
REVIEW ARTICLE

Punica Granatum(*POMEGRANATE*): A review on potential role in CoVID-19

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ABSTRACT

The SARS-CoV-2 belongs to the family of beta-coronaviruses. It is a single stranded positive-sense protein RNA virus. The structure includes envelope, membrane, nucleocapsid and spike proteins that are responsible for the viral infectivity. The host immune response comprising of innate and adaptive immunity against SARS-Cov-2 seems crucial to control the infection. However, the severity and outcome of the COVID-19 might be associated with the increased production of pro-inflammatory cytokines which leads to an acute respiratory distress syndrome. Currently proposed therapeutic measures propose the use of antioxidant drugs to help patients infected with the SARS-CoV-2. It improves oxygen and glutathione levels to strengthens the immune response. The effects produced are reduction in mechanical ventilation time, preventing multiple organ dysfunctions and reduced stay in the hospital and mortality rates. Immune modulation is the only way of regulation of the immune system. Punica Granatum has been used as a traditional medicine for centuries. The components of this plant are known for its rich immune-regulation, anti-inflammatory, and antioxidant benefits in specially in respiratory disorders.

Keywords: SARS-CoV-2, antioxidants, Immune system, Ellagic acid, Polyphenols

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INTRODUCTION

Viral infections suppress immune system of the host. SARS-CoV-2, Just like other viral infections weaken the host immunity. A strong immune system is the key to protection from virus and other pathogens. Severe cases admitted to the intensive care unit showed high level of pro-inflammatory cytokines which enhanced the disease severity. [1]The inflammatory response of the body also plays a crucial role in SARS-induced lung injury cases. It is important to control the mass production of cytokines and inflammatory response, given that they are responsible for the accumulation of cells and fluids in CoV pneumonia. A strategy for regulating the immune response and controlling excessive inflammation without compromising the beneficial host defense in needed.[2]Pomegranate extract shows potential for use as a supplemental food in improving immunity status of subjects in an emergency situation.[3]The addition of antioxidants such as beta-carotene might increase the activity of macrophages, protect macrophages from oxidative damage and enhance the T-lymphocyte proliferative response.[4] In vitro and animal studies also demonstrate that administration of plant extracts can improve and protect the immune systems.[5,6] Polyphenols and lycopene are secondary metabolites possessing antioxidant activity. Administration of polyphenols in humans can also enhance macrophage phagocytosis.[3] WHO guidelines recommend some Vitamins and antiviral therapies and oxygen inhalation and non pharmaceutical measures as supportive care for PandemicCovid-19.[7]Pomegranate extract contains bioactive compounds similar to *S. mialhesi*, where both the extracts have immune-stimulatory activities tested in vitro and in vivo.[3]

PHYTOCONSTITUENTS OF PUNICA GRANATUM

The primary bioactive constituents of pomegranate juice are the polyphenols. It is comprised of 85.4% water, 10.6% total sugars, 1.4% pectin, 0.2-1.0% polyphenols. Minerals in the juice and seed include Fe, Ca, Cu, K, Mg, Mn, Mo, Se, Sn, Sr, and Zn. [8] It is a rich source of Gallic acid, Ellagic acid, Flavonoids and their glycosides, Anthocyanins, Amino acids: Proline, Valine, Methionine, Glutamic and Aspartic Acid, Indoleamines and Tocopherols. [9,10] Pomegranate seed oil comprises 12–20% of total seed weight. The oil consists of approximately 80% conjugate octadecatrienoic fatty acids, with a high content of cis 9, trans 11, cis 13 acid (i.e. punicic acid).[11] Minor components of the oil include sterols, steroids, tocopherols, and a key component of mammalian myelin sheaths, cerebroside. The main chemical constituents isolated from Pomegranate Skin or Pericarp include Hydroxybenzoic acids: Gallic acid, Ellagic, Hydroxycinnamic acids & Chlorogenic acid. It also contains Flavon-3-ols/Flavonoids and their glycosides: Catechin, Epicatechin, Epigallocatechin-3-gallate, Quercetin, Kaempferol & Naringin. The Anthocyanins are Cyanidin, Pelargonidin, Delphinidin and Ellagitannins.[12]

ANTI INFLAMMATORY ACTIVITY OF PUNICA GRANATUM:

Rasheed et al reported that Pomegranate fruit extract decreased PMACI stimulated inflammatory gene expression and production of IL-6 and IL8 in KU812 cells. The inhibitory effect of the extract on the pro-inflammatory cytokines was MAPK subgroups c-junction N-terminal kinase (JNK- and extracellular-regulated kinase (ERK) dependent. The crude extract also inhibited NF- κ B by inhibiting I κ B-degradation in human basophil cells.[13] Based on their results obtained, the authors suggested that polyphenol rich pomegranate fruit extract exerts its inhibitory effect on IL-6 and IL-8 expression via modulation of the activation and DNA binding activity of NF- κ B. In COVID-19, the use of Interleukin 6 (IL-6) inhibitor (tocilizumab) had been suggested for the treatment of acute respiratory distress syndrome (ARDS) patients based on the concept of "cytokine storm" in COVID-19 but it has potential hazards of inducing infectious diseases.[14]

ANTI-VIRAL ACTIVITY OF PUNICA GRANATUM

An efficient approach to combat with the SARS-CoV2 was to test whether the existing antiviral drugs were effective in its treatment. In a study carried out by Wang et al, the antiviral efficiency of five FDA-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) were evaluated against a clinical isolate of 2019-nCoV in vitro. Standard assays were carried out to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates of 2019-nCoV. Cytotoxicity of the candidate compounds in Vero E6 cells (ATCC-1586) was determined by the CCK8 assay. Then, Vero E6 cells were infected with nCoV-2019 BetaCoV/Wuhan/WIV04/2019 at a multiplicity of infection (MOI) of 0.05 in the presence of varying concentrations of the test drugs. Remdesivir was found to effectively inhibit the coronavirus (2019-nCoV) in vitro.[15] Data from human trials is still in progress.

Natural antimicrobials from plant extracts have become increasingly popular for use as alternative antivirals. Pomegranate juice (PJ) and polyphenols (PP) were shown to have significant antiviral effects against foodborne viral surrogates, FCV-F9, MNV-1, and bacteriophage MS2. Xiaowei Su et al studied the effects of PJ and pomegranate polyphenols on foodborne viral infectivity. Viruses at high (~ 7 log(10) PFU/mL) or low (~ 5 log(10) PFU/mL) titers. They were mixed with equal volumes of PJ, 8, 16, and 32 mg/mL of PP, or water (control) and incubated for 1 h at room temperature. Viral infectivity after treatments was evaluated using standardized plaque assays. PJ decreased the titer of FCV-F9, MNV-1, and MS2 by 2.56, 1.32, and 0.32 log(10) PFU/mL, respectively, for low titers and 1.20, 0.06, and 0.63 log(10) PFU/mL, respectively, for high titers. Interestingly, FCV-F9 was undetectable after exposure to the three tested PP solutions using both low and high titers. MNV-1 at low initial titers was reduced by 1.30, 2.11, and 3.61 log(10) PFU/mL and at high initial titers by 1.56, 1.48, and 1.54 log(10) PFU/mL with 4, 8, and 16 mg/mL of PP treatment, respectively. MS2 at low initial titers was reduced by 0.41, 0.45, and 0.93 log(10) PFU/mL and at high initial titers by 0.32, 0.41, and 0.72 log(10) PFU/mL after 4, 8, and 16 mg/mL of PP treatment, respectively. PJ and PP resulted in titer reductions of foodborne virus surrogates after 1 h exposure, showing promise for use in hurdle technologies and/or for therapeutic or preventive use.[16] Pomegranate juice extracts have antiviral effects against human immunodeficiency virus (HIV); the mechanism of action appeared to inhibit the binding of the HIV-1 envelope glycoprotein gp 120, preventing the interaction of HIV-1 with the CD4 receptor, and thus reducing the infectivity of the virus. [17] In a previous study, 80 μ g/ml of Punica granatum peel extract inhibited the cytopathic effect completely due to HSV-1 replication in Vero cells. The extract was found to be more effective in increasing concentrations. The SI value of pomegranate peel extract and acyclovir on HSV-1 was 7.78 and 136.5,

respectively, the effect was probably due to inhibition of adsorption stage.[18]The lyophilized aqueous extract from the leaves of *Punica granatum* L., had promising activity against HHV-3 and the leaf compound Apigenin was found to interact with the protease of HHV-3 with an interaction energy of $-318.299 \text{ kcal mol}^{-1}$. [19]

OTHER CLINICAL BENEFITS OF DIFFERENT PARTS OF PUNICA GRANATUM PLANT:

The plant is known for its several other clinical benefits. In recent past the plant had been studied extensively and its beneficial effects are seen in various bacterial, viral, fungal, digestive and immunological conditions. [20]

Pomegranate Seed Oil (PSO)

Antioxidant and anti-inflammatory activities are the main features of Pomegranate seed oil which results from inhibition of lipid peroxidation and neutrophil activation. Effects of PSO on body weight and serum lipid profile are inconsistent and many studies confirmed weight reducing effects but the effects of PSO on reducing in serum triglyceride, phospholipid, cholesterol, and LDL-cholesterol levels are contradictory. PSO reduces body weight, leptin and insulin levels, enhances glucose tolerance, improves peripheral insulin sensitivity, increases carbohydrate oxidative capacity, and inhibits the progression of type 2 diabetes. [22] Seed oil extract of pomegranate has the highest concentration of polyphenols. Sarkaki et al. in their in vivo study demonstrated that, administration of PSO in permanent cerebral ischemia causes a remarkable improvement on memory with criterion condition responses (CCRs) in Y-maze and step-through latency (STL) in twoway shuttle box. The results showed that, both active and passive avoidance memories were meaningfully impaired in rats after cerebral hypoxia-ischemia (CHI). The Pomegranate seed oil has inhibitory effect on skin and breast cancers. PSO has a potent effect on tumor cells. [23] Hora et al. investigated the chemo preventive effect of PSO on skin tumor development in CD1 mice. They concluded that, PSO (5%) significantly decreased tumor incidence ($P < 0.05$), multiplicity, and TPA(12-O tetradecanoylphorbol 13-acetate) - induced ODC (ornithine decarboxylase) activity during 20 weeks of promotion. The mechanism for this effect can be inhibition of prostaglandin biosynthesis (COX-1, COX-2, and LOX) by punicic acid. In this study, in addition, topical application of 5% pomegranate seed oil remarkably inhibited ($P < 0.05$) the TPA-induced epidermal ODC activity. γ -Tocopherol is the most important constituents of PSO that is responsible for anti-cancer activity. Jiang et al. investigated that, γ -tocopherol, inhibits proliferation of prostate cancer cells. [24]

Fruit of pomegranate

Ellagitannins, the most abundant group of polyphenols in pomegranate, are hydrolyzed in ellagic acid in the gut before being further metabolized by the colon microbiota to form urolithin A and B. [24] In an in vitro study with fecal bacteria, pomegranate by-products enhanced the growth of *Bifidobacterium* spp. and *Lactobacillus* spp. acting as a prebiotic are used against intestinal parasites, dysentery, and diarrhea. [25]

Pomegranate Juice (PJ)

The consumption of pomegranate juice for a period of eight weeks showed beneficial effects on blood pressure, serum triglycerides, high-density lipoprotein cholesterol, oxidative stress and inflammation in hemodialysis patients. [26] In patients with type 2 diabetes, a consumption of 1.5 mL/kg body weight reduced serum erythropoietin level after three hours. [27], while a 200 mL/day consumption for six weeks reduced systolic and diastolic blood pressure without affecting the lipid profile. [28] In addition, the daily consumption of pomegranate juice (230 mL) has been associated with the stabilization of the ability to learn visual information over a 12 month period. [29] The consumption of pomegranate juice has also been proposed to athletes, and a systematic study for a 21 day period showed an improvement in malondialdehyde and carbonyls levels, and, thus, a decrease of the oxidative damage caused by exercise. [30] Finally, pomegranate juice has been associated with a reduction of inflammation, muscle damage, and an increase of platelets blood levels in healthy people. [31] A 30 day supplementation with pomegranate extracts in individuals with overweight and obesity beneficially affected body weight, serum glucose, insulin, triglyceride, total cholesterol, LDL-C, HDL-C (high-density lipoprotein-cholesterol) and LDL-C to HDL-C proportion, while also acting as an anti-inflammatory agent, lowering inflammatory and lipid peroxidation biomarkers. [32]

Pomegranate Flower (PF)

PF extracts have been shown to have beneficial effects against diabetes by reducing the fasting blood glucose in rats. [34] In another study Gil et al., a pomegranate extract made from a mixture of unspecified parts showed beneficial effects in humans with type II diabetes. The extracts antagonized the hyperglycemia-induced oxidative stress, illustrated by the drop in the levels of plasma malondialdehyde and the increase in the total level of plasma glutathione. [35]

Pomegranate leaves (PL)

Antioxidant and anti-inflammatory activities were the major bioactivities studied in PL.[36] In addition, many works identified the potential of antimicrobial effects of the PF extract on plant pathogenic fungi (*Penicillium italicum*, *Botrytis cinerea*, and *Rhizopus stolonifer*), for Gram negative bacteria (*Pseudomonas aeruginosa*, *E. coli*, and *Salmonella typhimurium*), Gram positive bacteria (*Staphylococcus aureus*, *Listeria monocytogenes*, *Enterococcus faecalis*, and *Bacillus cereus*), yeast (*Candida albicans*), and fungi such as *Aspergillus niger*. [37]

Pomegranate Peel (PP)

The pomegranate pericarp has proven to be effective against many types of bacteria. The compound isolated from the PP have been shown to be effective against Gram-negative bacteria (*Escherichia coli*, *Salmonella* sp, *Pseudomonas aeruginosa*, *P. putida*, *Enterobacter aerogenes* and *Klebsiella pneumonia*), and Gram-positive bacteria (*Bacillus subtilis*, *Listeria innocua*, *L. monocytogenes*, *Taphylococcus aureus*, and *Staphylococcus aureus*). [38] In one experiment, PP extracts also showed effects in preserving meat against 8 different strains of *Listeria monocytogenes*. In the mentioned study, the various extracts had different strengths, attributed to variability in the raw materials (different varieties). In a complementary manner, antifungal (*Penicillium digitatum*, *P. italicum*, *Botrytis cinerea*, *Rhizopus stolonifer*, and *Saccharomyces cerevisiae*) and antiviral (HSV-2) activities were also reported. [39]

COMBINATION OF DIFFERENT POMEGRANATES PARTS

Extracts made from mixtures of different pomegranate parts have different sets of compounds that may result in synergistic effects that are greater than those from single compounds [Olapour and Najafzadeh 2010]. [40] An emulsion made from the combination of PS oil and an extract from PJ, PP, PL, and PF demonstrated evidence of having a high chemo-preventive effect against experimental hepatocarcinogenesis in rats, resulting in fewer animals with visible hepatocyte nodules and lower nodule multiplicity. [41] According to the same study, this effect was probably due to pomegranate phytoconstituents that utilize antioxidant mechanisms to repeal the oxidative stress provoked during diethyl nitrosamine-initiated hepatocarcinogenesis.

Another study showed that the same emulsion reversed the increase of inducible nitric oxide synthase (responsible of generating nitric oxide that contributes to chronic inflammatory reactions) in hepatocellular carcinogenesis, indicating a clear anti-inflammatory effect. [42]

The anti-inflammatory activity of pomegranate extract made from different pomegranate parts showed effects against colon inflammation, due to the anti-inflammatory effects of the metabolites (in particular, urolithin-A). [43]

A study in transgenic mouse concluded that some compounds of pomegranate extract made from PJ and PS attenuated the nuclear factor of activated T-cells in a reported cell line, decreasing A β -stimulated tumor necrosis factor α secretion by murine microglia. This indicates that pomegranate produces anti-inflammatory effects in the brain and that adding pomegranate in the diet may attenuate AD development. [44]

CONCLUSION

The innumerable phytoconstituents of this rich fruit with supporting evidence from the studies conducted in the past, the potential role of *Punica Granatum* in management of COVID-19 can not be ignored. However, many of the study results are based on *in vitro* and cell-based assays. It necessitates further confirmation of *in vivo* efficacy through human clinical trials.

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Viral infections suppress immune system of the host. SARS-CoV-2, Just like other viral infections weaken the host immunity. A strong immune system is the key to protection from virus and other pathogens. Severe cases admitted to the intensive care unit showed high level of pro-inflammatory cytokines which enhanced the disease severity. [1]The inflammatory response of the body also plays a crucial role in SARS-induced lung injury cases. It is important to control the mass production of cytokines and inflammatory response, given that they are responsible for the accumulation of cells and fluids in CoV pneumonia. A strategy for regulating the immune response and controlling excessive inflammation without compromising the beneficial host defense in needed.[2]Pomegranate extract shows potential for use as a supplemental food in improving immunity status of subjects in an emergency situation.[3]The addition of antioxidants such as beta-carotene might increase the activity of macrophages, protect macrophages from oxidative damage and enhance the T-lymphocyte proliferative response.[4] In vitro and animal studies also demonstrate that administration of plant extracts can improve and protect the immune systems.[5,6] Polyphenols and lycopene are secondary metabolites possessing antioxidant activity. Administration of polyphenols in humans can also enhance macrophage phagocytosis.[3] WHO guidelines recommend some Vitamins and antiviral therapies and oxygen inhalation and non pharmaceutical measures as supportive care for PandemicCovid-19.[7]Pomegranate extract contains bioactive compounds similar to *S. mialhesi*, where both the extracts have immune-stimulatory activities tested in vitro and in vivo.[3]

PHYTOCONSTITUENTS OF PUNICA GRANATUM

The primary bioactive constituents of pomegranate juice are the polyphenols. It is comprised of 85.4% water, 10.6% total sugars, 1.4% pectin, 0.2-1.0% polyphenols. Minerals in the juice and seed include Fe, Ca, Cu, K, Mg, Mn, Mo, Se, Sn, Sr, and Zn. [8] It is a rich source of Gallic acid, Ellagic acid, Flavonoids and their glycosides, Anthocyanins, Amino acids: Proline, Valine, Methionine, Glutamic and Aspartic Acid, Indoleamines and Tocopherols. [9,10] Pomegranate seed oil comprises 12–20% of total seed weight. The oil consists of approximately 80% conjugate octadecatrienoic fatty acids, with a high content of cis 9, trans 11, cis 13 acid (i.e. punicic acid).[11] Minor components of the oil include sterols, steroids, tocopherols, and a key component of mammalian myelin sheaths, cerebroside. The main chemical constituents isolated from Pomegranate Skin or Pericarp include Hydroxybenzoic acids: Gallic acid, Ellagic, Hydroxycinnamic acids & Chlorogenic acid. It also contains Flavon-3-ols/Flavonoids and their glycosides: Catechin, Epicatechin, Epigallocatechin-3-gallate, Quercetin, Kaempferol & Naringin. The Anthocyanins are Cyanidin, Pelargonidin, Delphinidin and Ellagitannins.[12]

ANTI INFLAMMATORY ACTIVITY OF PUNICA GRANATUM:

Rasheed et al reported that Pomegranate fruit extract decreased PMACI stimulated inflammatory gene expression and production of IL-6 and IL8 in KU812 cells. The inhibitory effect of the extract on the pro-inflammatory cytokines was MAPK subgroups c-junction N-terminal kinase (JNK- and extracellular-regulated kinase (ERK) dependent. The crude extract also inhibited NF- κ B by inhibiting I κ B-degradation in human basophil cells.[13] Based on their results obtained, the authors suggested that polyphenol rich pomegranate fruit extract exerts its inhibitory effect on IL-6 and IL-8 expression via modulation of the activation and DNA binding activity of NF- κ B. In COVID-19, the use of Interleukin 6 (IL-6) inhibitor (tocilizumab) had been suggested for the treatment of acute respiratory distress syndrome (ARDS) patients based on the concept of "cytokine storm" in COVID-19 but it has potential hazards of inducing infectious diseases.[14]

ANTI-VIRAL ACTIVITY OF PUNICA GRANATUM

An efficient approach to combat with the SARS-CoV2 was to test whether the existing antiviral drugs were effective in its treatment. In a study carried out by Wang et al, the antiviral efficiency of five FDA-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) were evaluated against a clinical isolate of 2019-nCoV in vitro. Standard assays were carried out to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates of 2019-nCoV. Cytotoxicity of the candidate compounds in Vero E6 cells (ATCC-1586) was determined by the CCK8 assay. Then, Vero E6 cells were infected with nCoV-2019 BetaCoV/Wuhan/WIV04/2019 at a multiplicity of infection (MOI) of 0.05 in the presence of varying concentrations of the test drugs. Remdesivir was found to effectively inhibit the coronavirus (2019-nCoV) in vitro.[15] Data from human trials is still in progress.

Natural antimicrobials from plant extracts have become increasingly popular for use as alternative antivirals. Pomegranate juice (PJ) and polyphenols (PP) were shown to have significant antiviral effects against foodborne viral surrogates, FCV-F9, MNV-1, and bacteriophage MS2. Xiaowei Su et al studied the effects of PJ and pomegranate polyphenols on foodborne viral infectivity. Viruses at high (~ 7 log(10) PFU/mL) or low (~ 5 log(10) PFU/mL) titers. They were mixed with equal volumes of PJ, 8, 16, and 32 mg/mL of PP, or water (control) and incubated for 1 h at room temperature. Viral infectivity after treatments was evaluated using standardized plaque assays. PJ decreased the titer of FCV-F9, MNV-1, and MS2 by 2.56, 1.32, and 0.32 log(10) PFU/mL, respectively, for low titers and 1.20, 0.06, and 0.63 log(10) PFU/mL, respectively, for high titers. Interestingly, FCV-F9 was undetectable after exposure to the three tested PP solutions using both low and high titers. MNV-1 at low initial titers was reduced by 1.30, 2.11, and 3.61 log(10) PFU/mL and at high initial titers by 1.56, 1.48, and 1.54 log(10) PFU/mL with 4, 8, and 16 mg/mL of PP treatment, respectively. MS2 at low initial titers was reduced by 0.41, 0.45, and 0.93 log(10) PFU/mL and at high initial titers by 0.32, 0.41, and 0.72 log(10) PFU/mL after 4, 8, and 16 mg/mL of PP treatment, respectively. PJ and PP resulted in titer reductions of foodborne virus surrogates after 1 h exposure, showing promise for use in hurdle technologies and/or for therapeutic or preventive use.[16] Pomegranate juice extracts have antiviral effects against human immunodeficiency virus (HIV); the mechanism of action appeared to inhibit the binding of the HIV-1 envelope glycoprotein gp 120, preventing the interaction of HIV-1 with the CD4 receptor, and thus reducing the infectivity of the virus. [17] In a previous study, 80 μ g/ml of Punica granatum peel extract inhibited the cytopathic effect completely due to HSV-1 replication in Vero cells. The extract was found to be more effective in increasing concentrations. The SI value of pomegranate peel extract and acyclovir on HSV-1 was 7.78 and 136.5,

respectively, the effect was probably due to inhibition of adsorption stage.[18]The lyophilized aqueous extract from the leaves of *Punica granatum* L., had promising activity against HHV-3 and the leaf compound Apigenin was found to interact with the protease of HHV-3 with an interaction energy of $-318.299 \text{ kcal mol}^{-1}$. [19]

OTHER CLINICAL BENEFITS OF DIFFERENT PARTS OF PUNICA GRANATUM PLANT:

The plant is known for its several other clinical benefits. In recent past the plant had been studied extensively and its beneficial effects are seen in various bacterial, viral, fungal, digestive and immunological conditions. [20]

Pomegranate Seed Oil (PSO)

Antioxidant and anti-inflammatory activities are the main features of Pomegranate seed oil which results from inhibition of lipid peroxidation and neutrophil activation. Effects of PSO on body weight and serum lipid profile are inconsistent and many studies confirmed weight reducing effects but the effects of PSO on reducing in serum triglyceride, phospholipid, cholesterol, and LDL-cholesterol levels are contradictory. PSO reduces body weight, leptin and insulin levels, enhances glucose tolerance, improves peripheral insulin sensitivity, increases carbohydrate oxidative capacity, and inhibits the progression of type 2 diabetes. [22] Seed oil extract of pomegranate has the highest concentration of polyphenols. Sarkaki et al. in their in vivo study demonstrated that, administration of PSO in permanent cerebral ischemia causes a remarkable improvement on memory with criterion condition responses (CCRs) in Y-maze and step-through latency (STL) in twoway shuttle box. The results showed that, both active and passive avoidance memories were meaningfully impaired in rats after cerebral hypoxia-ischemia (CHI). The Pomegranate seed oil has inhibitory effect on skin and breast cancers. PSO has a potent effect on tumor cells. [23] Hora et al. investigated the chemo preventive effect of PSO on skin tumor development in CD1 mice. They concluded that, PSO (5%) significantly decreased tumor incidence ($P < 0.05$), multiplicity, and TPA(12-O tetradecanoylphorbol 13-acetate) - induced ODC (ornithine decarboxylase) activity during 20 weeks of promotion. The mechanism for this effect can be inhibition of prostaglandin biosynthesis (COX-1, COX-2, and LOX) by punicic acid. In this study, in addition, topical application of 5% pomegranate seed oil remarkably inhibited ($P < 0.05$) the TPA-induced epidermal ODC activity. γ -Tocopherol is the most important constituents of PSO that is responsible for anti-cancer activity. Jiang et al. investigated that, γ -tocopherol, inhibits proliferation of prostate cancer cells. [24]

Fruit of pomegranate

Ellagitannins, the most abundant group of polyphenols in pomegranate, are hydrolyzed in ellagic acid in the gut before being further metabolized by the colon microbiota to form urolithin A and B. [24] In an in vitro study with fecal bacteria, pomegranate by-products enhanced the growth of *Bifidobacterium* spp. and *Lactobacillus* spp. acting as a prebiotic are used against intestinal parasites, dysentery, and diarrhea. [25]

Pomegranate Juice (PJ)

The consumption of pomegranate juice for a period of eight weeks showed beneficial effects on blood pressure, serum triglycerides, high-density lipoprotein cholesterol, oxidative stress and inflammation in hemodialysis patients. [26] In patients with type 2 diabetes, a consumption of 1.5 mL/kg body weight reduced serum erythropoietin level after three hours. [27], while a 200 mL/day consumption for six weeks reduced systolic and diastolic blood pressure without affecting the lipid profile. [28] In addition, the daily consumption of pomegranate juice (230 mL) has been associated with the stabilization of the ability to learn visual information over a 12 month period. [29] The consumption of pomegranate juice has also been proposed to athletes, and a systematic study for a 21 day period showed an improvement in malondialdehyde and carbonyls levels, and, thus, a decrease of the oxidative damage caused by exercise. [30] Finally, pomegranate juice has been associated with a reduction of inflammation, muscle damage, and an increase of platelets blood levels in healthy people. [31] A 30 day supplementation with pomegranate extracts in individuals with overweight and obesity beneficially affected body weight, serum glucose, insulin, triglyceride, total cholesterol, LDL-C, HDL-C (high-density lipoprotein-cholesterol) and LDL-C to HDL-C proportion, while also acting as an anti-inflammatory agent, lowering inflammatory and lipid peroxidation biomarkers. [32]

Pomegranate Flower (PF)

PF extracts have been shown to have beneficial effects against diabetes by reducing the fasting blood glucose in rats. [34] In another study Gil et al., a pomegranate extract made from a mixture of unspecified parts showed beneficial effects in humans with type II diabetes. The extracts antagonized the hyperglycemia-induced oxidative stress, illustrated by the drop in the levels of plasma malondialdehyde and the increase in the total level of plasma glutathione. [35]

Pomegranate leaves (PL)

Antioxidant and anti-inflammatory activities were the major bioactivities studied in PL.[36] In addition, many works identified the potential of antimicrobial effects of the PF extract on plant pathogenic fungi (*Penicillium italicum*, *Botrytis cinerea*, and *Rhizopus stolonifer*), for Gram negative bacteria (*Pseudomonas aeruginosa*, *E. coli*, and *Salmonella typhimurium*), Gram positive bacteria (*Staphylococcus aureus*, *Listeria monocytogenes*, *Enterococcus faecalis*, and *Bacillus cereus*), yeast (*Candida albicans*), and fungi such as *Aspergillus niger*. [37]

Pomegranate Peel (PP)

The pomegranate pericarp has proven to be effective against many types of bacteria. The compound isolated from the PP have been shown to be effective against Gram-negative bacteria (*Escherichia coli*, *Salmonella sp*, *Pseudomonas aeruginosa*, *P. putida*, *Enterobacter aerogenes* and *Klebsiella pneumonia*), and Gram-positive bacteria (*Bacillus subtilis*, *Listeria innocua*, *L. monocytogenes*, *Taphylococcus aureus*, and *Staphylococcus aureus*). [38] In one experiment, PP extracts also showed effects in preserving meat against 8 different strains of *Listeria monocytogenes*. In the mentioned study, the various extracts had different strengths, attributed to variability in the raw materials (different varieties). In a complementary manner, antifungal (*Penicillium digitatum*, *P. italicum*, *Botrytis cinerea*, *Rhizopus stolonifer*, and *Saccharomyces cerevisiae*) and antiviral (HSV-2) activities were also reported. [39]

COMBINATION OF DIFFERENT POMEGRANATES PARTS

Extracts made from mixtures of different pomegranate parts have different sets of compounds that may result in synergistic effects that are greater than those from single compounds [Olapour and Najafzadeh 2010]. [40] An emulsion made from the combination of PS oil and an extract from PJ, PP, PL, and PF demonstrated evidence of having a high chemo-preventive effect against experimental hepatocarcinogenesis in rats, resulting in fewer animals with visible hepatocyte nodules and lower nodule multiplicity. [41] According to the same study, this effect was probably due to pomegranate phytoconstituents that utilize antioxidant mechanisms to repeal the oxidative stress provoked during diethyl nitrosamine-initiated hepatocarcinogenesis.

Another study showed that the same emulsion reversed the increase of inducible nitric oxide synthase (responsible of generating nitric oxide that contributes to chronic inflammatory reactions) in hepatocellular carcinogenesis, indicating a clear anti-inflammatory effect. [42]

The anti-inflammatory activity of pomegranate extract made from different pomegranate parts showed effects against colon inflammation, due to the anti-inflammatory effects of the metabolites (in particular, urolithin-A). [43]

A study in transgenic mouse concluded that some compounds of pomegranate extract made from PJ and PS attenuated the nuclear factor of activated T-cells in a reported cell line, decreasing A β -stimulated tumor necrosis factor α secretion by murine microglia. This indicates that pomegranate produces anti-inflammatory effects in the brain and that adding pomegranate in the diet may attenuate AD development. [44]

CONCLUSION

The innumerable phytoconstituents of this rich fruit with supporting evidence from the studies conducted in the past, the potential role of *Punica Granatum* in management of COVID-19 can not be ignored. However, many of the study results are based on *in vitro* and cell-based assays. It necessitates further confirmation of *in vivo* efficacy through human clinical trials.

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