

# The potential role of bromhexine in COVID-19 – Has a possible new candidate been “coughed” up?

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In the midst of the current COVID-19 global pandemic, a global search is underway to explore current medicines for possible repurposed potential in COVID-19. Drugs may show promise in theory, but are they supported by clinical evidence? Bromhexine is an example of such a drug which may be a promising candidate to explore further in COVID-19 as a TMPRSS2 protease inhibitor. In this article, the authors aim to review the stages of COVID-19 best suitable for prophylaxis and treatment, with a special focus on bromhexine as a potential therapeutic candidate. Studies that investigated bromhexine in COVID-19 showed promising results. However, it was concluded that current studies are not presenting strong evidence in its support due to various limitations. Future clinical trials should address current limitations of studies by focusing on improved trial design, larger sample sizes, with improved homogeneity related to participants and treatment regimens, in order to gain more information on the potential role of bromhexine in COVID-19.

**Keywords:** bromhexine, COVID-19, TMPRSS2, clinical trials

## Introduction

The world finds itself within the current COVID-19 global pandemic and the search for safe and effective treatment regimens are underway. This has led to a global drive to explore current medicines for possible repurposed potential in COVID-19. Many drugs and compounds may show promise in theory, but are they supported by clinical evidence? Bromhexine is an example of a well-known drug which may be a promising candidate to explore further in COVID-19. In this article, the authors aim to review the stages of COVID-19 best suitable for prophylaxis and treatment, with a special focus on bromhexine as a potential therapeutic candidate.

### The stages of COVID-19

It is known that patients may present with general symptoms of acute respiratory tract infection during the initial stages of SARS-CoV-2 infections.<sup>1,2</sup> Some cases are known to progress to acute respiratory failure and further complications.<sup>1,2</sup> COVID-19 may involve multiple organs with lasting effects; however, the lungs appear to be a common target.<sup>3</sup>

The disease progression of COVID-19 can be divided into three stages:

In stage 1 (early infection), the virus is confined to the upper airways and patients are either asymptomatic or present with mild symptoms.<sup>4,5</sup>

In stage 2 (pulmonary phase), the virus invades the lungs and lower respiratory tract.<sup>4</sup> During this stage, most patients improve, however, some cases are subjected to hypercytokinaemia where pneumonia-like signs and symptoms occur.<sup>4</sup> Depending on the

severity of infections, some patients may require supportive mechanical ventilation.<sup>4</sup>

Stage 3 (hyper-inflammation phase) is serious and could potentially result in death. Respiratory symptoms occur as a result of lung injury caused by inflammation from hypercytokinaemia.<sup>4</sup> This inflammation can trigger acute respiratory distress syndrome (ARDS). Patients affected by ARDS, heart failure, septic shock or multiple organ failure require intensive care.<sup>4</sup>

In the search for potential repurposed candidates which may play a role in COVID-19 prophylaxis and treatment, a better understanding of the role players involved during the early stage of COVID-19 is needed to identify potential target sites.

### Focus on early-stage COVID-19

Viral entry of SARS-CoV-2 into host cells occurs through the binding of the spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor, where it releases components for viral RNA replication within the nucleus.<sup>1</sup> SARS-CoV-2 entry occurs via the non-endocytosis pathway, which is activated by transmembrane protease, serine 2 (TMPRSS2).<sup>2</sup> Furthermore, TMPRSS2 could potentially be involved in the release of SARS-CoV-2 from the plasma membrane.<sup>6</sup> For effective host cell entry, proteolytic cleavage of the S protein at the S1/S2 cleavage site to produce S<sub>1</sub> and S<sub>2</sub> subunits is vital.<sup>1,6-8</sup> Proteolytic cleavage is carried out by TMPRSS2 proteases present in the epithelial cells of the gastrointestinal and respiratory tracts.<sup>6,8,9</sup>

### Potential target sites for intervention in early-stage COVID-19

Given the information on the role of TMPRSS2 in COVID-19, agents with the ability to inhibit or downregulate TMPRSS2

can be explored as promising therapeutic targets. Intervention during early-stage COVID-19 is thought to decrease disease severity in infected individuals and decrease viral entry into host cells.<sup>10-13</sup> Therefore, TMPRSS2 may be a promising therapeutic target for COVID-19 prophylaxis.<sup>14</sup>

### **The pharmacology of bromhexine**

Bromhexine is extracted from a plant-derived alkaloid known as vasicin, which is developed from *Adhatoda vasica*, an Indian lung herb.<sup>6,14</sup> Bromhexine has been approved by the Food and Drug Administration in numerous countries as an over-the-counter, cost-efficient drug with minimal side effects.<sup>14</sup> Bromhexine is classified as a mucolytic, cough suppressant that breaks down mucous to aid in the clearance of chest congestion. Bromhexine is usually prescribed for the treatment of respiratory conditions associated with abnormal mucous secretion.<sup>6,9,14</sup>

Bromhexine can be administered orally as a syrup or tablet.<sup>14</sup> It is absorbed in the gastrointestinal tract, with a bioavailability of 20%.<sup>15</sup> It is largely distributed throughout body tissues and can cross the blood–brain barrier.<sup>15</sup> Bromhexine undergoes extensive first-pass metabolism in the liver.<sup>15</sup> It decreases mucous viscosity and activates mucociliary clearance to elevate mucous transport, thereby relieving cough and improving expectoration.<sup>15</sup> Bromhexine is an inhibitor of TMPRSS2 in the gastrointestinal and respiratory tracts, which may interfere with viral entry.<sup>2</sup> Bromhexine has an elimination half-life of 13–40 hours and follows renal excretion.<sup>15</sup>

Despite its high safety profile, it is not recommended for use in children under the age of 6 years.<sup>16</sup> Precaution should be taken in patients with a history of renal and hepatic failure, asthma, and peptic ulcer disease.<sup>15,16</sup> Pregnant or lactating patients should proceed with caution.<sup>15</sup> Bromhexine occasionally elicits mild adverse effects such as nausea, bloating, skin rashes, sweating, headaches, indigestion and diarrhoea.<sup>16</sup>

### **Therapeutic potential of bromhexine in COVID-19**

The repurposing of bromhexine for its potential use in COVID-19 prophylaxis and early treatment is promising. Bromide compounds such as bromhexine have a high affinity toward serine-containing proteins and exerts its effects by selectively inhibiting TMPRSS2 in a dose-dependent manner.<sup>6,14</sup> TMPRSS2 inhibition blocks its ability to activate the S protein, thereby preventing viral entry and replication.<sup>6,14</sup> TMPRSS2 is one of the few proteases that can be inhibited by minimal concentrations of the drug.<sup>2</sup> Inhibitory effects of bromhexine are thought to be 4–6 times higher in bronchial and pulmonary epithelial cells when compared to that of plasma.<sup>6</sup> Inhibiting lung TMPRSS2 with bromhexine may provide a prophylactic strategy against SARS-CoV-2 transmission, for TMPRSS2 is abundant in pulmonary tissues.<sup>17</sup> In patients with mild cases of pneumonia caused by SARS-CoV-2, bromhexine can alleviate chest congestion and provide cough relief.<sup>14</sup> Additional benefits of bromhexine include its cost-efficiency and safety profile. Furthermore, bromhexine may be favourable for its ability to alleviate cough in symptomatic patients. Bromhexine's use as a TMPRSS2 inhibitor

and a mucolytic, highlight it as a promising candidate to explore for the prophylaxis and early treatment of COVID-19.

### **Methodology**

A literature review was conducted by utilising search engines: Google Scholar, PubMed and WorldCat Discovery. The search was limited to time periods between 2019–2021. The following keywords were used: “COVID-19 and pathophysiology”, “SARS-CoV-2”, “bromhexine and COVID-19”, “bromhexine and TMPRSS2”. A separate search was conducted utilising keywords “bromhexine” and “TMPRSS2”, with no date restrictions. Studies not written in the English language were excluded.

Due to the limited amount of information available on the specific use of bromhexine in COVID-19, the initial criteria were revised and an extended search was conducted to gain additional information. The extended search utilised keywords “bromhexine”, “bromhexine and study”, and “bromhexine and trial”, which was limited to time periods between 1969–2021. The extended search was conducted to assess the role of bromhexine in symptomatic treatment of COVID-19 by evaluating its use in ailments with symptoms similar to those of COVID-19.

Results are shown in tables I–III.

### **Discussion**

#### **Pre-clinical evidence**

Studies summarised in Table I have shown the influence of bromhexine on surfactant, mucous secretion, and expectoration. Studies are currently being conducted to assess the use of surfactants as treatment for ARDS related to COVID-19. Piva et al. showed surfactant as a promising candidate.<sup>29</sup> Gil and Thurner demonstrated that bromhexine increased surfactant in the alveolar space of the lungs.<sup>18</sup> This may be beneficial in patients enduring cough or ARDS to ameliorate breathing difficulties. Studies that utilised bromhexine as monotherapy showed that bromhexine can increase secretory materials, reiterating its role in the treatment or alleviation of cough and respiratory distress (Table I). Limitations are noted in the studies. Sample sizes were small and studies are outdated. It is recommended that a modernised approach to study design could add value in future research.

#### **Clinical evidence of bromhexine**

Studies summarised in Table II explored bromhexine in conditions that result in respiratory distress, namely: chronic bronchitis, lower respiratory tract infection and ARDS. Christensen et al. and Langlands investigated bromhexine as monotherapy in chronic bronchitis.<sup>23,24</sup> Christensen et al. showed that bromhexine was associated with clinical improvement in symptoms, whereas Langlands showed no significant difference in mucous viscosity or expectoration between groups.<sup>23,24</sup> Langlands also showed no significant difference in exacerbated chronic bronchitis with mucous sputum.<sup>24</sup> This may be due to the small sample size as well as the lack of diversity within the sample being tested, for almost 80% of the participants were male. Bromhexine is supported by other studies to be a reasonable

**Table I:** Pre-clinical evidence and properties of bromhexine

Reference	Aim	Sample	Treatment regimen	Outcomes	Limitations
<b>Gil and Thurnheer<sup>18</sup></b>	To examine the influence of bromhexine on bronchial secretory cells in rat lungs	20 rats: 10 in treatment group 10 in control group	<b>Treatment group:</b> 200 mg/kg bromhexine dissolved in distilled water for 3 days <b>Control group:</b> Received distilled water	Surfactant in alveolar space increased	Pre-clinical animal study  Sample size too small
<b>Harada et al.<sup>19</sup></b>	To determine the effects of bromhexine as an expectorant on the secretory action in the tracheal mucosa of dogs	Adult dogs	2 ml (4 g) of intravenous bisolvin was administered	A rapid response occurred showing an increase in secretion, followed by the emptying and shrinkage of the submucosal glands	Pre-clinical animal study  Sample size not indicated
<b>Janatuinen and Korhonen<sup>20</sup></b>	To determine the effect of bisolvin on the secretory sequence in guinea pig's trachea-bronchial and duodenal mucosa and submaxillary salivary gland	15 guinea pigs divided into 5 groups of 3	<b>Group 1:</b> Control group <b>Group 2:</b> IM administration of 2.0 ml of physiological saline daily <b>Group 3:</b> Single 20 mg/kg dose of bisolvin 4 hours before sacrifice administered intraperitoneally <b>Group 4:</b> subcutaneous administration of 10 mg/kg bisolvin for 3 days <b>Group 5:</b> subcutaneous administration of 5 mg/kg bisolvin for 7 days	Differences in acid mucosubstances, diminishing acid residues  Decreasing goblet cells with secretory material in the trachea, especially those containing mucosubstances  Secretory materials in airways increased	Pre-clinical animal study  Small sample size
<b>Martin et al.<sup>21</sup></b>	To assess the effects of oxytetracycline hydrochloride (OTC) and a combination of OTC with bromhexine on the rheological characteristics and wet weight of secreted tracheal	3 adult minipigs	40 mg/kg OTC and 0.5 mg/kg bromhexine in combination	Bromhexine increased the OTC concentration within the secreted mucus, but decreased secretion viscosity of OTC in vivo	Pre-clinical animal study  Small sample size

**Table II:** Clinical evidence of bromhexine

<b>Roa and Dantes<sup>22</sup></b>	To compare the effectiveness of combination therapy (amoxicillin & bromhexine) versus monotherapy (amoxicillin) in clinically diagnosed community-acquired bacterial lower respiratory tract infections	392 participants: 192 in experimental (combination therapy) group 200 in control (monotherapy) group	<b>Treatment group:</b> 250 mg amoxicillin and 8 mg bromhexine 4 times a day for 5–7 days  <b>Monotherapy:</b> 250 mg amoxicillin 4 times a day for 5–7 days	Treatment group displayed a greater reduction in cough discomfort, cough frequency and an increase in expectoration by the third day	Bromhexine not tested as monotherapy
<b>Christensen et al.<sup>23</sup></b>	To determine the effect of bromhexine in patients with chronic bronchitis	61 participants: 30 in treatment group 31 in control group	<b>Treatment group:</b> 24 mg of bromhexine daily  <b>Control group:</b> placebo	Better clinical improvement was observed in the bromhexine group	Patients over 65 years of age were excluded, as well as patients with bronchitis symptoms for over 8 years
<b>Langlands<sup>24</sup></b>	To compare bromhexine with a placebo in patients with exacerbations of chronic bronchitis with mucoid sputum	27 participants: 13 in treatment group 14 in control group	<b>Treatment group:</b> 8 mg bromhexine tablets 3 times a day <b>Control:</b> placebo tablets 3 times a day	No statistical difference in mucous viscosity or expectoration	Small sample size Almost 80% of participants were male
<b>Kuckelt et al.<sup>25</sup></b>	To test bromhexine-glucose solution (BGS) in ARDs patients	25 participants: 13 in treatment group 12 in control group	<b>Treatment group:</b> BGS solution (3 g bromhexine/1 000 ml glucose solution) and was continued intravenously for 4–6 days with 50 mg bromhexine/kg bodyweight	Pulmonary function was significantly ameliorated	Small sample size

**Table III:** Clinical evidence of bromhexine in COVID-19

Reference	Aim	Number of participants	Treatment regimen	Outcomes	Limitations
<b>Depfenhart et al.<sup>14</sup></b>	To evaluate the efficacy and safety of bromhexine hydrochloride tablets combined with standard treatment in patients with suspected and mild COVID-19	18 participants: 12 in treatment group 6 in standard treatment	<b>Treatment group:</b> bromhexine hydrochloride tablets (96 mg) with standard treatment (arbidol hydrochloride granules and recombinant human interferon α2b spray)	Tablets alleviated COVID-19-associated lung injury  Required less oxygen inhalation	Small sample size  Bromhexine was not tested as monotherapy, but in combination with standard treatment
<b>Ansarin et al.<sup>2</sup></b>	To evaluate the efficacy of bromhexine in ICU admissions, mortality and mechanical ventilation	78 participants: 39 in treatment group 39 in standard treatment group	8 mg of oral bromhexine tablets 3 times a day over the course of two weeks in addition to standard treatment (200 mg/d hydroxychloroquine)	Two patients from the treatment group were admitted to the ICU vs 11 patients in the standard group  No deaths (five deaths in control group)  One patient required mechanical ventilation vs nine in control  Cough remained in 6.9% vs 40% of patients in standard  No difference in hospitalisation time	Patients were of similar demographic  Bromhexine was not tested as monotherapy, but in combination with standard treatment
<b>Mikhaylov et al.<sup>26</sup></b>	To evaluate the prophylaxis of bromhexine over 8 weeks in medical personnel with regular COVID-19 exposure	50 participants: 25 in treatment group 25 in control group	8 mg of bromhexine tablets 3 times a day, starting a day before the participants' first COVID-19 exposure	Reduced rate of symptomatic COVID-19  Two hospitalisations occurred in the control group while none occurred in the treatment group  No participants in the treatment group tested positive for infection while five participants from the control group tested positive	Small sample size  Some participants were asymptomatic  Poor compliance noted in four participants  Participants were young and healthier
<b>Mareev et al.<sup>27</sup></b>	To assess efficacy and safety of bromhexine and spironolactone combination in subjects with confirmed COVID-19 cases	103 participants: 33 in the treatment group 70 in the control group	8 mg of bromhexine 4 times a day and 50 mg of spironolactone	Reduction in hospitalisation (1.5 days) and fever (2.5 days)  Viral elimination occurred within 10 days  Faster normalisation, reducing viral load and hospitalisation time	Small sample size  Treatment group had less than half the participants in the control group
<b>Tolouian et al.<sup>28</sup></b>	To determine the effect of bromhexine in hospitalised patients with COVID-19 pneumonia	100 participants: 48 in the treatment group 52 in the control group	8 mg of bromhexine 4 times a day in addition to standard treatment (lopinavir/ritonavir and interferon beta-1a)	No significant difference in clinical improvement	Small sample size  Bromhexine was not tested as monotherapy, but in combination with standard treatment

candidate for cough therapy in diseases such as lower respiratory tract infection, chronic bronchitis and ARDS.<sup>22,23,25</sup>

Bromhexine used in combination therapy showed improvement of cough and pulmonary function (Table II). However, studies

that investigated bromhexine as monotherapy are noted with limitations due to small sample sizes. These positive signals may have sparked interest in bromhexine's potential role in early-stage COVID-19 treatment.

### Clinical evidence of bromhexine in COVID-19

Studies summarised in Table III observed that bromhexine in COVID-19 treatment was associated with improvement of cough, decreased viral load, decreased hospitalisation period and shortened viral load elimination periods. A randomised clinical trial was conducted by Tolouian et al. to determine the effect of bromhexine in hospitalised patients with COVID-19 pneumonia.<sup>28</sup> The trial demonstrated no significant difference in clinical improvement between the treatment group, who received bromhexine in combination with standard treatment, compared to the control group.<sup>28</sup> The study is noted with limitations by its small sample size and that bromhexine was not tested as monotherapy, but in combination with standard treatment (lopinavir/ritonavir and interferon beta-1a) that could have influenced study outcomes. Studies conducted by Depfenhart et al., Ansarin et al. and Mareev et al. showed that bromhexine improved COVID-19-associated lung injury, decreased ICU admissions, decreased deaths, decreased the need for mechanical ventilation, improved cough, decreased hospitalisation, increased viral load elimination and encouraged normalisation.<sup>2,14,27</sup> Although these trials highlighted the positive effects of bromhexine, it was not investigated as monotherapy and the sample sizes were small. Due to these limitations, we cannot conclude whether bromhexine on its own may have a positive impact on COVID-19 treatment or not.

Mikhaylov et al. investigated the prophylactic use of bromhexine as monotherapy for medical personnel in a single-centre randomised open-label study.<sup>26</sup> The prophylactic use of bromhexine was associated with a reduced rate of symptomatic COVID-19.<sup>26</sup> However, no significant difference could be demonstrated between the groups with respect to positive PCR tests and/or COVID-19.<sup>26</sup> Several limitations are noted, such as small sample size, non-compliance, asymptomatic participants and the sample group consisting of younger and healthier individuals that could have influenced the outcome of the study.

### Conclusion

From current literature, bromhexine may be a promising candidate to explore as a TMPRSS2 protease inhibitor for its potential role in COVID-19 prophylaxis and treatment. Current studies are not presenting strong unquestionable evidence to support this notion, due to several limitations observed in studies. It is recommended that future clinical trials should address current limitations by focusing on improved trial design, larger sample sizes, with improved homogeneity related to participants and treatment regimens.

### Author contributions

All authors contributed equally to writing, reviewing and editing the manuscript. All authors have read and agreed to the published version of the manuscript.

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### Conflict of interest

The authors declare no conflicts of interest.

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