Chapter

Could Pomegranate Fight against SARS-CoV-2?

Sally Elnawasany

Abstract

Pomegranate, *Punica granatum* L., is an authentic, generous fruit which is cultivated in many parts of the world for thousand years. The divine fruit was born from nature to provide humanity with its effluent benefits for life and health. Through the ages, Pomegranate occupied an eminent place in ayurvedic medicine. It was prescribed for treatment of parasitic infection, diarrhea, and ulcers. Pomegranate wealth of prolific pharmacological activities makes it a rich culture for multiple studies in recent years. It will not be surprising if Pomegranate provides humans with a possible help in SARS-CoV-2 pandemic. The enemy that has raided the world since the end of 2019.

Keywords: ayurvedic medicine, phytochemicals, pomegranate, SARS-CoV-2

1. Introduction

Pomegranate (*Punica granatum* L.) is a common authentic fruit that is consumed for its health benefits in the globe. It contains many phytochemical constituents mainly Phenolic compounds which are responsible for most of its pharmacological properties [1, 2]. Several studies roamed in the Pomegranate field for its therapeutic benefits; anti- inflammatory, anti -oxidant, anti-cancer, anti- viral and immune modulation activities [3]. The fact that put pomegranate on the top of phytochemical agents with possible anti SARS-CoV-2 potential. Which has been attacking the earth for over a year. It is one of Coronaviruses, member of the subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales [4].

2. Severe acute respiratory syndrome coronavirus-2, SARS-CoV-2

Corona viruses are wide group of viruses of humans as well as some animals. The clinical impact is ranged from mild to severe respiratory disease. In the last two decades, the world faced two aggressive coronaviruses: severe acute respiratory syndrome coronavirus (SARS-COV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-COV) in 2012 [4]. At the end of 2019, SARS-CoV-2 was reported in China, as an abnormal highly contagious viral pneumonia. Then shortly, the virus invaded the whole world [5, 6]. SARS-CoV-2 is an enveloped positive-sense single stranded RNA virus. It consists of four subunits, spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein and nucleocapsid (N) protein [7]. Spike S protein with its two subunits, S1 and S2 is responsible for epithelial cell entry after its attachment to Angiotensin Converting

Enzyme 2, ACE2 receptors which is widely present in the respiratory tract and other parts of the body [8, 9]. While surface S1 subunit (specifically at receptor-binding domain, RDB region) attach to ACE2 receptor, transmembrane subunit (S2) starts membrane fusion between the virus and epithelial cell and begins endocytosis. This process is enabled by the two host cell enzymes; furin and transmembrane serine protease 2 (TMPRSS2) that cleaves S glycoprotein at S1/S2 [10, 11]. Then SARS-CoV-2 replicates and spreads down to the airways and occupies alveolar epithelial cells. Viral replication induces Intense immune response (Cytokine storm syndrome) with subsequent acute respiratory distress syndrome and respiratory failure, the main cause of death [12]. Treating SARS-CoV-2 infection is not easy, as we have not only to fight the virus and manage its respiratory sequalae, but we need to downregulate the hyper stimulated immune response as well. For this war, many agents have been recruited in different ways. Starting from Inhibition of virus entry as Umifenovir (Arbidol) that interferes with interaction between the viral S protein and ACE2 and block membrane fusion [13, 14]. Chloroquine and hydroxy-chloroquine (two drugs of plant origin) are also thought to inhibit viral entry but with controversial results [15, 16]. Using soluble recombinant hACE2, specific monoclonal antibodies to occupy ACE2 receptors is another method to counter act viral entry [17, 18]. Inhibition of virus replication is another modality for treatment. There are numerous trials on remedesivir [15], favipiravir [19], ribavirin, lopinavir and ritonavir to inhibit viral replication [20]. Since SARS-CoV-2 over stimulates the immune response causing what is called, cytokine storm syndrome [21]. Immune modulation is a promising target for treatment. Dexamethasone decreased mortality in mechanically ventilated and oxygen receiving patients [22]. Plasma from recovered patients, convalescent plasma-derived hyperimmune globulin and monoclonal antibodies targeting SARS-CoV-2 were also tried in many trials [23–26]. Interleukin-6 (IL-6) has an important role in the inflammatory response. Tocilizumab, interleukin-6 (IL-6) receptor-specific antibody downregulated the immune response in small trials [27, 28]. Moreover, inhibition of pro inflammatory Complement 5 by Eculizumab, a specific monoclonal antibody, helped to decrease pulmonary oedema in severe COVID-19 patients [29]. Interferon plays a role in reducing of viral replication, type I interferons provide a treatment options in COVID-19 infection [30, 31]. Protein kinases inhibitors as Baricitinib, a reversible Janus-associated kinase (JAK)-inhibitor can help in SARS-CoV-2 treatment through its anti-inflammatory, anti-viral and antifibrotic properties [32]. Baricitinib attenuated cytokine signaling in COVID-19 immune response. It also interfered with viral cell entry [33]. In another study, it improved with corticosteroids the respiration in SARS-CoV-2 pneumonia [34]. In addition, the Abl tyrosine kinase inhibitor (ATKI), imatinib was found to block viral fusion through attachment to receptor-binding domain (RBD) of SARS-CoV-2 spike protein [35]. In spite of all the previous treatment modalities, there is no proven curative agent for SARS-CoV-2 infection [36]. Which necessitates a continuous and hard search for new therapeutic agents including natural agents.

3. Could pomegranate fight against SARS-CoV-2?

3.1 Anti-viral action of pomegranate

Pomegranate attenuates many viruses [37]. Polyphenols and ellagic acid were proved to neutralized envelope virus via binding to the envelope lipid or sugar moieties [38]. Pomegranate juice succeeded to prevent Human immune deficiency virus-1 (HIV-1) cell entry by blocking CD4 and coreceptors CXCR4/CCR5

binding [39]. Ellagitannins of Pomegranate extract; punicalagin, punicalin and ellagic acid blocked the HCV NS3/4A protease activity in an in vitro study [40]. Furthermore, the activity of adenovirus was suppressed by Pomegranate peel ethanol extract on HeLa cell line. The 50% inhibitory concentration (IC50) and 50% Cytotoxicity Concentration (CC50) were 165 ± 10.1 and 18.6 ± 6.7 μg/ml, respectively [41]. In addition, Pomegranate juice and pomegranate polyphenol extract reduced viral titer of noroviruses with other foodborne viral surrogates [42]. A viricidal effect of Pomegranate powder extract with 800 μg/ml polyphenols was clarified. When the titer of influenza virus (PR8 (H1N1), X31 (H3N2), and a reassortant H5N1 virus of human isolate lowered by 3log in 5 min treatment at room temperature. This effect was explored by electron microscopy when disruption of viral structure appeared [43]. Moreover, the replication and agglutination of chicken RBC's by influenza virus was inhibited by Punicalagin, a phenol in pomegranate extract. Synergistic effect was noticed in oseltamivir combination [44]. The anti Influenza mechanism was emphasized in another study where Pomegranate peel ethyl alcohol extract (PPE) inhibited the influenza virus adsorption and replication though attenuation of viral polymerase activity and protein expression [45].

3.2 Immune modulatory action of pomegranate

Mast cells and basophils have a crucial role in inflammatory and immune response [46]. These cells release pro-inflammatory cytokines TNF-α, IL-6, IL-8, histamine which initiate acute- and late-phase inflammatory response [47]. Cytokine expression is induced by many pathways such as extra-cellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) and Nuclear factor (NF)-κB [48–50]. Immune modulation action of pomegranate was confirmed in many studies. Pomegranate fruit extract strongly attenuated phorbol-12-myristate 13-acetate plus calcium inophore A23187 (PMACI) induced inflammatory gene expression and reduced the release of interleukin (IL)-6 and IL-8 in the myeloid pre-cursor cell line KU812 cells. Through its action on c-jun N-terminal kinase (JNK), extracellular-regulated kinase (ERK) and Neucular factor Kappa β (NF-κB) dependent pathways [51]. NF-κB signaling stimulation is mediated by IL-1β binding to its specific cell surface receptor that activates IKKs with subsequent phosphorylation and degradation of IκB. This cascade was suppressed in human chondrocyte by pomegranate extract. Which interfered with the mRNA and protein expression of IL-6 and downregulated the activation of NF-κB/p65. Through inhibition of the IL-1β-mediated phosphorylation of IKKβ, expression of IKKβ mRNA and degradation of IκBα [52]. Moreover, in another in vitro study, Pomegranate flower (PFE) ethanol extract reduced IL-6, IL-1β and TNF-α production with IC_{50} value of 48.7, 71.3 and 62.5 μg/mL respectively, in lipo-poly saccharides (LPS) -induced RAW264.7 cell macrophage. This effect was attributed to inhibition of phosphorylation of mitogen-activated protein kinase (MAPK) subgroups, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and P38 and translocation of the NF-B p65 subunit [53]. Pomegranate peel extract decreased the secretion of CXCL8 in both Caco-2 cells and colonic explants. Furthermore, it attenuated the expression of IL 1A, IL 6 and CXCL8 in lipopoly saccharide, LPS stimulated colonic tissues at a concentration of 5 g/ml [54].

3.3 Anti-tyrosine kinase action of pomegranate

Janus kinase (JAK) is a member of the non-receptor tyrosine kinase family. It triggers many inflammatory signaling pathways like signal transducer and activation of transcription (STAT) that induce chemotaxis of inflammatory cells such

as mast cells, T cell, B cells, macrophages [55]. Baricitinib is a Janus kinase (JAK) inhibitor and is a numb-associated kinase NAK inhibitor which attenuates AP2-associated protein kinase-1 (AAK1), the protein that promotes viral endocytosis [56, 57]. Fortunately, Pomegranate shares Baricitinib its janus kinase inhibitory action. The fact that introduces Pomegranate as a possible treating agent of SARS-CoV-2. This action was highlighted in a study where Pomegranate leaf extract antagonized Janus Kinase1 (JAK1) enzyme activity in macrophage raw cells [58]. In another study, among ellagitannins containing fruits, pomegranate was the superior in JAK2 inhibition [59].

3.4 Anti-converting enzyme (ACE) action of Pomegranate

The renin-angiotensin-aldosterone system, RAAS organizes blood pressure, fluid balance and controls the vascular response to inflammation [60]. Imbalance in that system induces hypertension, fluid retention, and inflammatory and thrombotic complications [61]. Juxtaglomerular apparatus of the kidney secretes renin which acts on angiotensinogen to form Angiotensin I (A1). Angiotensin-converting enzyme (ACE) breaks AI to AII. Angiotensin II is the main controlling agent of RAAS through stimulation of type 1 receptor (AT_1 receptor) with subsequent vasoconstriction, water retention and inflammation. While The type 2 receptor, ATR2 counteract these effects [62]. ACE2 counterbalance ACE actions. It breaks down AI into angiotensin 1-9(A1-9), and AII into angiotensin 1-7(A1-7) which has vasodilator and anti-proliferative action [63]. The renin-angiotensin system is claimed to induce severe acute lung injury in SARS-CoV-2 infection and ACE2 protects against acute lung failure and its deficiency is associated with lung damage [64]. Binding of SARS-Cov-2 to ACE2 receptor attenuates ACE2 action with subsequent lung damage [65]. On that basis, soluble ACE2 was supposed to be a possible approach for coronavirus infection [66]. It was speculated that, The use of ACE Inhibitors is associated with increased concentration of angiotensin I which upregulates ACE2 [67]. It is ambiguous, whether this postulate increases the probability of SARS-CoV-2 infection. Or ACE2 upregulation will be beneficial for counterbalance the ACE2 virus-induced downregulation with improvement of lung defense [65]. Although the role of Angiotensin converting enzyme, ACE inhibitors in SARS-CoV-2 infection is controversial, Pomegranate has the potential of ACE inhibition and may help in this battle. *Punica granatum* juice extract lowered ACE level and mean arterial blood pressure. When it was given in a dose of (PJ- 100 mg/kg and 300 mg/kg: p.o.) in angiotensin-II treated rats for 4 weeks [68]. Similar effect was emphasized in a parallel study. When Pomegranate peel extract was administered to female rats for 30 days. It inhibited coronary angiotensin-converting enzyme (ACE) activity and oxidative stress [69]. In a clinical trial, Pomegranate juice reduced serum ACE activity and systolic blood pressure in hypertensive patients when it was consumed for 2 weeks at a dose of (50 ml, 1.5 mmol of total polyphenols per day) [70].

3.5 Anti-SARS-CoV-2 action of pomegranate

Pomegranate potentials against SARS-CoV-2 infection have been investigated in many studies.

3.5.1 Anti-SARS-CoV-2 action of pomegranate

In a Computational study, Pomegranate peel extracts components; ellagic acid, gallic acid and specially punicalagin, punicalin showed promising anti SARS-CoV-2 activity through interaction with SARS-CoV-2 spike glycoprotein, angiotensin

converting enzyme 2, furin and transmembrane serine protease2. They formed more stable complexes with amino acid residues at the active sites of the selected protein targets in comparison to positive controls (umifenovir, lopinavir, camostat) with more significant binding affinity. Punicalin showed the most potent interaction with the S glycoprotein with free binding energy of −7.406 kcal/mol. All Pomegranate components ligands exerted a significant binding affinity at the ACE2 predicted active site. Furthermore, they formed the most stable complexes with furin. Amazingly, Punicalagin and punicalin strongly interacted with TMPRSS2 amino acid residues at the predicted active site by binding energy values of −7.358 and − 8.168 kcal/mol, respectively with higher affinity for the target protein than camostat (−7.069 kcal/mol) [71]. In an in vitro study, Pomegranate juice reduced the infectivity of SARS-Cov-2 and influenza virus in VeroE6 cells [72]. In another study, Pomegranate peel extract showed an ability to block the binding between SARS-CoV-2 Spike glycoprotein and the human Angiotensin-Converting Enzyme 2 (ACE2) receptor, furthermore, it downregulated the activity of the virus bind 3-chymotrypsin-like cysteine protease ($3CL^{Pro}$) (an enzyme which is important for viral replication) [73].

3.5.2 Anti-SARS-CoV-2 action of natural compounds that are found in pomegranate

In a virtual study, pedunculagin, tercatain, and castalin (hydrolysable tannins) showed an ability to bind ($3CL^{Pro}$) catalytic site that is involved in SARS-CoV-2 replication. Which sheds the light on tannins as possible anti SARS-CoV-2 agents [74]. Other virtual study investigated the action of natural compounds on SARS-CoV-2 Spike protein, viral Protease and RNA-dependent RNA polymerase and host cell protease TMPRSS2. Triterpenoids was found to be the superior in blocking the Spike protein binding site of SARS-CoV-2 [75].

4. Conclusion

Pomegranate is still surprising the world by its great therapeutic benefits. This chapter highlights the anti-SARS-CoV-2 potentials of Pomegranate. Where Antiviral, immune modulation, tyrosine kinase and ACE inhibition actions, all enable Pomegranate to fight in this war. Further future studies are needed to confirm the utility of Pomegranate in treating SARS-CoV-2 infection.

Conflict of interest

I confirm that there are no conflicts of interest.

Author details

Sally Elnawasany
Tropical Medicine, Tanta University, Egypt

*Address all correspondence to: elnawasany_s@hotmail.com

IntechOpen

References

[1] Ismail T, Akhtar S, Riaz M. Pomegranate Peel and Fruit Extracts: A Novel Approach to Avert Degenerative Disorders–Pomegranate and Degenerative Diseases. InExploring the Nutrition and Health Benefits of Functional Foods 2017 (pp. 165-184). IGI Global.

[2] Goertz A, Ahmad KA. Biological activity of phytochemical compounds in pomegranate-a review. EC Nutri-tion. 2015;1:115-127.

[3] Elnawasany S. Clinical Applications of Pomegranate. In: Soneji J, Nageswara-Rao M, editors. Breeding and Health Benefits of Fruit and Nut Crops, Intechopen; 2018. p. 127-148. DOI: 10.5772/intechopen. 75962

[4] Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nature Reviews Microbiology. 2019 Mar;17(3):181-192.

[5] Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. The Lancet. 2020 Feb 29;395(10225):689-697.

[6] Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, Ippolito G, Mchugh TD, Memish ZA, Drosten C, Zumla A. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. International Journal of Infectious Diseases. 2020 Feb 1;91:264-266.

[7] Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends in immunology. 2020 Apr 2

[8] Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and coronavirus disease 2019: what we know so far. Pathogens. 2020 Mar;9(3):231.

[9] Boström KI, Yao Y. Options for COVID-19 Entry into Pulmonary Cells. Biomedical journal of scientific & technical research. 2020 Aug;29(2):22337.

[10] Hoffmann M, Hofmann-Winkler H, Pöhlmann S. Priming time: How cellular proteases arm coronavirus spike proteins. InActivation of Viruses by Host Proteases 2018 (pp. 71-98). Springer, Cham.a

[11] Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020 May;581(7807):221-224.

[12] Tufan A, GÜLER AA, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turkish Journal of Medical Sciences. 2020 Apr 21;50(SI-1):620-632.

[13] Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, Li Y, Zhao L, Li W, Sun X, Yang X. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. Cell Discovery. 2020 May 2;6(1):1-5.

[14] Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, Lu J, Xue Y. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. Journal of Infection. 2020 Jul 1;81(1):e21-e23.

[15] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research. 2020 Mar;30(3):269-271.

[16] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L,

Dong E, Song C, Zhan S. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases. 2020 Mar 9.

[17] Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Del Pozo CH, Prosper F, Romero JP. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020 Apr 24.

[18] Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z, Wu Y, Ying T. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerging microbes & infections. 2020 Jan 1;9(1):382-385.

[19] Agrawal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. Medical Journal Armed Forces India. 2020 Sep 2.

[20] Zeng YM, Xu XL, He XQ, Tang SQ, Li Y, Huang YQ, Harypursat V, Chen YK. Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate novel coronavirus disease 2019: study protocol. Chinese medical journal. 2020 May 5;133(9):1132-1134.

[21] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, HLH Across Speciality Collaboration. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England). 2020 Mar 28;395(10229):1033.

[22] Ahmed MH, Hassan A. Dexamethasone for the Treatment of Coronavirus Disease (COVID-19): a Review. SN comprehensive clinical medicine. 2020 Oct 31:1-0.

[23] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. Jama. 2020 Apr 28;323(16):1582-1589.

[24] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, Hu C. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. Jama. 2020 Jun 3.

[25] Wang C, Li W, Drabek D, Okba NM, van Haperen R, Osterhaus AD, van Kuppeveld FJ, Haagmans BL, Grosveld F, Bosch BJ. A human monoclonal antibody blocking SARS-CoV-2 infection. Nature communications. 2020 May 4;11(1):1-6.

[26] Brouwer P, Caniels T, van Straten K, Snitselaar J, Aldon Y, Bangaru S, Torres J, Okba N, Claireaux M, Kerster G, Bentlage A. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. bioRxiv. 2020 Jan 1.

[27] Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020 May 19;117(20):10970-10975.

[28] Alzghari SK, Acuña VS. Supportive treatment with tocilizumab for COVID-19: a systematic review. Journal of Clinical Virology. 2020 Jun;127:104380.

[29] Diurno F, Numis FG, Porta G, Cirillo F, Maddaluno S, Ragozzino A, De Negri P, Di Gennaro C, Pagano A, Allegorico E, Bressy L. Eculizumab

treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. European Review for Medical and Pharmacological Sciences. 2020 Apr 1;24(7):4040-4047.

[30] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006 Sep 12;3(9):e343.

[31] Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C. Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral research. 2020 Apr 29:104811.

[32] Weisberg E, Parent A, Yang PL, Sattler M, Liu Q, Liu Q, Wang J, Meng C, Buhrlage SJ, Gray N, Griffin JD. Repurposing of kinase inhibitors for treatment of COVID-19. Pharmaceutical research. 2020 Sep;37(9):1-29.

[33] Jorgensen SC, Tse CL, Burry L, Dresser LD. Baricitinib: a review of pharmacology, safety, and emerging clinical experience in COVID-19. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2020 Aug;40(8):843-856.

[34] Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizuete JM, Martinez-Alfaro E. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. Rheumatology. 2021 Jan;60(1):399-407.

[35] Mulgaonkar NS, Wang H, Mallawarachchi S, Ruzek D, Martina B, Fernando S. Bcr-Abl tyrosine kinase inhibitor imatinib as a potential drug for COVID-19. bioRxiv. 2020 Jan 1.

[36] Janković S. Current status and future perspective of coronavirus disease 2019: a review. Scripta Medica. 2020;51(2):101-109.

[37] Howell AB, D'Souza DH. The pomegranate: effects on bacteria and viruses that influence human health. Evidence-Based Complementary and Alternative Medicine. 2013 Oct;2013.

[38] Kotwal GJ. Genetic diversity-independent neutralization of pandemic viruses (eg HIV), potentially pandemic (eg H5N1 strain of influenza) and carcinogenic (eg HBV and HCV) viruses and possible agents of bioterrorism (variola) by enveloped virus neutralizing compounds (EVNCs). Vaccine. 2008;26(24):3055-3058

[39] Neurath AR, STRICK N, LI YY, DEBNATH AK. Punica granatum (pomegranate) juice provides an HIV-1 entry inhibitor and candidate topical microbicide. Annals of the New York Academy of Sciences. 2005 Nov;1056(1):311-27.

[40] Reddy BU, Mullick R, Kumar A, Sudha G, Srinivasan N, Das S. Small molecule inhibitors of HCV replication from pomegranate. Scientific reports. 2014 Jun 24;4:5411.

[41] Karimi A, Moradi MT, Rabiei M, Alidadi S. In vitro anti-adenoviral activities of ethanol extract, fractions, and main phenolic compounds of pomegranate (Punica granatum L.) peel. Antiviral Chemistry and Chemotherapy. 2020 Apr;28:2040206620916571.

[42] Su X, Sangster MY, D'Souza DH. In vitro effects of pomegranate juice and pomegranate polyphenols on foodborne viral surrogates. Foodborne Pathogens and Disease. 2010 Dec 1;7(12):1473-1479.

[43] Sundararajan A, Ganapathy R, Huan L, Dunlap JR, Webby RJ, Kotwal GJ, Sangster MY. Influenza virus variation in susceptibility to inactivation by pomegranate polyphenols is determined by envelope glycoproteins. Antiviral research. 2010 Oct 1;88(1):1-9.

[44] Haidari M, Ali M, Casscells III SW, Madjid M. Pomegranate (Punica granatum) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. Phytomedicine. 2009 Dec 1;16(12):1127-1136.

[45] Moradi MT, Karimi A, Rafieian-kopaei M, Rabiei-Faradonbeh M, Momtaz H. Pomegranate peel extract inhibits internalization and replication of the influenza virus: An in vitro study. Avicenna Journal of Phytomedicine. 2020 Mar;10(2):143.

[46] Galli SJ. New concepts about the mast cell. New England Journal of Medicine. 1993 Jan 28;328(4):257-265.

[47] Woolley DE, Tetlow LC. Mast cell activation and its relation to proinflammatory cytokine production in the rheumatoid lesion. Arthritis Research & Therapy. 1999 Dec;2(1):1-0.

[48] Cobb MH, Goldsmith EJ. Dimerization in MAP-kinase signaling. Trends in biochemical sciences. 2000 Jan 1;25(1):7-9.

[49] Lewis TS, Shapiro PS, Ahn NG. Signal transduction through MAP kinase cascades. In Advances in cancer research 1998 Jan 1 (Vol. 74, pp. 49-139). Academic Press.

[50] Collart MA, Baeuerle P, Vassalli P. Regulation of tumor necrosis factor alpha transcription in macrophages: involvement of four kappa B-like motifs and of constitutive and inducible forms of NF-kappa B. Molecular and cellular biology. 1990 Apr 1;10(4):1498-1506.

[51] Rasheed Z, Akhtar N, Anbazhagan AN, Ramamurthy S, Shukla M, Haqqi TM. Polyphenol-rich pomegranate fruit extract (POMx) suppresses PMACI-induced expression of pro-inflammatory cytokines by inhibiting the activation of MAP Kinases and NF-κB in human KU812 cells. Journal of inflammation. 2009 Dec 1;6(1):1.

[52] Haseeb A, Khan NM, Ashruf OS, Haqqi TM. A polyphenol-rich pomegranate fruit extract suppresses NF-κB and IL-6 expression by blocking the activation of IKKβ and NIK in primary human chondrocytes. Phytotherapy Research. 2017 May;31(5):778-782.

[53] Xu J, Zhao Y, Aisa HA. Anti-inflammatory effect of pomegranate flower in lipopolysaccharide (LPS)-stimulated RAW264. 7 macrophages. Pharmaceutical Biology. 2017 Jan 1;55(1):2095-2101.

[54] Mastrogiovanni F, Mukhopadhya A, Lacetera N, Ryan MT, Romani A, Bernini R, Sweeney T. Anti-inflammatory effects of pomegranate peel extracts on in vitro human intestinal caco-2 cells and ex vivo porcine colonic tissue explants. Nutrients. 2019 Mar;11(3):548.

[55] Wong WF, Leong KP. Tyrosine kinase inhibitors: a new approach for asthma. Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics. 2004 Mar 11;1697(1-2):53-69.

[56] Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. The Lancet Infectious Diseases. 2020 Apr 1;20(4):400-402.

[57] Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet (London, England). 2020 Feb 15;395(10223):e30.

[58] Sarithamol S, Pushpa VL, Manoj KB. Comparative Study on Janus Kinase Enzyme activity of Pomegranate Leaf Extract and its Active Component

Ellagic Acid for Asthma. Oriental Journal of Chemistry. 2018;34(2):1041.

[59] Martin H, Burgess EJ, Smith WA, McGhie TK, Cooney JM, Lunken RC, de Guzman E, Trower T, Perry NB. JAK2 and AMP-kinase inhibition in vitro by food extracts, fractions and purified phytochemicals. Food & function. 2015;6(1):304-311.

[60] Ferrario CM. Role of angiotensin II in cardiovascular disease—therapeutic implications of more than a century of research. Journal of the Renin-angiotensin-aldosterone System. 2006 Mar;7(1):3-14.

[61] Brewster UC, Perazella MA. The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. The American journal of medicine. 2004 Feb 15;116(4):263-272.

[62] Zaman MA, Oparil S, Calhoun DA. Drugs targeting the renin–angiotensin–aldosterone system. Nature reviews Drug discovery. 2002 Aug;1(8):621-636.

[63] Macia-Heras M, Del Castillo-Rodriguez N, Navarro González J. The renin-angiotensin-aldosterone system in renal and cardiovascular disease and the effects of its pharmacological blockade. J Diabetes Metab. 2012 Feb 1;3(2).

[64] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nature medicine. 2005 Aug;11(8):875-879.

[65] Perrotta F, Matera MG, Cazzola M, Bianco A. Severe respiratory SARS-CoV2 infection: Does ACE2 receptor matter?. Respiratory Medicine. 2020 Apr 25:105996.

[66] Batlle D, Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy?. Clinical science. 2020 Mar 13;134(5):543-545.

[67] Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. International journal of peptides. 2012;2012.

[68] Harshal W, Mahalaxmi M, Sanjay K, Balaraman R. Punica granatum attenuates angiotensin-II induced hypertension in Wistar rats. International Journal of PharmTech Research. 2010;2(1):60-67.

[69] dos Santos RL, Dellacqua LO, Delgado NT, Rouver WN, Podratz PL, Lima LC, Piccin MP, Meyrelles SS, Mauad H, Graceli JB, Moyses MR. Pomegranate peel extract attenuates oxidative stress by decreasing coronary angiotensin-converting enzyme (ACE) activity in hypertensive female rats. Journal of Toxicology and Environmental Health, Part A. 2016 Nov 1;79(21):998-1007.

[70] Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. Atherosclerosis. 2001 Sep 1;158(1):195-198.

[71] Suručić R, Tubić B, Stojiljković MP, Djuric DM, Travar M, Grabež M, Šavikin K, Škrbić R. Computational study of pomegranate peel extract polyphenols as potential inhibitors of SARS-CoV-2 virus internalization. Molecular and cellular biochemistry. 2020 Nov 16:1-5.

[72] Conzelmann C, Weil T, Groß R, Jungke P, Frank B, Eggers M, Müller JA, Münch J. Antiviral activity of plant juices and green tea against SARS-CoV-2 and influenza virus in vitro. bioRxiv. 2020 Jan 1.

[73] Tito A, Colantuono A, Pirone L, Pedone EM, Intartaglia D, Giamundo G, Conte I, Vitaglione P, Apone F. A pomegranate peel extract as inhibitor of SARS-CoV-2 Spike binding to human ACE2 (in vitro): a promising source of novel antiviral drugs. bioRxiv. 2020 Jan 1.

[74] Khalifa I, Zhu W, Mohammed HH, Dutta K, Li C. Tannins inhibit SARS-CoV-2 through binding with catalytic dyad residues of 3CLpro: An in silico approach with 19 structural different hydrolysable tannins. Journal of food biochemistry. 2020 Oct;44(10):e13432.

[75] Gowtham HG, Monu DO, Ajay Y, Gourav C, Vasantharaja R, Bhani K, Koushalya S, Shazia S, Priyanka G, Leena C. Exploring structurally diverse plant secondary metabolites as a potential source of drug targeting different molecular mechanisms of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pathogenesis: An in silico approach.