International Journal of Basic & Clinical Pharmacology
Noor AU et al. Int J Basic Clin Pharmacol. 2021 Apr;10(4):453-456
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20211032

Review Article

Plants metabolites as a prospective approach against the COVID-19

Aijaz Ul Noor, Ruqaya Aziz*

Department of Biochemistry, SKIMS, MCH Bemina, Srinagar, Kashmir, Jammu and Kashmir, India

Received: 26 January 2021
Accepted: 03 March 2021

***Correspondence:**
Dr. Ruqaya Aziz,
Email: azizruqaya@gmail.com

ABSTRACT

The Coronavirus disease 2019 (COVID-19) caused by an RNA virus SARS-CoV-2 is an emerging global health pandemic. With currently no approved treatment or prophylaxis, the SARS-CoV-2 is rapidly transmitted via touch, droplets, and fomites. In most affected patients, the disease will have mild flu-like symptoms (fever, dry cough, and difficulty in breathing) and in selected patients may cause severe complications such as progressive pneumonia, acute respiratory distress syndrome, and organ failure due to hyper-inflammation and cytokine storm syndrome. Understanding the pathogenesis of the disease is essential for identification and rational design of effective drug targets. The plant metabolites can provide as a prospective approach for SARS-CoV-2, due to lowest possible side effect and antiviral properties. In this report, we provide an overview of the disease pathogenesis and highlight the potential therapeutic interventions.

Keywords: Covid-19, Plant medicine, Drug targets

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging global health crisis, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 virus is rapidly transmitted by contact, droplets, and fomites with presently, no approved treatment or prophylaxis. The symptoms may vary with the severity of the disease, with the majority reporting little or mild flu-like symptoms (fever, dry cough, and difficulty in breathing). Some patients with the COVID-19 disease may have severe complications such as progressive pneumonia, acute respiratory distress syndrome, organ failure driven by hyper-inflammation and a cytokine storm syndrome (increased cytokine levels via interleukins (IL) and tumor necrosis factor (TNF)-α) require hospitalization.[1-10]

The World Health Organization (WHO) has declared this a global pandemic by March 2020.[5] Daily reports of sharp rises in the number of new cases continue to emerge from many countries and / or regions, but efforts to overcome the virus are hampered by a lack of knowledge of several important aspects of SARS- CoV-2 infection, ranging from pathogen biology to host response and treatment options.

The drug that is identified to be effective in Covid-19 are hydroxyl-chloroquine, HIV protease inhibitors ritonavir/lopinavir, convalescent plasma and remdesivir.[6] The current management of the disease includes prevention of infection, supportive care, symptomatic management and mechanical ventilation in critically ill patients.[7]

The plant medicines are in use since ages by the mankind in order to treat and cure various diseases. Several phytochemicals showing antiviral properties are isolated can be used as a therapeutic drug for the management of the diseases. They are the best possible tools in order to tackle the disease as they have lowest possible side effects as compared to other forms of drugs available and in use to treat the diseases. This article briefly reviews the pathogenesis of the SARS-CoV-2 and various plant metabolites as a prospective approach for effective management of COVID-19.

STRUCTURE OF VIRUS, REPLICATION AND PATHOGENESIS

The SARS CoV-2 encode four structural proteins, Spike (S) protein, Membrane (M) protein, Envelop (E) protein and Nucleocapsid (N) protein embedded in host membrane-derived lipid bilayer encapsulating the genetic material comprising positive-sense, single-stranded viral RNA. The S-protein via S1 and S2 domain mediates the binding of the virus to the host cell membrane via ACE2 receptor and also, mediate cell fusion to facilitate viral entry.[8] The M-protein is most abundant glycoprotein on the virion surface; whereas E-protein is a small membrane protein (glycoprotein) composed ~76 to 109 amino-acid. The M and E proteins are required for virus morphogenesis, assembly, and budding.[9,10] The N-protein is the internal component of the single positive – strand RNA virus, possibly plays a vital role in its replication and transcription. The development of an efficient drug that can stop viral replication and transcription by preventing interaction between the N – protein present at N – terminal and the single positive RNA strand is an important area open to research. Sarma et al. showed that two major groups of compounds, theophylline and pyrimidine, are potential RNA inhibitors that bind to the N-terminal domain of coronavirus N-protein, providing new avenues for invitro validation.[11]

Virus infections initiate with binding of viral particles to host surface cellular receptors. Receptor recognition is therefore an important determinant of the cell and tissue tropism of a virus. The coronavirus spike (S) protein attaches to angiotensin converting enzyme 2 (ACE2) receptors that is found on the surface of many human cells, including those in the lungs allowing virus entry. The S protein has been found to exhibit a furin cleavage site (PRRARS'V) at the interface between S1 and S2 subunits which trigger the activation of the membrane fusion mechanism.[12]

The endosome release the viral genetic material a single stranded RNA into the cytoplasm. There takes place the replication and transcription processes which are mediated by the so-called replication / transcription complex (RTC). Such complex is encoded in the viral genome and it is made of non-structural proteins (nsp).[13] The polyproteins are produced which is later cleaved by the protease to form structural / non – structural proteins. These proteins are assembled together and the corona virions leaves the cell by exocytosis, in the process infecting other cells.[14] Meanwhile, the stress on endoplasmic reticulum caused by viral development inevitably contributes to cell death.

ROLE OF PLANT METABOLITES IN COVID 19

Plant metabolites targeting the virus uptake pathways

The coronaviruses enter the cell by two ways, (A) endocytosis, the virus is taken up into the cell along with the endosomes, (B) fusion of the viral spike protein with the cell surface receptor angiotensin-converting enzyme - 2 (ACE2), the latter being the predominant pathway of virus entry.[15,16] Blockade of entry pathways may be effective targets for treatment (Table 1).

Table 1: Steps involved in pathogenesis.

Steps	Drugs / targets
ACE Inhibitor	Flavonoids
Endocytosis Inhibitor	Cinnamomi species
Viral Replication and Transcription Inhibitor	Glycyrrhizin, Houttuynia cordata, Quercetin

Angiotensin converting enzyme (ACE) inhibitors

The binding of SARS-CoV-2 spike glycoprotein to the human receptor ACE2 is well established.[17] The spike glycoprotein is a key target for vaccines, therapeutic antibodies, and diagnostics. 18 The expression of ACE-2 is observed in different tissues, including the upper and lower respiratory tract, myocardium and the gastrointestinal mucosa.[19] Wrapp et al observed that the spike (S) glycoprotein of the SARS-CoV-2 binds ACE-2 with higher affinity than SARS-CoV.[18]

The discovery of novel angiotensin receptor blockers (ARBs) from natural products will affect the attachment of SARS-CoV-2 RBD to ACE-2 expressing cells, thus inhibiting their infection to host cells. The active lead compounds from natural products can be further modified to enhance their biological activity in order to be developed as drug candidates.[20, 21] Recent progress on natural products resulted in compounds being developed to treat viral infections.[22] Utomo et al reported the biological activity of natural products in inhibiting SARS-CoV-2 using in silico methods. Islam et al. comprehensively reviewed studies on natural products with inhibitory activity against SARS-CoV.[23]

Natural products such as flavonoids, xanthones, proanthocyanidins, secoiridoids, and peptides were reported to contain anti-ACE activity; however, further research is needed to confirm the findings.[24] A study by Muchtaradi et al reported that that flavonoids are the most effective plant metabolite (natural compound) with regard to ACE inhibition activity.[25] Another study by Wu, C et al showed that Hesperidin inhibits the interaction between the RBD of the S protein of SARS-CoV-2 and the ACE2 receptor in humans; thus, it was also predicted to potentially inhibit the entry of SARS-CoV-2.[26]

Endocytosis inhibitors

Many viruses depend on the host cell endocytic pathways for entry. SARS-CoV S- glycoprotein mediates viral entry through pH-dependent endocytosis, like vesicular stomatitis virus (VSV).[27] The endocytic pathways taken by viruses can be divided into clathrin-mediated and clathrin-independent pathways.[28] Recently, Inoue et al.

demonstrated that SARS-CoV mainly utilizes the clathrin-mediated endocytosis pathway for its entry to target cells.[29] The Zhuang et al. showed that extracts of Cinnamomi species inhibit the clathrin-dependent endocytosis pathway, thus preventing viral entry to the host cells.[30]

Viral replication and transcription (replicase – RNA dependent RNA polymerase) inhibitors

Cinatl et al. reported that Glycyrrhizin, a saponin isolated from Glycyrrhiza glabra roots, inhibit SARS-CoV replication.[31] Recently, Yu et al have identified the viral activity of water extract of Houttuynia cordata against SARS-CoV. This compound shows its inhibitory effect on 3C-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp) of the virus.[32] The protease 3CLpro is an effective drug target due to its essential role in processing the polyproteins that are translated from the viral RNA. There are few reports that have shown 3CLpro inhibition function.[33-34] So far, our understanding about the structural similarities and comparable modes of replication between SARS-CoV and SARS-CoV-2, these compound might be effective for the management of COVID-19.

CONCLUSION

Currently, the medication available for COVID-19 shows uncertain efficacy and adverse effects. In order to determine the effectiveness of these drugs, more major randomized controlled clinical studies are needed. In view of the vast range of plant phytochemicals with potent antiviral activity will be alternate approach to reduce disease severity and viral load for effective management of COVID-19. This implies the need for studying plant-based compounds to circumvent the viral load.

ACKNOWLEDGEMENTS

Authors gratefully acknowledge the management of Department of Biochemistry, SKIMS Medical College, Bemina for providing the facilities to carry out this work.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Burke RM, Midgley CM, Dratch A, Fenstersheib M, Haupt T, Holshue M, et al. Active monitoring of persons exposed to patients with confirmed COVID-19 — United States, January–February 2020. MMWR Morb Mortal Wkly Rep. 2020.
2. Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA. 2020;323(16):1610-12.
3. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020;M20-0504.
4. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020;20(6):656-57.
5. World Health Organization. WHO Director- General's opening remarks at the media briefing on COVID-19 - 11 March 2020. WHO. https://www.who.int/dg/speeches/detail/who- director- general- s- opening remarks-at- the- media- briefing- on- covid-19-11-march-2020. Last accessed on 3rd January, 2021.
6. Khan Z, Karataş Y, Rahman H. Anti COVID-19 drugs: need for more clinical evidence and global action. Adv Ther. 2020;37(6):2575-79.
7. CDC. Coronavirus Disease 2019 (COVID-19). Information for Clinicians on Investigational Therapeutics for Patients with COVID-19. Centers for Disease Control and Prevention. 2020. Available from https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Last accessed on 12 May, 2020.
8. Kirchdoerfer RN, Cottrell CA, Wang N, Pallesen J, Yassine HM, Turner HL et al. Pre-fusion structure of a human coronavirus spike protein. Nature. 2016;531(7592):118-21.
9. Gupta MK, Vemula S, Donde R, Gouda G, Behera L, Vadde R. In-silico approaches to detect inhibitors of the human severe acute respiratory syndrome coronavirus envelope protein ion channel. Journal of Biomolecular Structure and Dynamics. 2020;1-11.
10. Kumar S, Maurya VK, Prasad AK, Bhatt MLB, Saxena SK. Structural, glycosylation and antigenic variation between 2019 novel coronavirus (2019-nCoV) and SARS coronavirus (SARS-CoV). Virus disease. 2020;31(1):13-21.
11. Sarma P, Sekhar N, Prajapat M, Avti P, Kaur H, Kumar S et al. In-silico homology assisted identification of inhibitor of RNA binding against 2019-nCoV N-protein (N-terminal domain). Journal of Biomolecular Structure and Dynamics. 2020;1-9.
12. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 2020;176: 104742.
13. Hemert VMJ, Worm VD, Knoops K, Mommaas AM, Gorbalenya AE, Snijder EJ. SARS-coronavirus replication/transcription complexes are membrane protected and need a host factor for activity in vitro. PLoS Pathogens. 2008;4(5):e1000054.
14. Valencia DN. Brief Review on COVID-19: The 2020 pandemic caused by SARS-CoV-2. Cureus. 2020;12(3):e7386
15. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012;4:1011-33.

16. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.
17. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV- 2. Nature Medicine. 2020;26(4):450-452.
18. Wrapp D, Wang M, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;10.
19. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative RNA expression profiling of ACE2, a novel homologue of angiotensin converting enzyme. FEBS Letter. 2002;532(1-2):107-10.
20. Guo, Z. The modification of natural products for medical use. Acta Pharm Sin. 2017;7(2):119-36.
21. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J Nat Prod. 2020;83(3):770-803.
22. Ganjhu RK, Mudgal PP, Maity H, Dowarha D, Devadiga S, Nag S, Arunkumar G. Herbal plants and plant preparations as remedial approach for viral diseases. Virus disease. 2015;26:225-36.
23. Utomo R.Y., Ikawati M., Meiyanto E. Revealing the Potency of Citrus and Galangal Constituents to Halt SARS-CoV-2 Infection. Preprints. 2020;214:1-8.
24. Islam MT, Sarkar C, El-Kersh DM, Jamaddar S, Uddin SJ, Shilpi JA et al. Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. Phytother. Res; 34(10):2471-2492.
25. Muchtaridi M, Fauzi M, Khairul Ikram NK, Mohd Gazzali A, Wahab HA. Natural Flavonoids as Potential Angiotensin-Converting Enzyme 2 Inhibitors for Anti-SARS-CoV-2. Molecules 2020; 25(17):3980.
26. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm. Sin. B 2020; 10(5):766-788.
27. Sun X, Yau VK, Briggs B, Whittaker GR. Role of clathrin-mediated endocytosis during vesicular stomatitis virus entry into host cells. Virology. 2005;338:53-60.
28. Marsh M, Helenius A. Virus entry: open sesame. Cell. 2006;124:729-740.
29. Inoue Y, Tanaka N, Tanaka Y, Inoue S, Morita K, Zhuang M et al. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. J. Virol 2007; 81:8722–29.
30. Zhuang M, Jiang H, Suzuki Y, Li X, Xiao P, Tanaka T et al. Procyanidins and butanol extract of Cinnamomi Cortex inhibit SARS-CoV infection. Antiviral Res. 2009; 82(1):73-81.
31. Cinatl J, Morgenstern B, Bauer G. Glycyrrhizin, an active component of liquorice roots, and replication of SARS associated coronavirus. Lancet. 2003;361:2045-46.
32. Yu M, Lee J, Moo J. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorganic Med Chem Lett. 2020;22:4049-54.
33. Ryu YB, Jeong HJ, Kim JH. Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. Bioorganic Med Chem. 2010;18:7940-47.
34. Lin CW, Tsai FJ, Tsai CH. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antivir Res. 2005;68:36-42.

Cite this article as: Noor AU, Aziz R. Plants metabolites as a prospective approach against the COVID-19. Int J Basic Clin Pharmacol 2021;10:453-6.