, and 0.23 log (10) PFU mL⁻¹ for murine norovirus 1, feline calicivirus (strain F9), and MS2 bacteriophage, respectively [27].

In particular, pomegranate juice has revealed a potential antiinfluenza activity, for example, Sundararajan and coworkers (2010) found that five minutes treatment with pomegranate juice powder extract at 800 µg·mL⁻¹ significantly reduced (by approximately 3 log) the titers of influenza viruses: influenza A virus subtype H1N1, PR8 virus, influenza A virus subtype, and reassortant H5N1 avian influenza virus derived from a human isolate [14]. In the same study, Sundararajan and coworkers have demonstrated that the antiinfluenza activity of pomegranate juice is significantly modulated by some alterations in envelope glycoproteins [14]. Moreover, an experimental in vitro study conducted by Madjid and coworkers revealed that pomegranate polyphenol extract from pomegranate juice significantly inhibited the replication of influenza A virus subtype H3N2 (human influenza A/Hong Kong) [15]. The same researchers evaluated some polyphenols (luteolin, ellagic acid, punicalagin, and caffeic acid) in pomegranate polyphenol extract and found that punicalagin is the main bioactive antiinfluenza compound. It has been found to block the replication of virus RNA and inhibit the agglutination of chicken red blood cells by the virus [15]. This evidence is strongly revealing the effectiveness of pomegranate juice in viral infection conditions, particularly in influenza.

Newly published studies have revealed that some anthocyanins and tannins rich plants such as pomegranate

could be very beneficial to cure COVID-19 [28, 29]. In particular, structurally, it was found that some polyacylated anthocyanins (e.g., phacelianin, cyanodelphin, gentiodelphin, and tecophilin) and hydrolysable tannins (e.g., tercatain, pedunculagin, and castalin) may inhibit SARS-CoV-2 papain-like protease and hence the replication of virus [28, 29].

3. Possible Beneficial Effects of Pomegranate Juice in COVID-19 Patients with Chronic Diseases

3.1. Pomegranate Juice and COVID-19 Patients with Hypertension. The activity of serum angiotensin-converting enzyme (ACE) reduced by approximately 36% in seven out of ten hypertensive patients after two weeks following pomegranate juice consumption at 50 mL per day [30]. Also, the similar in vitro inhibitory effect (31%) of pomegranate juice on activity of serum ACE was observed [30]. As a consequence of such enzymatic inhibition, there was a reduction in systolic blood pressure by approximately 5% in the recruited patients [30]. A randomized placebo-controlled study conducted on fifty-one healthy adults revealed that consumption of 330 mL per day pomegranate juice, for 4 weeks, significantly reduces both systolic and diastolic blood pressures [31]. Another randomized clinical trial has shown that hemodialysis patients ($n = 101$) received 100 mL of pomegranate juice three times a week, for 1-year, and had significant improvement in their pulse pressure and systolic blood pressure compared to the placebo group [32]. Moreover, a later randomized controlled trial has shown that patients administered natural pomegranate juice at 500 mL per day, for one week, had lower systolic and diastolic blood pressures [33]. Collectively, this evidence confirms the ACE inhibition activity and consequently the hypotensive response of pomegranate juice in the human body. Alternatively, in our recent published clinical trial, we have shown that the observed antihypertensive effect of fresh pomegranate juice in humans may be modulated by a reduction in the cortisol level [34].

Mechanistically, angiotensin-converting enzyme 2 (ACE2), a membrane-bound and a zinc-containing metalloenzyme, has been found to be present in several bodily organs such as the lung, arteries, small intestine, and kidneys [35]. In particular, at most, ACE2 is attached to the type II pneumonocytes in the alveoli, arterial smooth muscle cells, venous endothelial cells, and small intestinal absorptive cells (or enterocytes of the small intestine) [36]. Biochemically, ACE2 is an aminopeptidase that cleaves angiotensin II (AT-II), which is a vasoconstrictor, into angiotensin-(1-7), which is a vasodilator [35]. Very recently, ACE2 has been recognized as a receptor and an entry point for the acute respiratory syndrome coronavirus 2 into the host cells; therefore, it has a critical role in the onset of coronavirus disease 2019 [37].

Even though administration of ACE inhibitors was found to increase cardiac mRNA levels of ACE2, it has no effect on the activity of ACE2 in the experimental animal models [35, 38, 39]. Li et al. showed that treatment with captopril (brand name: Capoten), which is a commonly used

ACE inhibitor, increases expression of ACE2 in rats with acute lung damage [40]. Also, it was documented that, in rats with acute respiratory distress syndrome, expression of AT-II and ACE activities increased, while activity of ACE2 and level of angiotensin-(1-7) decreased [41]. In fact, decreasing the amount of ACE2 will shift the balance of the renin-angiotensin-aldosterone system (RAAS) to promote the ACE-AT-II-AT-II receptor type I axis, leading to progression of inflammatory storms and lung injury [42]. Increased level of ACE2 will move the balance to the AT-(1-7)-Mas receptor axis, which has antioxidant as well as anti-inflammatory effects, and hence a cardiopulmonary protective consequence [42]. Accordingly, the above evidence suggested that even though ACE2 is considered as an entry point for SARS-CoV-2, increased expression of ACE2 by the effect of ACE inhibitors is suggested not to worsen SARS-CoV-2 infection or COVID-19. In fact, alternatively, certain RAAS inhibitors may behave differently, for example, diabetic nephropathy models, chronic administration of aliskiren, a direct renin inhibitor, was found to be associated with a decrease in the expression of ACE2, which is suggested to be an interesting research route in context of infection by SARS-CoV-2 [43].

3.2. Pomegranate Juice and COVID-19 Patients with Diabetes.

In our randomized clinical trials published in 2014 and 2020, we found that pomegranate juice administered at 1.5 mL per kg of bodyweight significantly reduces fasting serum glucose in patients with type 2 diabetes and people with impaired fasting glucose compared to control [21, 44]. Previous preclinical *in vivo* study has shown that pomegranate seed extract at approximately $0.45 \text{ g}\cdot\text{kg}^{-1}$ reduced fasting (12 hours fasting) blood glucose in diabetic models [45]. Also, punical acid, an organic acid in pomegranate juice, at 1000 mg per 100 g of the fed diet, for 30 days, reduced fasting blood glucose in obese mice models [24, 46]. Moreover, other organic acids in pomegranate juice (ellagic acid, gallic acid, ursolic acid, oleanolic acid, and uallic acids) were identified to have antihyperglycemic response [47–50].

Mechanistically, pomegranate juice may exert its antihyperglycemic response via enhancing β -cell function, reducing insulin resistance, decreasing cortisol level [34], and minimizing oxidative stress state [24], which is an imbalance between oxidants (e.g., reactive oxygen species) and antioxidants [51, 52]. The later mechanistic route may be attributable to enhancing activity of vital antioxidant enzymes such as catalase, superoxide dismutase, and glutathione reductase [53], direct neutralization of free radicals such as hydroxyl radical or superoxide ion, decreasing synthesis of resistin [54], which is a hormone secreted from adipose tissue and found to be associated with type 2 diabetes [55], increasing metal binding activity [56], and activating or inhibiting transcriptional factors such as peroxisome proliferator-activated receptor gamma (PPAR- γ) and/or nuclear factor- κ B (NF- κ B) [24, 57, 58]. These results provide robust evidence to the beneficial effects of pomegranate juice in diabetic conditions, which therefore may provide beneficial effects to patients with diabetes and infected with SARS-CoV-2.

3.3. *Pomegranate Juice and COVID-19 Patients with Cardiovascular Disease.* Pomegranate juice has been presently known as a cardioprotective natural product due to its ability to reduce ACE activity [30, 59], thereby decreasing systolic and diastolic blood pressures (as explained above) [60], increasing total serum antioxidant capacity [61, 62], enhancing activity of certain antioxidant enzymes [63, 64], decreasing levels of plasma lipids [65, 66], reducing lipid peroxidation [65], decreasing H₂O₂-induced toxicity [67], and decreasing the uptake of oxidized low-density lipoprotein by macrophages [68, 69]. In addition, it was found to decrease thickness of intima media by macrophages and reduce the atherosclerotic lesion areas [70]. Moreover, pomegranate juice was found to enhance the biological action of nitric oxide and decrease inflammation [18, 19]. Therefore, it causes overall beneficial effects against the development of atherosclerosis and the consequent progression of coronary artery disease. Such cardioprotective effect of pomegranate juice could be valuable for patients with COVID-19 and with the clinical history of cardiovascular diseases.

3.4. Pomegranate Juice and COVID-19 Patients with Cancer.

To date, there are more than 88 research studies and reports in the PubMed database that are linking pomegranate to cancer. Such research accumulation is attributable to the encouraging anticancer properties of pomegranate juice and its derived compounds [71]. In fact, pomegranate juice has been suggested to be a promising chemoprotective and/or chemotherapeutic agent against various types of cancer, mainly prostate [72–75], skin [76, 77], colon [78–80], breast [81–84], and lung cancer [20]. Mechanistically, in context of cancer, pomegranate juice has been identified as having antioxidant [73, 85, 86], anti-inflammatory [18, 80], anti-proliferative [67, 87], and antitumorigenic [88, 89] effects, modulating different signaling pathways.

In effect, the anticancer biological properties of pomegranate juice may due to the presence of bioactive chemical compounds such as ellagitannins [90, 91], anthocyanins [28, 76, 92], hydrolysable tannins [92, 93], ellagic acid [75, 85, 94], luteolin [94], and punical acid [82, 87, 95]. Accordingly, the anticancer properties of pomegranate juice and its derived compounds suggest a possible accommodating effect for cancer patients infected with SARS-CoV-2.

4. Conclusion

Collectively, in view of that pomegranate juice is an edible and safe natural product, there is accepted, however, indirect evidence that ingesting fresh pomegranate juice could be beneficial in SARS-CoV-2 infection conditions, especially in the conditions that coincide with the existence of the history of other chronic diseases such as hypertension, cardiovascular disease, diabetes, or cancer.

The current possible beneficial effect in pomegranate juice in viral infection conditions, including SARS-CoV-2 infection, may be due to the presence of several potential bioactive compounds (e.g., polyacylated anthocyanins and

hydrolysable tannins). However, human interventional studies that recruit, for example, patients with SARS-CoV-2 and directly probe the effect of fresh pomegranate juice shall provide the direct and the robust evidence toward such implied effectiveness of pomegranate juice in such exceptional diseased condition.

Conflicts of Interest

The author declares that there are no conflicts of interest.

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