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Pomegranate: A miracle fruit against COVID-19

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Abstract

COVID-19 is the one of the most fatal pandemics caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with highest morbidity as well as mortality while development of antiviral drugs is the greatest challenge faced by the scientists and pharmaceutical companies. Due to health emergency declared by World Health Organisation (WHO), the only option was to use the existing antiviral or anti-malarial drugsfor controlling SARS-CoV-2 infection.Usingethno-medicinal information and anti-viral potential, several natural plant products are being tested for their efficacy against SARS-CoV-2 activity. In this review, we summarise various reports that highlights the significant role of pomegranate against SARS-CoV-2. The bioactive metabolites in pomegranate are the promising candidatesthat have potential to develop novel and effective therapeutics against SARS-CoV-2.

The mankind has witnessed various epidemics and pandemics which affected the lives of millions, despite of great advances in the field of medicines and research. Emerging infections due to novel pathogens are continuously posing serious risk to human lives globally. Novel coronavirus that originated in Wuhan is responsible for recent pandemic (2019-2021) that took lives of million worldwide[9,33]. Efforts are being made to screen therapeutics drugs from medicinal plants with antiviral properties as well as screen novel plant compounds that have potential to avert the COVID-19 crisis. However, scientists are facing challenges in developing effective therapeutics against SARS-CoV-2 and its variants, which led to increase in mortality rate throughout the world. Coronaviruses are the group of viruses belonging to Coronaviridae family that causes mild to severe respiratory infection in humans. The first human Coronaviruses (229e and OC43) was identified as harmless virus in late 1960s[40,50]. In 2002, the outbreak of SARS-CoV had 10% fatality rate among infected patient in the Southern China but the spread of the disease was under control in July 2003[36,42]. The viral studies performed on SARS-CoV concluded that bats are the natural reservoirs and raccoon dogs and civet cats as intermediate hosts. Later, in the year 2012, Middle East respiratory syndrome corona virus (MERS-COV) was reported in humans that resulted in severe respiratory infections[60]. These two viruses with unexpected consequences

emerged as a new public health concern.

A novel coronavirus SARS-CoV-2 was first identified in the Wuhan, Central China in December 2019, which raised a threat to mankind and global economic security. The infected people showed the viral pneumonia like symptoms that includes cough, fever, diarrhoea and chest discomfort[14]. These symptoms were similar to SARS and MERS infection but in some severe cases, patients developdyspena and bilateral lung infiltration[52]. The retrospective study showed the first known case of SARS-CoV-2 on 12th December 2019[62]. On December 31, Wuhan municipal health commission informed the World Health Organisation about the pneumonia outbreak. This novel coronavirus was officially announced as a causative agent for the outbreak on 10th January 2020. On 11th February, WHO named this novel virus as SARS-CoV-2 on the basis of its homology to SARS-CoV genome[49]. The SARS-CoV-2 spread rapidly all over the world and was announced as a global pandemic by WHO on 11th March, 2020[54]. Till 2nd week ofMay 2021, more than 158 million confirmed cases and 3.29 million deaths across the world had been reported. The rate of infection of SARS-CoV-2 is in the range of 1.5-3.5[58]. The challenges faced during this pandemicaredue to the nature of the virus, uncertain infection periods, changing viral symptoms and lack of effective therapeutics.

About 80% of world population use medicinal plants and their derivatives in traditional practises and by pharmaceutical industries to fulfil their medicinal needs[56]. In 2004, World Health Organisation initiated many research projects during outbreak of SARS-CoV in 2002 which focussed on the integrated use of traditional Chinese medicine and Western medicine for the treatment[55]. This combination therapy introduced the use of plant metabolites as a complementary aid in the treatment of the SARS infection. There are numerous reports on the potential use of the natural plant products against various Coronaviruses[22,27,53]. The targeted mode of action and identification of active secondary metabolites resulted in the emergence of plant products as anti-coronavirus compounds.

Cultivated Pomegranate (*Punica granatum* L.) and its wild forms are the oldest edible fruits which are rich source of secondary metabolites such as polyphenolics, tannins, flavonoids, anthocyanins and terpenoids[23,57]. The chemo-diversity in pomegranate fruit depends on the cultivar, geographical region and the climate. The fruitconstitutes 50% peel and 50% edible portion which in turn consist of 40% arils and 10% seeds[41]. Both the arils and peel of pomegranate have been reported to have nutraceuticals, antioxidant and anti-inflammatory properties[5,24]. There are numerous reports that highlights the role of various metabolites present in pomegranate against degenerative disorders, cardiovascular disease, diabetes and most types of cancer[8,44]. In addition, pomegranate has shown to possessantioxidant and antiviral activity including inhibition of replication of influenza and Herpes Virus[20,21,35]. Pomegranate juice has been reported to have antiviral potential that efficiently reduces the SARS-CoV-2 and influenza virus infection[11]. Recently, the studies were conducted on pomegranate extracts and a strong potential

against SARS-CoV-2was observed thatprevents the entry of the virus into host cells[46]. In this review,we emphasize on the potential role of pomegranate fruits as a natural remedy to prevent SARS-CoV-2 infection.

SARS-CoV-2morphology and Target Identification :

Coronaviruses are positive single stranded RNAs with genome size 26 to 32 kilobases. These are divided into four subfamilies namely: alpha, beta, gamma and delta coronaviruses.SARS-CoV-2 belongs to the beta-coronavirus subfamily sharing 75-80% genome with MERS-CoV and SARS-CoV[58]. It constitutes three important envelope viral proteins namely Spike (S) proteins, Membrane (M) proteins and envelope (E) proteins whichare responsible for the viral entry into host cell and maintaining membrane structure of the coronavirus[31]. In addition to these proteins, there are Nucleocaspid (N) proteins that include the RNA genome. Receptor binding domain of S proteins binds to angiotensin-converting enzyme 2 (ACE2) receptors present in epithelial cells of oral and nasal cavity, lung aveoli, small intestine and kidney. S proteins consist of two subunits namely S1 which binds to ACE 2 receptors and S2 subunit which is responsiblefor the membrane fusion of virus with the host cell leading to endocytosis[16,19]. There are various host cell proteases that are responsible for membrane fusion. Among them is the transmembrane serine protease 2 (TMPRSS2) which mediates the cleavage of the S-protein and alongwith ACE2 is responsible for virus entry into host cell[18]. However, activation of S protein is two step process that requires another enzyme known as Furin belonging to proprotein convertase family[29]. During viral entry into the host cell, S-proteins are first pre-cleaved by Furin enzyme and then cleaved by TMPRSS2. The viral genome is then released into cytoplasm that undergoes replication and translation in the host cell[32].

Pomegtanate as potential drug against SARS-CoV-2 :

The inhibitory effects of pomegranate extracts have been reported on influenza virus, HIV, poxvirus and Herpes virus[21]. A computational study was conducted on bioactivemetabolites such as punicalagin, punicalin and ellagic acid present in pomegranate and a strong ligand interaction was observed with catalytic and substrate binding sites of hepatitis C virus[38]. It was reported that anti-inflammatory potential of pomegranate was due to the presence of various polyphenolsand flavonoids[15]. These phytochemicals have an important role in the activation of NO pathway or members of the TRP superfamily, mainly TRPA1 or TRPV1 and can play a positive effect in therapy given to COVID-19 patients. Recently, antiviral effect of pomegranate peel was reported against influenza virus, where the various metabolites present in peel inhibits the entry of virus in host cell and transcription of viral RNA[34]. Thus these pomegranate peels being rich in bioactive molecules can be ultimately used as natural herbal drug against the influenza virus. Similarly inSARS-CoV-2 infection also,viral internalization is a crucial step that draws researcher attention to identify or manipulate the specific binders that can block the viral entry.

The four main proteins that control are S protein, Angiotensin-converting enzyme 2 (ACE2), Furin and Transmembrane serine protease 2 (TMPRSS2). A computational analysis of various metabolites present in pomegranate peel and their potential role in the inhibition of SARS-CoV-2 internalization was reported[45]. This study targeted the four main tannin compounds (punicalagin, punicalin, ellagic acid, and gallic acid) as ligands, to check their efficacy against SARS-CoV-2 using *in silico* tools. The protein targets were S protein, Angiotensin-converting enzyme 2 (ACE2), Furin and Transmembrane serine protease 2 (TMPRSS2) enzymes that controls the viral internalization into the host cell. The molecular docking studiesconducted revealed thatpunicalin and punicalagin showed higher affinity towards amino acid residues present in S-protein active sites as compared to positive controls or reference compounds (lopinavir and urnifenovir). These active site residues responsible for complex formation are the potential candidates for allosteric disruption of S-protein and ACE2 complex. In case of ACE2 target, docking studies showed that these tannins are efficient binders with ACE2 and could block the interaction of ACE2 with S-protein, thus regarded as a novel therapeutics approach for inhibiting the SARS-CoV-2internalization[39]. Also, these tannins formed stable complexes with proteases (Furin and TMPRSS2) that have a significant role in cleavage of S-protein during SARS-CoV-2 internalization into the host cell[45].

In addition to viral structural protein such as S-protein, there are number of non-structural protein like 3C-like protease ($3CL^{pro}$), Papain-like protease (PL^{pro}) and RNA-dependent RNA polymerase (RdRp) which are promising candidates for releasing the viral proteins[4]. Docking studies was conducted with structures of19 hydrolysable tannins retrieved from PubChem database and observed that these compounds bind efficiently with$3CL^{pro}$ for SARS-CoV-2 therapy development[25]. Virtual screening of pomegranate compounds through molecular docking studies help in understanding structure-activity relationship which marks as a first promising step in developing an effective and efficient drug targeting a desired protein of SARA-CoV2. There are number of reports that investigated the various natural plant products against SARS-CoV infection, thus confirming their positive role in controlling virus internalization[1,3,37]. Pomegranate fruit being rich source of bioactive metabolites, so trials are being conducted in hospitals in Yasuj city, Iran to study the potential of pomegranate juice asan anti-inflammatory biomarker,after 14 days of treatment in case of patients hospitalized for mild to moderate COVID-19 infection[59].

Role of plant secondary metabolites against COVID-19 :

Efforts are being made to develop effective drug compounds to control COVID-19. There are many strategic approaches such as monoclonal antibodies, vaccines, peptides or interferon therapies to control COVID-19. Existing/repurposing drugs like favipiravir, remdesivir and lopinavir are available as first line of treatment. The ultimate solution to control COVID-19 crisis is development of effective vaccines or specific therapeutic drugs which works effectively against SARS-CoV-2

and its variants. Since, bioengineered antibodies and cytokines or nucleic acid based therapies have shown promising results in treatment of SARS-CoV-2 infection. However, there are severe adverse effects of these synthetic drugs[26,48,51]. At the present time, the microbial pathogens are showing enhanced resistance to various allopathic drugs which increases the demand forplant-based drugs. Scientists are working effortlessly to discover the multi-epitope drugs that are safe, inexpensive and effective. Plant based drugs are gaining popularity for being cost effective and eco-friendly as compared to synthetic drugs. The crude extracts of plants contain several secondary metabolites that could target multiple virion sites at the same time.There are several reports that highlights the role of natural plant products in disruption of cell membrane, intermediate metabolism, nucleic acid synthesis and cell communication that affect various events of pathogenesis[2,10,61].

Natural plant products cover 35% of global medicine market which highlight their popularity worldwide[12]. Numerous secondary metabolites such as phenols, tannins, flavonoids, lignans, stilbenes and terpenoids have diverse action of mechanism against coronavirus that includes inhibition of various cellular pathways, attenuating PL^{pro} and 3-CL^{pro} and inactivates various enzymes that block or halt the viral pathogenesis[7]. Secondary metabolites such as curcumin, chrysophanol, quercetin, magnoflorine, apigenin, luteolin target the spike proteins that control the virus entry into host cells[28,43]. Carnosol, ellagic acid, ursolic acid, cyanidin 3-glucoside, digitoxigen are among several metabolitestargeting main protease (M^{pro}) of SARS-CoV-2[22,47]. 3-CL^{pro} is targeted by myricitrin, amaranthin, coumarine, cryptoquindoline, licoleafol and colistin[26,17] whereas TMPRSS2 are targeted by withanone and withaferin compounds[30]. In addition to this, plant natural products also affect the various stages of SARS-CoV-2 life cycle. Viral attachment is inhibited by phytoestrogens, chlorogenic acid, caffeic acid, p-coumaric acid, palmitic acid and cinnamaldehyde[13]. Similarly, the virus entry is inhibited by dihydrotanshinone-1 and desmethoxyreserpine whereas multiplication is halted by betulinic acid, lignin and desmethoxyreserpine[6]. These reports particularly point the wide scope of use of secondary metabolites as alternative to find the efficient therapeutic drugs to fight COVID-19.

Pomegranate being rich in bioactive compounds, can serve as a promising natural therapy against SARS-CoV-2 by inhibiting the viral structural and non structural proteins y to control viral replication and infection. Computational strategies are being used to analyse the structure-activity relationship of natural plant products in order to develop safe and cost effective candidates to supplement SARS-CoV-2 drugs. In addition, more *in-vitro* research and computational advances are required to study the underlying action mechanism and interaction of these phytochemicals with SARS-CoV-2 proteins.

Author's contributions :

Authors Ramanjeet Kaur, Lubna Aslam, Nisha Kapoor and Ritu Mahajan contributed to the conception of the study, preparation and design of this review article. The literature survey was done by the authors Ramanjeet Kaur and Ritu Mahajan. Ramanjeet

Kaur wrote the first draft of the manuscript and all the authors made their comments on it. All authors read, revised and approved the final manuscript.

Conflicts of interest :

The authors declare no conflict of interest.

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References :

1. Anand, A.V., B. Balamuralikrishnan, M. Kaviya, K. Bharathi, A. Parithathvi, M. Arun, N. Senthilkumar, S. Velayuthaprabhu, S. Saradhadevi, M., Al-Dhabi, N.A, Arasu, M.I. Yatoo, R Tiwari, and K. Dhama (2021). *Molecules 26*(6): 1775. doi: 10.3390/molecules26061775.
2. Anandhi, D., P.T. Srinivasan, G.P. Kumar, and S. Jagatheesh (2014) *Int. J. Curr Microbiol Appl Sci 3:* 66-73.
3. Ansari, W.A., T. Ahamad, M.A. Khan, Z.A. Khan and M.F. Khan (2020). *Comput. Chem.doi:* 10.21203/rs.3.rs-35368/v1.
4. Báez-Santos, Y.M., S.E. St John, and A.D. Mesecar (2014). *Antiviral Res115:* 21-38.
5. BenSaad, L.A., K.H. Kim, C.C. Quah, W.R. Kim, and M. Shahimi (2017). *BMC Complement Altern Med 17:* 47. doi: 10.1186/s12906-017-1555-0.
6. Bhardwaj, V.K., R. Singh, J. Sharma, V. Rajendran, R. Purohit, and S. Kumar (2020). *J Biomol Struct Dyn 1:* 11.
7. Bhuiyan, F.R., S. Howlader, T. Raihan, and M. Hasan (2020). *Front Med 7:* 444. doi: 10.3389/fmed.2020.00444.
8. Caruso, A., A. Barbarossa, A. Tassone, J. Ceramella, A. Carocci, A. Catalano, G. Basile, A. Fazio, D.I.C. Franchini, and M.S. Sinicropi (2020). *Appl Sci 10:* 6915.doi: 10.3390/app10196915.
9. Chams, N., S. Chams, R. Badran, A. Shams, A. Araji, M. Raad, S. Mukhopadhyay, E. Stroberg, E. J. Duval, L. M. Barton, and I. Hajj Hussein (2020). *Frontpublic health 8:* 383. https://doi.org/10.3389/fpubh.2020.00383.
10. Chitemerere, T.A. and S. Mukanganyama (2014). *BMC Complement Altern Med 14:* 278. doi: 10.1186/1472-6882-14-278.
11. Conzelmann, C., T. Weil, R. Grob, P. Jungke, B. Frank, M. Eggers, J.A. Müller, and J. Münch (2020). *bio Rxiv.* https://doi.org/10.1101/2020.10.30.360545.
12. Ebenezer, K.S., R. Manivannan, A. Punniyamoorthy, and C. Tamilselvan (2019). *J. Drug Deliv. Ther 9:* 161–7.
13. Elfiky A.A. (2020). J. Biomol Struct Dyn 1–10.
14. Guan, W., Z. Ni, Yu. Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin. Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua. Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu and N. Zhong (2020). *N Engl J Med 382*(18): 1708-1720.

15. Guerrero-Solano, J.A., O.A. Jaramillo-Morales, C. Velázquez-González, O. De la M. Arciniega, A. Castañeda-Ovando, G. Betanzos-Cabrera and M. Bautista (2020). *Plants (Basel) 9*(4): 419. doi: 10.3390/plants9040419.
16. Gui, M., W. Song, H. Zhou, J. Xu, S. Chen, Y. Xiang, and X. Wang (2017). *Cell Res 27:* 119-129.
17. Gyebi, G.A., O.B. Ogunro, A.P. Adegunloye, O.M. Ogunyemi, and S.O. Afolabi (2020). *J. Biomol* Struct Dyn 1-13.
18. Hoffmann, M., H. Kleine-Weber, N. Krüger, M.A. Mueller, C. Drosten and S. Pöhlmann (2020). *bio Rxiv. doi:* 10.1101/2020.01.31.929042.
19. Hofmann, H. and S. Pöhlmann (2004). *Trends Microbiol 12:* 466-472.
20. Houston, D.M.J., J.J. Bugert, S.P. Denyer, and C.M. Heard (2017). *PLoS One 12*(6): e0179291. doi:10.1371/*journal.pone*.0179291.
21. Howell, A.B. and D.H. D'Souza (2013). *Complement Alternat Med 2013:* 606212. doi:10.1155/2013/606212.
22. Islam, M.T., C. Sarkar, D.M. El-Kersh, S. Jamaddar, S.J. Uddin, J.A. Shilpi and M.S. Mubarak (2020). *Phytother. Res. 34*(10): 2471-2492.
23. Kaur, R., L. Aslam, N. Kapoor, and R. Mahajan (2018). *Biotechnol. Res. Asia 15*(2): 335-341.
24. Kaur, R., L. Aslam, N. Kapoor, and R. Mahajan (2020). *Braz J Bot 43:* 883-896.
25. Khalifa, I., W. Zhu, H.H.H. Mohammed, K. Dutta, and C. Li (2020). *J. Food Biochem.doi*:10.1111/jfbc.13432.
26. Khan, S.A., K. Zia, S. Ashraf, R. Uddin, and Z. Ul-Haq (2020). *J. Biomol Struct Dyn 39*(7): 2607-2616.
27. Kim, D.W., K.H. Seo, M.J. Curtis-Long, K.Y. Oh, J.W. Oh, J. K. Cho, K.H. Lee, and K.H. Park (2014). *J. Enzyme Inhib Med Chem 29*(1): 59-63.
28. Kiran, G., L. Karthik, M.S. Shree Devi, P. Sathiyarajeswaran, K. Kanakavalli, K.M. Kumar, and D. Ramesh Kumar (2020). *J. Ayurveda Integr Med. doi:* 10.1016/j.jaim.2020.05.009.
29. Kleine-Weber, H., M.T. Elzayat, M. Hoffmann, and S. Pohlmann (2018). *Sci. Rep 8:* 16597. https://doi.org/10.1038/s41598-018-34859-w.
30. Kumar, V., J.K. Dhanjal, P. Bhargava, A. Kaul, J. Wang, H. Zhang, S.C. Kaul, R. Wadhwa, and D. Sundar (2020) *J. Biomol Struct Dyn* 1-13.
31. Li, F. (2016). *Annu. Rev. Virol 3:* 237-261.
32. Lukassen, S., R.L. Chua, T. Trefzer, N.C. Kahn, M.A. Schneider, T. Muley, H. Winter, M. Meister, C. Veith, A.W. Boots, B.P. Hennig,, Kreuter, M., C. Conrad, and R. Eils (2020). *EMBO J.* 2020;39:e105114. https://doi.org/10.15252/embj.20105114.
33. Mazinani, M. and B.J. Rude (2021). *J. Healthc. Qual. Res. 36*(1): 47-51.
34. Moradi, M.T., A. Karimi, M. Rafieian-Kopaei, M. Rabiei-Faradonbeh, and H. Momtaz (2020). *Avicenna J. Phytomed 10*(2): 143-151.
35. Moradi, M.T., A. Karimi, M. Shahrani, L. Hashemi, and M.S. Ghaffari-Goosheh (2019). *Avicenna J. Med. Biotechnol 11*(4): 285-291.
36. Peiris, J.S.M., Y. Guan, and K.Y. Yuen (2004). *Nat. Med 10:* S88–S97.
37. Puttaswamy, H., H.G. Gowtham, M.D.

Ojha, A. Ydav, G. Choudhir, V. Raguraman, B. Kongkham, K. Selvaraju, S. Shareef, P. Gehlot, F. Ahamed, and L. Chauhan (2020). *Sci Rep. 2020;10:* 20584. https://doi.org/10.1038/s41598-020-77602-0.

38. Reddy, B.U., R. Mullick, A. Kumar, G. Sudha, N. Srinivasan, and S. Das (2014). *Sci. Rep 4:* 5411. https://doi.org/10.1038/srep05411.
39. Roshanravan, N., S. Ghaffari, and M. Hedayati (2020). *Diabetes Metab. Syndr. 14:* 637-639.
40. Simmons, G., P. Zmora, S. Gierer, A. Heurich and S. Pöhlmann (2013). *Antiviral Res 100:* 605-614.
41. Sreekumar, S., H. Sithul, P. Muraleedharan, J.M. Azeez, and S. Sreeharshan (2014). *Biomed Res Int* 686921. doi: 10.1155/2014/686921.
42. Stadler, K. and R. Rappuoli (2005). Curr. *Mol. Med 5:* 677–697.
43. Subbaiyan, A., K. Ravichandran, S.V. Singh, M. Sankar, P. Thomas, K. Dhama, Y.S. Malik, R.K. Singh, and P. Chaudhuri (2020). *J. Pure Appl. Microbiol 14:* 989-98.
44. Sudhakar, S., D. Venugopal, D. Vignesh, and S. Karthikeyan (2015). *Int. J. Life Sci. Res 3:* 77-84.
45. Suručić, R., B. Tubić, M.P. Stojiljković, D.M. Djuric, M. Travar, M. Grabež, K. Šavikin, and R. Škrbić (2021). *Mol Cell. Biochem 476:* 1179-1193.
46. Tito, A., A. Colantuono, L. Pirone, E. Pedone, D. Intartaglia, G. Giamundo, I. Conte, P. Vitaglione, and F. Apone (2020). *Front Chem 9:* 638187.https://doi.org/10.3389/fchem.2021.638187.
47. Umesh, U., D. Kundu, C. Selvaraj, S.K. Singh, and V.K. Dubey (2020). *J. Biomol Struct Dyn* 1–8.
48. Vankadari N. (2020). *Int. J. Antimicrob Agents 28:* 105998. doi: 10.1016/j.ijantimicag.2020.105998.
49. Velavan, T.P. and C.G. Meyer (2020). *Trop. Med. Int. Health 25:* 278-280.
50. Wan, Y., J. Shang, R. Graham, R.S. Baric, and F. Li (2020). *J. Virol 94:* e00127-e220. doi: 10.1128/JVI.00127-20.
51. Wang, Y., D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Y. Hu, G. Luo, K. Wang, Y. Lu, H. Li, S. Wang, S. Ruan, C. Yang, C. Mei, Y. Wang, D. Ding, F. Wu, X. Tang, X. Ye, Y. Ye, B. Liu, J. Yang, W. Yin, A. Wang, G. Fan, F. Zhou, Z. Liu, X. Gu, J. Xu, L. Shang, Y. Zhang, L. Cao, T. Guo, Y. Wan, H. Qin, Y. Jiang, T. Jaki, F.G. Hayden, P.W. Horby, B. Cao, and C. Wang (2020). *Lancet. 395*(10236): 1569-1578.
52. Wang, Z., B. Yang, Q. Li, L. Wen, and R. Zhang (2020). *Clin. Infect. Dis 71*(15): 769-777.
53. Wen, C.C., Y.H. Kuo, J.T. Jan, P.H. Liang, S.Y. Wang, H.G. Liu, C.K. Lee, S.T. Chang, C.J. Kuo, S.S. Lee, C.C. Hou, P.W. Hsiao, S.C. Chien, L.F Shyur, and N.S. Yang (2007). *J. Med. Chem 50:* 4087–4095.
54. WHO (2020). Director-General's Opening Remarks at the Media Briefing on COVID-19. Available online at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19.
55. World Health Organization (2004). Clinical trials on treatment using a combination of traditional Chinese medicine and Western medicine.https://apps.who.int/medicinedocs/pdf/s6170e/s6170e.
56. World Health Organization (2019). WHO global report on traditional and comple-

mentary medicine. WHO.https://apps.who. int/iris/handle/10665/312342.

57. Wu, S. and L. Tian (2017). *Molecules 22*(10): 1606. doi:10.3390/molecules 22101606.
58. Yesudhas, D., A. Srivastava, and M.M. Gromiha (2021). *Infection 49*(2): 199-213.
59. Yousefi, M., M. Sadriirani, A. Pour Mahmoudi, S. Mahmoodi, B. Samimi, M. Hosseinikia, Z. Saeedinezhad, and S.B. Panahande (2021). *Trials 22:* 246. https://doi.org/10.1186/s13063-021-05194-9.
60. Zaki, A.M., S. Van Boheemen, T.M. Bestebroer, A.D.M.E. Osterhaus, and R.A.M. Fouchier (2012). *N Engl J Med 367:* 1814-1820.
61. Zhao, X., F. Zhao, and N. Zhong (2018). *Itratech Open. doi:* 10.5772/intechopen. 74658.
62. Zhu, N., D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi,R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, and W. Tan (2020). *N Engl J Med 382:* 727-733.