Review Article

THERAPEUTIC POTENTIAL OF POMEGRANATE IN SARS-CoV-2 AND ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

ABSTRACT

COVID-19 is a viral disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which has rapidly spread across the world causing a global health crisis. As such researchers across the world have focused on identifying potential treatments for COVID-19. Due to the paucity of therapeutics against SARS-CoV-2, there is an urgency for the identification of safe and effective treatments for this global pandemic. Thus, existing drugs are being evaluated as potential candidates and also an extensive amounts of research is conducted to develop novel therapeutics against COVID-19. Since ancient times natural products have been used as a treatment for a variety of diseases and to aid in the synthetic drug development process. The phytochemical constituents of Pomegranate have been extensively investigated in the past decade for their anti-tumor activity. The purpose of this review is to elaborate how the major phytochemicals of pomegranate such as delphinidin, cyanidin, ellagitannin, punicalagin could be utilized as pharmacological agents to suppress SARS-CoV-2 cell entry, replication, and immunological sequences that give rise to ARDS, based on current knowledge of interactome between host cells and SARS-CoV-2. The SARS-CoV-2 uses various biological mechanisms to modulate immune reactions, uncontrolled gene expression, and cell invasion to improve their survival inside the human host cells similar to those observed in certain tumors. Therefore, this review utilizes the findings of existing tumor-related research which describe how pomegranate extract interact with various biological

pathways associated with tumor suppression as indirect evidence for its ability to act as a potential therapeutic agent against SARS-CoV-2.

Keywords – COVID-19, Pomegranate, Polyphenols, Acute Respiratory Distress Syndrome, Flavonoids.

INTRODUCTION

Novel Coronavirus (COVID-19) has been one of the most devastating diseases faced by mankind since it emerged in Wuhan City, Hubei Province, China in late 2019. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has been identified as the pathogen responsible for this outbreak which has caused a severe threat to public health globally(1). As of the 24th of September 2021 over 230 million cases and 4.7 million deaths have been reported globally across over 180 countries(2). The World Health Organization (WHO) declared the novel coronavirus as a global pandemic on the 11th of March 2020(3).

The SARS-CoV-2 is a positive-sense single-stranded RNA virus belonging to the Beta-Coronavirus family(4, 5). It was not the first coronavirus to infect humans causing an outbreak in recent history. The SARS-CoV that emerged first in 2002 in China and the Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) that emerged first in Saudi Arabia in 2012 are two serious infections caused by coronaviruses(6). SARS-CoV-2 has a mean incubation period between 4.8 to 9 days resulting in a weighted pool incubation period of COVID-19 been 6.5 days(7). Available SARS-CoV-2epidemiological data suggest that asymptomatic cases range from 1.6% to 51.7% however, around 6.5% to 31.7% of hospitalized patients require ICU admission due to Acute Respiratory Distress Syndrome (ARDS) or multiorgan failure(8).

Currently, there are no clinically proven anti-viral drugs specifically designed for the treatment of COVID-19, and treatment is mostly based on several existing anti-viral drugs(9). The U.S Food and Drug Administration has approved the use of the existing antiviral drug Velkury (Remdesivir) for use in adults and children patients above 12 years of age and not less than 40 kg in weight when requiring hospitalization. Baricitinib, Bamlanivimab and Etesevimab, Sotrovimab and Tocilizumab are few drugs that have been approved under COVID-19 Emergency Use Authorization (EUA)(10). The lack of therapeutics to combat the novel coronavirus has highlighted the urgent need for potential novel therapeutics. Natural products have been a promising source for lead compounds in the process of drug discovery and development since ancient times. Aspirin, Penicillin and their derivatives, Taxol and Quinine are some widely used therapeutics that are of natural product-based origin.

Pomegranate, *Punica granatum* is a small fruit-bearing tree that has been cultivated for many years across the world. Since ancient times many civilizations and cultures have been using it as a treatment for a wide range of clinical conditions. In indigenous medicine, pomegranate is considered “A pharmacy unto itself” due to its huge medical value(11). It has been used as an antidiabetic, antimicrobial, antidiarrheal, and antitumor agent(12). Current evidence suggests that pomegranates could be effective in the management of serious disease conditions such as prostate cancer, breast cancer, skin cancer, and several other cancers(13). Even though recent scientific findings suggest that polyphenols of pomegranates could be successful in controlling various types of carcinomas, substantial attention has not been focused on evaluating their potential as an anti-viral agent(14, 15). This review systematically analyses the role of pomegranate and its bioactive constituents in relation to SARS-CoV-2 host cell entry, replication, and the biological mechanisms leading to Acute Lung Injury (ALI) and ARDS in order to provide insights into the therapeutic potential of pomegranate.

CHEMICAL CONSTITUENTS ISOLATED FROM *Punica granatum.*

Bioactive compounds of pomegranate has been widely studied in the past resulting the isolation of numerous bioactive compounds. Anthocyanins, flavonols, flavanols, ellagtannins and phenolic acids are some of the major classes of compounds to which the isolated metabolites belong. **Table 1** summarizes the bioactive compounds present in pomegranate according to the class of compound to which it belong. Furthermore, location and the chemical structures of the bioactive compounds have been included as these compounds might need further optimizations to modify their pharmacological characteristics to make them orally druggable. Anthocyanins are red, blue and purple coloured pigments found in flowers and in the fruits of plants which are a subclass of phenolic phytochemicals(15). Delphinidin, cyanidin and pelarginidin are some of the anthocyanins that has been isolated from the peel extract and juice of pomegranate(16, 17). Flavonols such as quercitrin, kaempferol and flavanols such as epigallocatechin gallate and catechin have been isolated from the peel extract and juice of pomegranate(16-18). Other bioactive compounds include ellagitannins such as punicalagin, punicalin and phenolic acids such as gallic acid and ellagic acid.

POTENTIAL OF POLYPHENOLS OF *Punica granatum* AS INHIBITORS OF SARS-CoV-2 CELL ENTRY.

The pathogenicity of SARS-CoV-2 resembles that of the Coronavirus responsible for the outbreak in 2002. It contains four structural proteins namely the spike (S), envelop (E), membrane (M), and nucleocapsid (N)(4, 5). Spike proteins are crown-like proteins that are being cleaved into S1 and S2 subunits host cell proteases. The S1 subunit contains a receptor-binding domain for angiotensin-converting enzyme 2 (ACE2) that binds with the host cell(4). This receptor binding domain of the spike glycoprotein (RBD-S) binds with the protease domain (PD-ACE2) of the host cell leading to infection of the host cell by the virus. The S2 subunit of the spike protein mediates the membrane fusion(4, 5).

Trance Membrane Protein Serine S2 (TMPRSS2) is most evidently involved in cleaving the spike protein of SARS-CoV-2 into the S1 subunit and S2 subunits. Other potential cleaveage proteins are cathepsin, furin, or trypsin(4, 5, 19). Therefor TMPRSS2 is a potential therapeutic target in preventing cell entry of SARS-CoV-2(20). Quercitrin and myricitrin isolated from the pomegranate peel extract have been identified as potential anti-TMPRSS2 molecules(21). The amount of quercetin in pomegranate peel extract has been found to be 88.6mg for every 100g which is far higher than in any other fruit extract previously recorded(22). Studies on TMPRSS2 have also noted that TMPRSS2 gene expression is up-regulated in androgen-dependent prostatic cancers(5, 6). It has been found out that punicalagin, a bioactive constituent of pomegranate is capable of inhibiting the tumor growth associated with prostatic cancer(23). Therefore, it could be suggested punicalagin may involve in the inhibition of TMPRSS2 and thereby could inhibit the viral entry reducing the risk of COVID-19.

It has been found that SARS-COV-2 spike protein contains a furin cleavage site which facilitates the virus entry into the specific host cells, making SARS-CoV-2 is more infectious than the other SARS viruses(5). Furin is a serine protease that has been proposed to act as a mediator in the cleavage of spike protein into S1 and S2 subunits during viral entry(6, 19, 22). It has been suggested this specific furin cleavage site is responsible for some of the unique properties of SARS-CoV-2 infection(4). Furin is abundantly found in the human respiratory tract, hence SARS-CoV-2 may successfully exploit furin to activate surface glycoproteins to enhance its pathogenicity (24). Therefore, it indicates that furin could be a potential target for the development of therapeutics for the prevention of COVID-19 disease(20, 25). Several studies have shown that many polyphenols including Quercetin and Epigallocatechin Gallate (EGCG) found in pomegranate could inhibit furin and thereby could inhibit the viral entry into the host cells(26). It has also been found out that the 88.6mg of quercetin in 100g of pomegranate peel extract is far higher than any other fruit extract(22).

Cathepsins are endosomal and lysosomal proteases(27). They selectively cleave proteins by cleaving the peptide bonds that link specific amino acids. Cathepsin could mediate the membrane fusion and cleavage of the spike proteins(27). SARS-COV infection could be prevented by specific inhibitors of the pH-sensitive endosomal protease cathepsin L(5, 6, 19, 26). It has been suggested that cathepsin L selective inhibitors are a potential therapeutic agent for SARS CoV-2 infection(28). Pomegranate peel and fruit extracts show a strong inhibitory effect on cathepsin activity. These cathepsin inhibitory properties of pomegranate fruit and peel extract could be a potential mechanism that could be utilized to prevent the entry of the virus into the host cell(29).

Integrins are a group of heterogenic cell surface receptors. They are involved in cell adhesion, migration, signaling, angiogenesis and coagulopathy(30). The RGD motif comprised of the tripeptide arginine, glycine, aspartic acid which is found in the receptor-binding domain (RBD) of the spike protein of SARS CoV-2 shows a strong affinity to integrins, particularly αVβ3. It has been found out that the RGD motif is absent in all other coronaviruses. Thus it is thought to have a function working as an alternative receptor for SARS-CoV-2 cell entry(31, 32). Binding of the spike proteins with the integrin heterodimers activates the transduction pathways involving phosphatidylinositol-3kinase (PI-3K) or Mitogen Activator Protein Kinase (MAPK) which promotes the viral entry(31). Delphinidin is a major polyphenol present in pomegranate extract proven to be effective in inhibition of PI-3K and MAPK expression. Therefore delphinidin is a potential molecule that could prevent integrin mediated SARS-CoV-2 entry into the host cell and coagulopathy by inhibiting downstream mediators such as PI-3K and MAPK kinases(33, 34).

PATHOPHYSIOLOGY OF SARS-CoV-2 VIRAL INFECTION.

The spike protein of SARS-CoV-2 binds to the ACE2 through a mechanism similar to that used by SARS-CoV in 2002(35). ACE2 is a natural protector in the human body against lung injury.

Along with the viral infection, ACE2 expression is downregulated and in compensation ACE 1 expression is up-regulated causing an excess amount of Angiotensin 2 to be produced with the aid of ACE1(36). Uncontrolled increase in Angiotensin 2 causes overstimulation of type 1A angiotensin receptors (AGTR 1A) leading to increased vascular permeability in the lungs. This dysregulation of the renin angiotensin system is a key turning point of Acute Respiratory Distress Syndrome (ARDS)(37). ARDS has been found as the leading cause of death in SARS CoV-2 infection. ARDS has also been found to be associated with the up-regulation of pro-inflammatory cytokines production termed a 'cytokine storm'(38). Cytokines such as interleukin 1β.IL-1, IL-6, IL-8, CC chemokine ligand 2 (CCL-2), CXC chemokine ligand 10 (CXCL-10), interferon α, and interferon-γ are released during the cytokine storm(39, 40).

The progression of an infected patient to ARDS in SARS CoV-2 has been marked by the upregulation of proinflammatory cytokines and chemokines(39, 40). Initial onset of rapid viral replication causes massive epithelial and endothelial damage are those which associate with hypercytokinemia and increase mononuclear macrophages and neutrophil infiltration(41). The damaged alveolar cells stimulate macrophages to secrete TNFα, IL-1, IL-6, IL-8, and chemokines. Cytokines such as TNFα, IL-1 increase vascular permeability and increase fusion molecules which attracts a large number of neutrophils and monocytes to the infected area(42). Neutrophils play a key role in the development of ARDS(43). It triggers dysfunction of both type1 and type2 pneumocytes leading to reduction of surfactants causing atelectasis. Inter leukin-6 causes an increase in capillary permeability, interstitial edema, alveolar edema, vasodilatation, and also attracts neutrophils which further enhance damage to the alveolar cells(44).

EFFECT OF POLYPHENOLS OF *Punica granatum* AS ATTENUATORS OF COVID-19 INDUCED INFLAMMATION.

Nuclear Factor kappa Beta (NF-κB) is a transcription protein complex. It has been established that the NF-κB pathway plays an important role in SARS-CoV-2 infection by increasing viral replication, delaying apoptosis, and modulating host immune response which leads to increase production of IL-2, IL-6, IL-8, TNF-α(45). NF-κB complex is activated by the nuclear capsid protein of the SARS-CoV-2(46). Previous studies have proved that treatment with NF-κB inhibitors reduces expression of TNF-α, CCL2, and CXCL2, hence it is suggested that NF-κB plays an important role in SARS-CoV-2 mediated induction of pro-inflammatory cytokines(45, 47) and hence inhibition of NF-κB mediated inflammation can increase the chance of survival(48, 49). The major anthocyanins of pomegranate juice such as delphinidin, cyanidin, pelargonidin (Table 01) and ellagitannins such as punicalagin and quercetin show potential inhibitory effects on NF-kB, TNF-α and TNF-α induce COX-2 production(13, 50-53). Therefore it could be suggested that consumption of pomegranate extract rich in the above-mentioned polyphenols reduces SARS-COV-2 viral replication, induces apoptosis, and inhibits the NF-kB triggered inflammatory cascade.

The Vascular Endothelial Growth Factor (VEGF) plays a pivotal role in both angiogenesis and microvascular permeability in Acute Lung Injury (ALI) and ARDS which leads to protein-rich pulmonary edema(53, 54). VEGF expression is significantly elevated in SARS-CoV-2 infected patients who are critically ill compared to the healthy controls(55). Anti VEGF medications have been suggested as a potential target for SARS CoV-2 induced ALI and ARDS(37). Major anthocyanins such as delphinidin, cyanidin, and pelargonidin isolated from the peel of pomegranate(56) have been shown to suppress VEGF through several pathways(15, 57). Delphinidin is known to inhibit TNFα induced VEGF receptor expression in endothelial cells of the host(15) whilst ellagitannin has been found to inhibit VEGF through PIK/Akt pathway and NF-kB pathway(50, 58). These effects have been previously proven in various in vitro and in vivo studies.

Matrix Metalloproteinases (MMPs) are known to be involved in the degradation of the extracellular matrix. In vitro and in vivo studies have revealed the role of MMPs and protein kinases in the pathogenicity of SARS-CoV-2 in ALI and ARDS(54). These molecules are capable of acting independently or in a coordinated manner through activation of the tyrosine regulatory pathway in the development of ARDS. It has been suggested the concentration of MMP's has a direct correlation with the severity of ALI and ARDS(59) and hence inhibition of MMP's attenuates the inflammation and improves one's chance of survival(60). Anthocyanins of pomegranate are found to stimulate Tissue Inhibitors of Metalloproteinase 2 (TIMP-2) and Plasminogen Activator Inhibitor (PAI) both of which counteract MMPs and Urokinase Plasminogen Activators (uPA)(61, 62). Epigallocatechin gallate which is also a polyphenol constituent of pomegranate has been found to inhibits the collagenase activity of MMP2(63).

Clinical data has shown the pathophysiological role of Fibroblast Growth Factors (FGF) in ARDS and its direct correlation with morbidity and mortality(64). The fibroproliferative phase of ARDS which occurs within 24 hours of infection is characterized by fibroblast accumulation, deposition of collagen in the extracellular matrix(54). FGF plays a critical role in the development of pulmonary fibrosis(65) which is associated with the poor quality of life and poor prognosis. It has been proved that the health-related quality of life (HRQL) is poor at 06 months upon recovery from ARDS in comparison with a healthy individual(54). This occurs as a consequence of the impairment of removal or reabsorption of the provisional extracellular matrix. Many clinical studies have suggested that the potential therapeutic role of anti-fibrotic therapy in SARS-CoV-2 infection(66). Delphinidin, an anthocyanin present in pomegranate peel extract has proven its regulatory potentials in pathological conditions associated with overexpression of FGF in a number of clinical studies(57). Consequently, it could be suggested that pomegranate peel extract could be a potential source in improving the clinical outcome and

health-related quality of life of patients with the risk of suffering from COVID-19 associated ARDS.

The p38 MAPK pathway activation has been reported in cells infected with SARS-CoV(6, 67). The p38 MAPK inhibitors can suppress IL-6 and TNF-α expression in monocytes and mast cells. Current clinical evidence suggests that the p38 MAPK signaling pathway may be one of the principal mechanisms of acute lung injury and ARDS. Previous research has shown that p38 MAPK inhibitors can inhibit infection and replication of human coronaviruses(68) therefore p38 MAPK inhibition could be an effective therapeutic target for the development of therapeutics against SARS-CoV-2 infection(69). Delphinidin and Punicalagin present in pomegranate extract inhibit the p38 MAPK pathway(15, 51, 70, 71). Therefore the pomegranate extract which is rich in polyphenolic substances may function as a potent antiviral and anti-inflammatory agent for SARS CoV-2 infection.

Valosin Containing Protein (VCP) or transitional endoplasmic reticulum ATPase is an enzyme that belongs to the ATPase superfamily. It has been revealed by genome-wide screen that VCP is necessary for the exit of coronavirus from the endosomes(6, 72). Inhibition of a VCP resulted in virus accumulation in early endosome leading to a lower rate of viral replication(72). It has been recently revealed that SARS-CoV-2 ORF9c, a highly unstable membrane protein could disturb the anti-viral immune response of human lung epithelial cells(73). The VCP inhibitors have been found to possess a significant potential to attenuate the effects of SARS-CoV-2 ORF9c(73). Pomegranate extract has been found to be able to down-regulate the VCP expression(74, 75) and thereby reduce the release of the virus from the endosomes. A decrease in expression of VCP is also known to reduce the effects of NF-kB induced inflammatory cascade.

POTENTIAL ROLES OF *Punica granatum* IN CELL FUNCTIONS

Improving immune dysfunction.

The total number of NK cells and CD8 T cells are markedly depleted in severe cases of COVID-19 infection(5). Their functions were also markedly depleted. The functions of NK cells are exhausted in consequence of the increased expression of NK inhibitory receptor CD94/NK Group 2 member A (NKG2A) in SARS-CoV-19 patients(76). NKG2A is a ligand that binds to inhibit NK cells Receptor (iNKR's) and suppress the activity of NK cells. Preventing the expression of NKG2A could aid to overcome the resistance to NK cells(77). Pomegranate is a fruit rich in polyphenolic flavonoids. Punicalagin, a type of polyphenolic compound is responsible for more than 50% of the potent antioxidant activity of pomegranate juice(78-80). Punicalagin is a compound that is well known for its anti-cancer activity. A number of clinical studies have suggested that punicalagin can induce autophagic cell death in papillary thyroid carcinoma through down-regulation of expression of NKG2A(79, 81). Quercetin, a flavonoid polyphenol found in pomegranate promotes natural killer cell activity(82) and epigallocatechin-3-0 gallate (EGCG) induces the function of NK cells(83). Hence pomegranate has a great potential as an agent to overcome resistance to NK cells associated with SARS-CoV-2.

Inducing Apoptosis.

Apoptosis, also known as programmed cell death is a part of the host defense mechanism against viral replication and proliferation. Apoptosis is initiated by specific cytotoxic T cells or cytokines. Many viruses manipulate host cell apoptosis in order to ensure their survival. Viruses could encoat proteins that can inhibit apoptosis, thereby allowing prolong survival of the virus in the host cells maximizing the production of viral progeny(84, 85).

Punicalagin, the major ellagitannin found in pomegranate is hydrolyzed into ellagic acid in the gut by gut flora(13). Other ellagitannins found in pomegranate are punicalin and gallic acid(13). Ellagitannins found in the pomegranate peel extract can accelerate various apoptosis pathways(13, 86). Immunological analysis has revealed that pomegranate fruit extract induces apoptosis in human PC3 cell lines of the prosthetic cancer in a dose-dependant manner. It has

been proven by previous research that pomegranate fruit extract induces the production of Bax and Bak which are pro-apoptotic proteins whilst reducing the production of BCL-2 which is an anti-apoptotic protein. Thus pomegranate fruit extract facilitates the death of the viral or tumor affected cells(87).

Luteolin is a common flavonoid found in most parts of the pomegranate. Kaempferol another natural flavonoid is found in pomegranate juice. Both luteolin and kaempferol have been identified as substances capable of inducing apoptosis through several mechanisms with the help of Reactive Oxygen Species (ROS) and Bcl-2 proteins(14). The ROS are species that are important in regulating normal cellular processes but deregulation of ROS leads to delayed apoptosis. Kaempferol and luteolin are found to increase intracellular ROS levels and thereby inducing apoptosis(88, 89). Some members of the Bcl-2 family can act as a prototype inhibitor of apoptosis blocking the death of the infected cells. Anti-apoptotic Bcl-2 inhibits caspase-dependent apoptosis. Increased expression of anti-apoptotic Bcl-2 proteins has been identified to be responsible for delaying apoptosis in SARS-CoV infection(90).

The activity of anti-apoptotic Bcl-2 protein is opposed by pro-apoptotic Bax, a homologous protein that accelerates the rate of cell death. The Bcl-2/Bax ratios are known to affect cell survival. It has been proven that ellagic acid, kaempferol, and luteolin present in pomegranate fruit juice decreases the Bcl2/Bax ratio in PC3 cell lines of human prostate carcinoma producing a dose-dependent response to promote apoptosis(87, 91).

The p53 is a transcription factor that prevents tumor development through induction of cell cycle arrest and cell death by apoptosis. As many as several hundred genes or more are known to be regulated by p53. Certain viruses are known to delay apoptosis by inhibition of the p53 transcription factor. Through various studies, it has been suggested that the p53 transcription factor has the ability of down-regulating the replication of SARS-CoV infection(92). The flavonoids kaempferol and luteolin are known to trigger the activation of p53(88, 89). Quercetin

another polyphenolic flavonoid found in pomegranate fruit extract also induces apoptosis in tumor cells by increasing ROS levels, decreasing the Bcl2/Bax ratio, and triggering the activation of p53(92).

Reducing overexpression of cell adhesion molecules

Recruitment of neutrophils and monocytes to the intra-alveolar space occurs in acute inflammation triggered by cell adhesion molecules(93, 94). The immune histochemical analysis demonstrates that Intra Cellular Adhesion Molecule-1(ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1), and Monocyte Chemo Attractant Protein-1 (MCP-1) are significantly upregulated during ARDS. Pomegranate juice is a major source of Delphinidin whilst pomegranate peel is a major source of Pelargonidin and Gallic acid. These polyphenols exhibit potent anti-inflammatory properties by decreasing the expression of MCP-1, ICAM-1, and VCAM-1(15, 95). Therefore the above-mentioned polyphenols are capable of attenuating the neutrophils and monocyte infiltration into the intra-alveolar space preventing acute lung injury and acute respiratory distress syndrome in SARS CoV-2 infection.

Reduction of oxidative stress.

The imbalance between free radicals and antioxidants in the body of an individual is known as oxidative stress. Oxidative stress is characterized by the presence of free radicals which causes damage to tissues leading to an uncontrolled inflammatory response. Antioxidant effects are the best-described properties of flavonoids(14, 15). Anthocyanins are naturally occurring plant pigments that belong to the flavonoid family of polyphenols(12, 15). Pomegranate is known to contain three times more anthocyanins than green tea, and higher total polyphenols content compare to common fruit-based beverages such as like orange juice, grape juice(96) . Anthocyanins are found in all components of pomegranate and are found in the highest concentration in the pomegranate peel(97).

The principal anthocyanins found in pomegranate are delphinidin, cyanidin, and pelargonidin(14, 78, 97). These molecules are capable of inhibiting different free radical forming pathways such as direct radical scavenging, nitric oxide pathway, and xanthene oxidase pathway(14, 15, 78). During inflammation, inflamed endothelial-derived mediators and complement factors cause the adhesion of leukocytes to the endothelial wall. Immobilization stimulates the degradation of neutrophils causing the release of oxidants and inflammatory mediators resulting in tissue damage(14). It has been scientifically proven in many research that oral administration of purified micronized flavonoids of pomegranate reduces the number of immobilized leucocytes during the reperfusion and thereby reduces reperfusion injury(14). Cyanidin is an anthocyanin that has shown to cause reduction of serum Malonaldehyde, a biological marker of oxidative stress cell membrane injury, when given to the patient with acute inflammation(14, 15).

Reduction of mucus secretion.

All anthocyanins of pomegranates are known to be mild to moderate astringents(96). It has been well known in medicine that astringents cause constrictions or contraction of mucous membranes in exposed tissues and are used to reduce the discharge of blood, serum, mucous, secretions(98). This property of astringent is used to treat diarrheas, sore throat, hemorrhages, peptic ulcers, allergies, fungal infection, and upper respiratory tract infections(99, 100). Autopsy studies have revealed that there had been a substantial amount of mucous secretions in patients who died due to ARDS associated with COVID-19(98). Therefore it could be suggested that the astringent property of anthocyanins found in pomegranate may help to reduce mucous secretion in patients with SARs-CoV-2 infection.

Inhibiting RNA-dependent RNA polymerase.

SARS-CoV-2 uses an RNA-dependent RNA polymerase (RdRP) in the process of viral replication. Therefore RdRP is a potential target for the development of antiviral therapy for SARS CoV-2(4). Zinc is known to block the activity of RNA-dependent RNA polymerase(101, 102). Pomegranate is one of the best-known sources of Zinc amongst common fruits. Quercetin and epigallocatechin-gallate found in the extract of pomegranate fruit function as a zinc ionophore to facilitate transportation of zinc across the cell membrane(103). Therefore it could be suggested that the consumption of pomegranate fruit extract rich in Zinc could help in reducing the viral replication and the viral load which directly correlates with the clinical outcome of the infected individual.

OTHER POSSIBLE THERAPEUTIC ACTIONS OF POMEGRANATE

Delphinidin directly binds with fyn kinase and inhibits its function(104). Fyn kinase belongs to the Scr family of tyrosine kinases. It is associated with the phosphorylation of a variety of intracellular signaling molecules. One of the best-known functions of fyn kinase is phosphorylation of SLAM (Signaling Lymphocyte Activation Molecule) in T cell(104). Fyn kinase inhibitors have shown to be effective in the control of SARS and MERS viral infection thus showing the potential of pomegranate to be used against SARS-CoV-2(105, 106).

It has been found that Raf/MEK/ERK pathway has a significant effect on SARS CoV-2 viral survival in human host cells(107). Therefore the inhibition of this pathway could have a beneficial therapeutic effect on the treatment of COVID-19. Anthocyanins such as delphinidin and cyanidin are abundant in pomegranate have been proven to be effective in inhibiting the Raf/MEK/ERK pathway(107, 108).

Catechin, a type of natural phenol found in pomegranate peel extract affects endothelium-dependent vasodilatation which regulates normal blood flow(109, 110). Catechins are found to

inhibit NF-KB, IL-6, TNFα, CRP, lipoprotein-associated phosphatase A2 (Lp-PLAz)(110). This suggests that catechin may help control the severity of COVID 19 infection.

Ellagitannins are water-soluble hydrolyzable tannins, belonging to the family of polyphenols. They are found in the peel, pith, and capillary membrane of pomegranate fruits(111). It is suggested that the hypoxia-induced factor 1α (HIF-1α) inhibition could be a potential therapeutic target to minimize organ damage associated with SARS-CoV-2 infection(112). Ellagitannins inhibit angiogenesis under hypoxic conditions triggered by HIF-1α and cellular proliferation along with the stimulation of apoptosis(12, 50). In addition to ellagitannins, common anthocyanins isolated from pomegranate are also found to inhibit HIF-1α(13, 15).

Autophagy is an intracellular self-digestion process that has recently been shown to regulate inflammatory processes. Forkhead Box O (FOXO) transcription proteins are found to be involved in the regulation of Autophagy(113). Inhibition of autophagy causes accumulation of autophagosomes in viral infected cells which in-turn induce apoptosis. Therefore inhibition of autophagy is suggested to be a potential therapeutic target for the treatment of SARS CoV-2 infection(114). Punicalagin, abundantly present in pomegranate, plays an important role in attenuation of Lipopolysaccharidase (LPS) induced inflammatory response in RAW 264.7 macrophage potentially by downregulation of FOXO3/autophagy signaling pathway(51).

CONCLUSIONS AND FUTURE PERSPECTIVES

In brief, this study provides new insight on potential mechanisms by which various types of polyphenols of pomegranate extract works against rapid viral replication, cytokine storm, immune dysfunction, oxidative stress, and delayed apoptosis in SARS CoV-2 infection. We suggest further studies to be conducted preferably in vivo to determine whether and to which extent, the polyphenols of pomegranate whole fruit extract and their metabolites play roles in the prevention and management of SARS CoV-2 infection and ARDS. Furthermore, research

should be conducted to identify the most potent species of pomegranate with promising levels of phytochemicals. Also, pharmacokinetic and pharmacodynamic studies could be conducted to evaluate the potency of bioactive constituents of pomegranate to be developed as therapeutic agents. With the tremendous impact of SARS CoV-2 infection on global health and the paucity or lack of therapeutic measures, it is worth investigating the potential use of pomegranate whole fruit juice and peel extract as a prophylactic, anti-viral, and anti-inflammatory agent based on the available knowledge as it has been used in several systems of medicine since ancient times without significant side effects.

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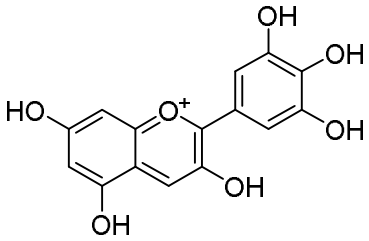
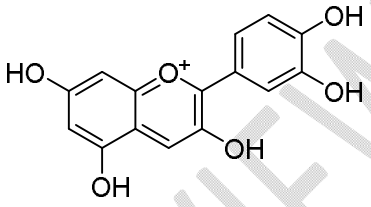
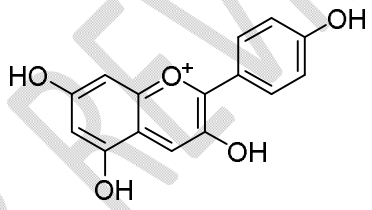
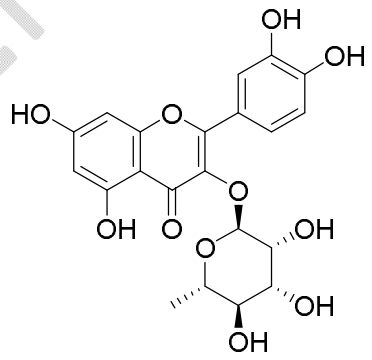
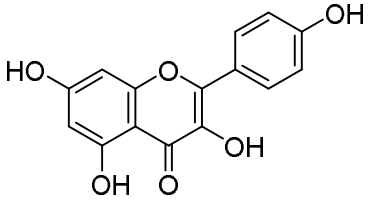
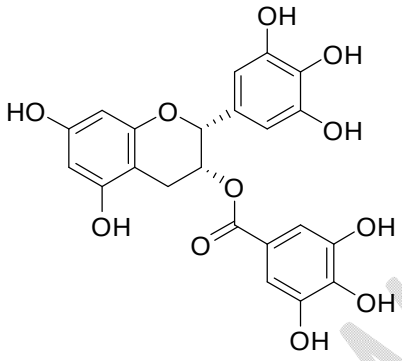
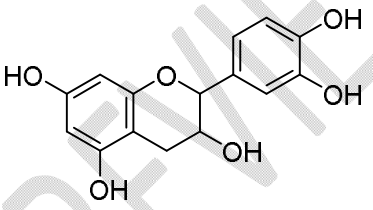
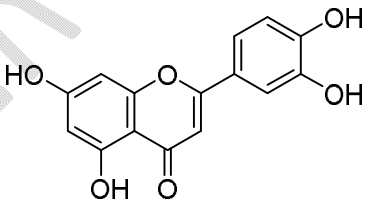
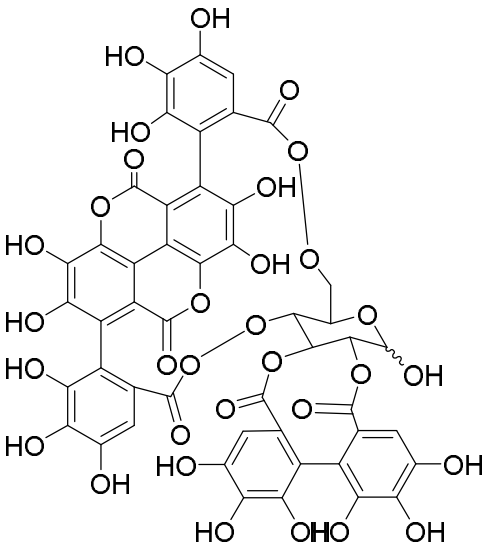
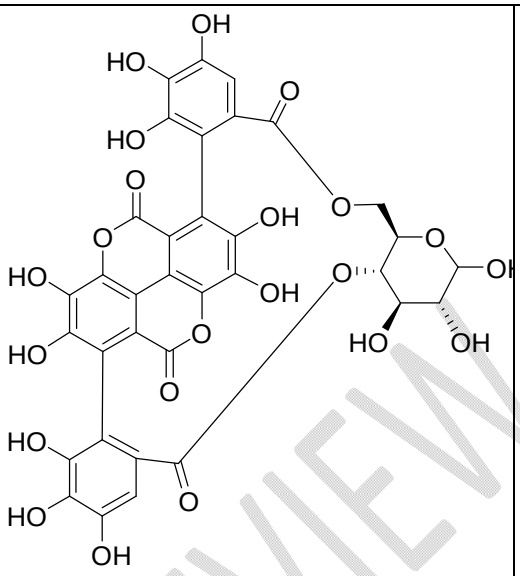
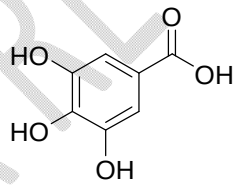
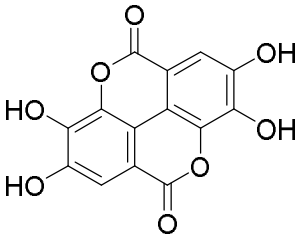
TABLE 1 – Distribution of phytochemicals in pomegranate and their chemical structures

Compound Class	Compound	Location	Chemical Structure	Ref.

Anthocyanins	Delphinidin	Peel extract, Juice		(16, 17)
	Cyanidin	Peel extract, Juice		(16, 17)
	Pelarginidin	Peel extract, Juice		(16, 17)
Flavonols	Quercitrin	Peel extract, Juice		(17, 18)
	Kaempferol	Peel extract		(16-18)

Flavanols	Epigallocatechin Gallate	Peel extract, Juice		(17, 115)
	Catechin	Peel extract, Juice		(16, 17, 115)
Flavones	Luteolin	Peel extract		(16-18)
Ellagitannins	Punicalagin	Peel extract, Juice		(16-18)

	Punicalin	Peel extract, Juice		(16-18)
Phenolic Acids	Gallic Acid	Peel Extract, Juice, Flower		(16-18)
	Ellagic Acid	Peel extract, Juice, Seed		(16-18)