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Concept note

The potential role of Bromhexine in the management of COVID-19: Decipher and a real game-changer

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ABSTRACT

Primary infection of SARS-CoV-2 (novel coronavirus or 2019-nCoV), which leads to Covid-19, targets specific cells, such as nasal, bronchial epithelial and pneumocytes, through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Also, type 2 transmembrane serine protease (TMPRSS2) present in the host cell promotes viral uptake by cleaving ACE2 and triggering the SARS-CoV-2 S protein, which facilitates SARS-CoV-2 entry into host cells. One of the TMPRSS2 inhibitors with a greater distribution capacity into the lung tissue is bromhexine hydrochloride which attenuates the entry and proliferation of SARS-CoV-2. Bromhexine is an effective drug in the management and treatment of Covid-19 pneumonia via targeting ACE2/ TMPRSS2 pathway. However, prospective and controlled clinical trials are recommended to confirm this observation.

INTRODUCTION

The existing epidemic of the novel coronavirus SARS-CoV-2 (coronavirus disease 2019; previously 2019-nCoV), in Hubei Province of China, has spread to numerous other countries and on 30 January 2020, the WHO Emergency Committee declared a global health emergency based on growing case notification rates at Chinese and international locations (Al-Kuraishy et al., 2020a).

Coronaviruses are enveloped and positive single-stranded large RNA viruses that infect humans, and a varied range of animals. SARS-CoV-2 belongs to the β-coronaviruses have four structural genes encode the nucleocapsid protein (N), the spike protein (S), a small membrane protein (SM) and the membrane glycoprotein (M) with an additional membrane glycoprotein (HE). The SARS-CoV-2 is 96% matching at the whole-genome level to a bat coronavirus (Fig. 1) (Al-Kuraishy et al., 2020b; Semwal et al., 2020)

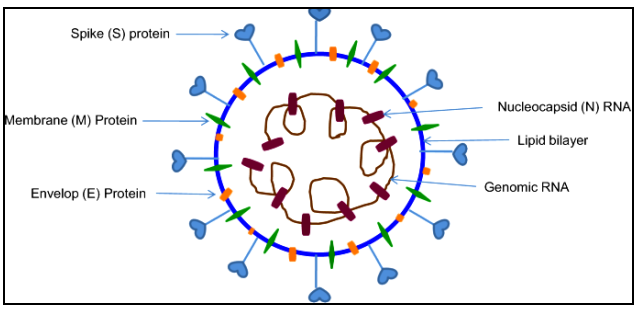

Fig. 1. Structure of SARS-CoV-2

The primary infection of novel coronavirus targets specific cells including nasal and bronchial epithelial cells through the spike protein which binds to the ACE2 receptor. Similarly, type 2 transmembrane serine protease (TMPRSS2), present in the host cell promotes viral uptake by cleaving ACE2 and triggering the SARS-CoV-2 S protein, which facilitates SARS-CoV-2 entry into host cells (Fig. 2) (Al-Kuraishy et al., 2020c).

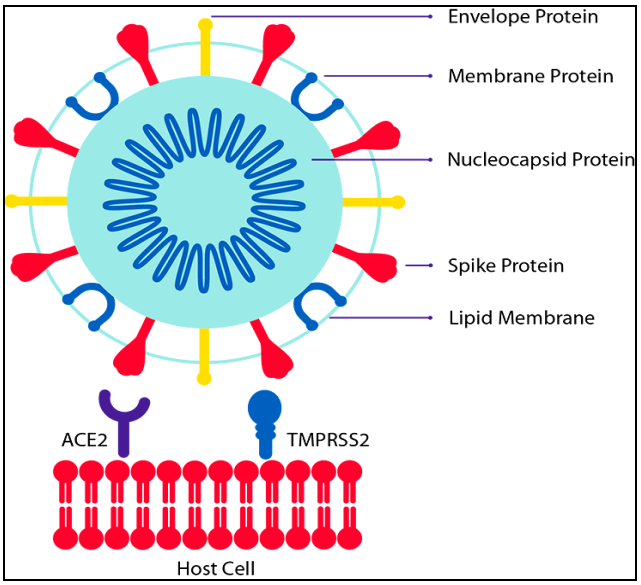

Fig. 2. SARS-CoV-2 binds to ACE2 receptor

ACE2 and TMPRSS2 are expressed in host target cells, predominantly alveolar epithelial type II cells. Furthermore, the viral inflammatory response, consisting of both the innate and the adaptive immune response blights lymphopoiesis and increases lymphocyte apoptosis. Although up-regulation of ACE2 receptors from ACE inhibitor and angiotensin receptor blocker medications has been hypothesized to increase susceptibility to SARS-CoV-2 infection, large observational cohorts have not found an association between these medications and risk of infection or hospital mortality due to Covid-19 (Al-Kuraishy et al., 2020d).

ANTI-COVID-19 MEDICATIONS

Numerous dissimilar beneficial options like anti-malaria, HIV medications, antivirals, and steroids have been tried with limited results. The most notable was the considerate use of remedisivir in the scenery of Covid-19 infection. The innovative data primarily fortified the FDA to approve this medication for use in Covid-19 infections, but additional clinical trials have not been able to support significant clinical benefit. Presently, no therapeutic agents have been established to be effective in plummeting the mortality and treatment of patients with Covid-19. There is some apprehension near the low distribution of these drugs in the respiratory system. One of TMPRSS2 inhibitors with a greater distribution capacity into the lung tissue is bromhexine hydrochloride (Hoffmann et al., 2020).

Bromhexine is planned to support the body's mechanisms for clearing mucus from the respiratory tract. It is secretolytic and increasing the production of serous mucus in the respiratory tract, which makes the phlegm thinner and less viscous (Zanasi et al., 2017). This donates to secreto-motoric effect, allowing the cilia to more easily transport the phlegm out of the lungs. For this reason, it is often added to cough syrups. It has been shown to increase the proportion of serous bronchial secretion, making it more easily expectorated. It is indicated as secretolytic therapy in bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport. Bromhexine is contained in various formulations, high and low strength syrups (8 mg/5 mL, 4 mg/5 mL), tablets and soluble tablets (both with 8 mg bromhexine) and solution for oral use (10 mg/5 mL), adapted to the need of the patients. The posology varies with the age and weight, but there are products for all age groups from infant on. Bromhexine is well established and tolerated (El-Sayed and Hashem, 2020).

ANTI-SARS-COV-2 EFFECTS OF BROMHEXINE

Blocking the non-endosomal pathway might be an effective option to control Covid-19 infection. The TMPRSS2 could be a good target to prevent viral infection by blocking the fusion and priming the processes of the virus (Li et al., 2020). There are some medications such as camostat mesylate or nafamostat, which are used in chronic pancreatitis to inhibit the TMPRSS2 and eventually cell entry of SARS-COV-2 (Depfenhart et al., 2020).

TMPRSS2 is a member of the type II transmembrane serine protease (TTSP) family. TTMPRS2 is expressed in the lungs, kidneys, and prostate. It has been shown that the presence of TMPRSS2 is very essential for the influenza virus infection (Shrimp et al., 2020). TMPRSS2 cleaves the surface glycoprotein hemagglutinin (HA) of the influenza virus and ensures virus fusion and propagation. The inhibition of TMPRSS2 by bromhexine can prevent influenza infection (Fu et al., 2020). As well to bromhexine, other synthetic inhibitors of TMPRSS2 have been developed and have demonstrated efficacy in preventing influenza infection. However, these inhibitors also have strong affinities for other proteases, such as matriptase, making their precise therapeutic mechanism unclear (Rosa and Santos, 2020). TMPRSS2 expression in the prostate is driven by androgen receptor signalling. TMPRSS2 mRNA expression is upregulated and remains elevated in androgen-stimulated prostate cancer. The admin-istration of bromhexine hydrochloride, an inhibitor of TMPRSS2, was able to suppress distant metastasis to the liver and lungs sites in mice models via modulating of ERG oncogene (Song et al., 2020). This link between androgen receptor signalling and TMPRSS2 expression could explain the higher prevalence and severity of coronavirus in males as compared to females (Kron et al., 2017).

Bromhexine is a potent inhibitor of TMPRSS2, a key protease in the infection and transmission of novel coronavirus SARS-CoV-2, bromhexine has the advantage of low price and greater safety (Sagawa et al., 2020). Also, bromhexine and its

metabolites can competitively bind to cellular receptor angiotensin-converting enzyme 2 (ACE2). This strongly inhibits the key M proteases of novel coronavirus SARS-Cov-2, promotes the release of endogenous active substances in the lungs, maintains alveolar function, and promotes sputum excretion (Sanders et al., 2020).

Related studies have pointed out that effective drugs to prevent novel coronavirus infection must contain either TMPRSS2 inhibitors or competitive ACE2 binding inhibitors, and it is particularly recommended that bromhexine, a specific TMPRSS2 inhibitor, be used to prevent and treat Covid-19 (Fig. 3) (Azimi, 2020). In addition, several university and institutional experts have jointly published articles to evaluate the importance of TMPRSS2 for respiratory virus infection and introduce the therapeutic potential of bromhexine as a TMPRSS2 inhibitor for Covid-19 (Barzegar et al., 2021).

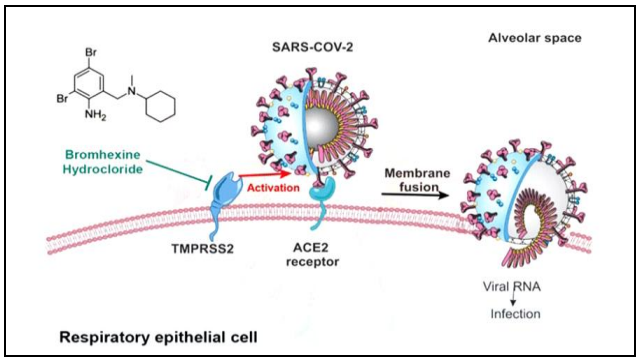

Fig. 3. Bromhexine blocks TMPRSS2 during SARS-CoV-2 invasion

A combination of bromhexine and amoxicillin in lower respiratory tract infection enhance clinical effectiveness. Additionally, patients in the group of bromhexine had a significantly greater reduction of their symptom scores for symptoms of cough discomfort, cough frequency, ease of expectoration and sputum volume. The patients taking bromhexine had treated rapidly of pneumonia (Azimi, 2020). The role of the mucociliary system in the development of immunity and protection against microorganisms is very important. Bromhexine is also used to treat coughs caused by bronchitis, chronic obstructive pulmonary disease (COPD) or cystic fibrosis (Al-Kuraishy et al., 2020e). Accordingly, the effect of bromhexine metabolites in children with respiratory disorders, the positive effect of this drug was observed in the treatment of sputum caused by respiratory infections. Hence is likely to be beneficial for the treatment of Covid-19 to prevent viral entry, the drug should be an ACE2 (angiotensin-converting enzyme 2)-binding inhibitor or TMPRSS2-specific inhibitor. It is of great importance to conduct some trials on the efficacy of bromhexine as a prophylactic or curative agent in Covid-19 patients (Al-Kuraishy et al., 2020f).

The mechanism of bromhexine is inhibition of TMPRSS2, since this pathway showed its effect in patients with the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) some years ago (Al-Kuraishy, 2021). In an ongoing trial, bromhexine hydrochloride is given to Covid-19 patients as a mucolytic agent to suppress cough in patients with suspected Covid-19 in China which shows the effectiveness of this drug to suppress cough (Al-Kuraishy and Al-Gareeb, 2020). Also, bromhexine may have a main role in the prevention of Covid-19. There is no absolute contraindication reported for bromhexine, except for rare allergy reactions to bromhexine. Meanwhile, only a few adverse effects of bromhexine are reported such as nausea, vomiting, diarrhoea and fever. For these reasons, bromhexine is a safe drug. It should be noted that, by preventing the progress of Covid-19 by using bromhexine, the renal involvement by SARS-CoV-2 may be indirectly prevented or ameliorated, while acute kidney injury is frequently observed in severe Covid-19 patient (Al-Niemi et al., 2021). Moreover, the use of bromhexine as a prophylactic and in a favourable combination with hydroxyl chloroquine as an effective endosomal protease inhibitor for the treatment of moderate to severe COVID-19 cases (Al-Kuraishy et al., 2020g).

CONCLUSION

Bromhexine is an effective drug in the management and treatment of Covid-19 pneumonia via targeting ACE2/ TMPRSS2 pathway. However, prospective and controlled clinical trials are recommended to confirm this observation.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATION

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