Plants metabolites as a prospective approach against the COVID-19

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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 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
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, theephalline 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>
<thead>
<tr>
<th>Steps</th>
<th>Drugs / targets</th>
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<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>Flavonoids</td>
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<tr>
<td>Endocytosis Inhibitor</td>
<td>Cinnamomi species</td>
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<tr>
<td>Viral Replication and Transcription Inhibitor</td>
<td>Glycyrrhizin,</td>
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<td></td>
<td>Houttuynia cordata,</td>
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<td>Quercetin</td>
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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. The Zhuang et al. showed that extracts of Cinnamomi species inhibit the clathrin-dependent endocytosis pathway, thus preventing viral entry to the host cells.

**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. 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. 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. 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.

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