REVIEW ARTICLE
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Bromhexine is a potential drug for COVID-19; From hypothesis to clinical trials

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COVID-19 (novel coronavirus disease 2019), caused by the SARS-CoV-2 virus, has various clinical manifestations and several pathogenic pathways. Although several therapeutic options have been used to control COVID-19, none of these medications have been proven to be a definitive cure. Transmembrane serine protease 2 (TMPRSS2) is a protease that has a key role in the entry of SARS-CoV-2 into host cells. Following the binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptors of the host cells, TMPRSS2 processes and activates the S protein on the epithelial cells. As a result, the membranes of the virus and host cell fuse. Bromhexine is a specific TMPRSS2 inhibitor that potentially inhibits the infectivity cycle of SARS-CoV-2. Moreover, several clinical trials are evaluating the efficacy of bromhexine in COVID-19 patients. The findings of these studies have shown that bromhexine is effective in improving the clinical outcomes of COVID-19 and has prophylactic effects by inhibiting TMPRSS2 and viral penetration into the host cells. Bromhexine alone cannot cure all of the symptoms of SARS-CoV-2 infection. However, it could be an effective addition to control and prevent the disease progression along with other drugs that are used to treat COVID-19. Further studies are required to investigate the efficacy of bromhexine in COVID-19.

Key words: *SARS-CoV-2, COVID-19, bromhexine, TMPRSS2, COVID-19 prevention, COVID-19 treatment*

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Бромгексин как потенциальный препарат против COVID-19: от гипотезы к клиническим исследованиям

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Новая коронавирусная инфекция (COVID-19), вызываемая вирусом SARS-CoV-2, имеет различные клинические проявления и несколько механизмов патогенеза. Хотя для борьбы с COVID-19 используется целый ряд терапевтических подходов, ни один из препаратов не является эффективным лекарством. Трансмембранная сериновая протеаза 2 (TMPRSS2) является протеазой, играющей ключевую роль в проникновении SARS-CoV-2 в клетку. После присоединения спайкового (S) белка вируса к рецептору на поверхности клетки – ангиотензинпревращающему ферменту 2 (ACE2), TMPRSS2 процессирует и активирует S-белок на поверхности эпителиальной клетки. В результате происходит слияние мембран клетки и вирусной оболочки. Бромгексин является специфичным ингибитором TMPRSS2, потенциально способным подавлять жизненный цикл SARS-CoV-2. В настоящее время в нескольких клинических исследованиях проводится оценка эффективности бромгексина у пациентов с COVID-19. Результаты этих исследований показывают, что бромгексин позволяет улучшать клинические исходы COVID-19 и обладает профилактическим действием, ингибируя TMPRSS2 и проникновение вируса в клетку. Бромгексин в качестве монотерапии не позволяет лечить все симптомы инфекции, вызванной SARS-CoV-2. Однако он может выступать как эффективное дополнение для профилактики и терапии прогрессирования заболевания в сочетании с другими препаратами, используемыми для лечения COVID-19. Необходимы дальнейшие исследования для оценки эффективности бромгексина при COVID-19.

Ключевые слова: *SARS-CoV-2, COVID-19, бромгексин, TMPRSS2, профилактика COVID-19, терапия COVID-19*

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Over the last two decades, the coronaviruses SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) have emerged and transmitted from animals to human [1]. SARS-CoV-2 is the third emergence that has currently led to a pandemic. COVID-19 (novel coronavirus disease 2019), caused by the SARS-CoV-2 virus, has various clinical manifestations and several pathogenic pathways [2]. The Center for Disease Control (CDC) classifies the severity of COVID-19 into five categories: asymptomatic, mild, moderate, severe, and critical. In symptomatic patients, about 81% experience a mild to moderate COVID-19. Furthermore, knowledge about the mutations and transmission of the virus is still limited. For example, the emergence of new variants of the virus has increased and more effective treatment options are required. The recently emerged SARS-CoV-2-Omicron variant encodes 37 amino acid substitutions in the spike (S) protein, 15 of which are in the receptor-binding domain (RBD). These have raised concerns about the effectiveness of available vaccines and

antibody therapies [3]. Several treatments have been implemented to control COVID-19 including antimalarial drugs, anti-HIV (human immunodeficiency virus) drugs, corticosteroids, and antiviral drugs such as remdesivir [4, 5]. Recently, the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for using molnupiravir (from Merck) and Paxlovid (from Pfizer) in the treatment of mild-to-moderate COVID-19. Several monoclonal antibodies and a variety of immunomodulators are also used in the treatment of COVID-19 [6]. However, none of these medications have been proven to be a definitive cure for the disease and the virus continues to take lives globally. The SARS-CoV-2 virus penetrates the host cell through two pathways; endocytosis and non-endocytosis. In addition, each pathway has several subsets with various mechanisms that depend on the topology of the virus's outer surface, protein content, and host cell type [7, 8]. This virus has a single-stranded RNA (ribonucleic acid) that encodes a class I fusion protein called the 'spike (S) protein' that has two main subunits. The S1 subunit binds the virus to the receptors of the host cell. The S2 subunit is involved in the ongoing process and membrane integration of the virus and host cell. Consequently, the virus penetrates the host cell. In addition, the virus also penetrates the host cells through a non-endocytic pathway [9 10]. Angiotensin-converting enzyme-2 (ACE2) acts as a receptor for the virus S protein. ACE2 is present in most organs including the throat, heart, kidneys, lungs, and intestines. About 85% of the cells that express ACE2 in the lungs are type 2 alveolar epithelial cells (AEC II); therefore, the lungs are the most susceptible organ to SARS-CoV-2 infection [11, 12]. Following the binding of the S protein to the ACE2 receptor of the host cells, TMPRSS2 (type II transmembrane serine protease), which is a group of proteases, processes and activates the S protein on the epithelial cells. As a result, the membranes of the virus and host cell fuse. After penetrating the cell, the coronavirus recruits two cysteine proteases for replication; papain-like protease (PL^{pro}) and 3-chymotrypsin-like protease ($3CL^{pro}$) [13]. Therefore, in addition to TMPRSS2, these proteases, especially $3CL^{pro}$, can be an appropriate target for antiviral drugs. This protease has been targeted by drugs such as lopinavir-ritonavir and chloroquine [14]. As a result, inhibition of this serine protease may be a suitable target to control coronavirus infections [15, 16]. The TMPRSS2 inhibitors, camostat and nafamostat, have a role in inflammatory reactions and have been used in treating pancreatitis [17]. It has been reported that nafamostat has inhibitory effects in MERS-CoV infection [16]. In addition, Hoffmann M. et al. reported that camostat may be effective in COVID-19 due to its antiviral effects in addition to its potential role in decreasing excessive cytokine release in severe cases [18]. Bromhexine is effective in treating COVID-19 as well as preventing this infection in high-risk individuals by significantly inhibiting TMPRSS2 in the epithelial cells of the lungs. The prophylactic effect of this drug which is achieved by its ability to prevent viral penetration into host cells can distinguish its effective mechanism against SARS-CoV-2 infection from other standard treatments. On the other hand, bromhexine has the potential to improve the outcome of COVID-19 by inhibiting the replication of cysteine protease $3CL^{pro}$ and disrupting the viral replication by improving anti-inflammatory markers, especially the C-reactive protein (CRP) level. Bromhexine is a benzylamine derivative of the quinazoline alkaloid of vasicine which is extracted from a plant called *Adhatoda vasica*. For decades, it has been used as an over-the-counter (OTC) drug because of its mucolytic and cough suppressant effects [19]. Bromhexine can be taken orally three times a day with a dose range of 8–16 mg. Inhaled or nasal forms of bromhexine are suitable alternatives to the oral form since they have a more rapid effect and reduced first-pass effect. Pharmacokinetically, bromhexine has an appropriate distribution in the lung tissue and as a result, has high concentrations in bronchial epithelial cells. Therefore, bromhexine significantly inhibits the TMPRSS2s that are present on the surface of the lung epithelial cells and prevents viral penetration (shown in **Figure**). Lucas J.M. et al. have reported that bromhexine has a selective inhibitory effect on TMPRSS2 due to its bromide derivative. In addition, it has a high binding affinity to $3CL^{pro}$ and its inhibitors [20]. Shen L.W. et al. reported that bromhexine, as an inhibitor of TMPRSS2, has been effective in controlling SARS-CoV and MERS infections [21]. Bromhexine is generally a safe drug. The incidence of side effects caused by bromhexine hydrochloride has been reported to be similar in children and adults. Following the signs or symptoms of allergic reactions, patients should urgently terminate bromhexine hydrochloride. In addition, bromhexine is not recommended for use in children under 2 years of age due to the risk of serious side effects [22]. Several clinical trials are evaluating the efficacy of bromhexine in COVID-19 and some of them are listed in **Table**. The clinical trial with the registration number NCT04273763 was the first clinical trial to investigate the effect of adding bromhexine to the standard anti-coronavirus regimen in patients with suspected or confirmed COVID-19. The results of this trial showed that the number of patients that required oxygen inhalation as well as the required duration of oxygen inhalation decreased by 50.01% and 50.0%, respectively. This indicates the effectiveness of this drug on the clinical improvement of patients even in the most severe cases. In addition, the reduced incidence of COVID-19 in high-risk patients in this study confirmed the prophylactic effect of bromhexine through its inhibitory mechanisms on TMPRSS2 and viral penetration into the host cells [23]. Another clinical trial that was conducted on 78 patients in Iran examined the effect of bromhexine in addition to the standard regimen in SARS-CoV-2 infection. The results showed a decrease in the hospitalization rate by about 22.92%, and the need for intubation and ventilation by 20.5%. It also reported that the mortality rate of the group that had received bromhexine dropped from 12.8% to zero [24]. Moreover, symptoms such as cough and dyspnea, and inflammatory markers such as lactate dehydrogenase (LDH), neutrophil-lymphocyte ratio (NLR), and CRP improved significantly. These results indicate the positive effect of bromhexine on preventing excessive cytokine release and controlling inflammatory reactions. In addition, after two weeks of taking bromhexine, CRP was

surprisingly negative in all of the respondents in the study group (received bromhexine), while it was still positive in 83.3% of the patients in the control group [24]. In an open-label randomized controlled pilot study, patients with moderate COVID-19 were randomly divided into bromhexine hydrochloride (BRH) or control groups. Both groups received routine treatment according to China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan. However, the patients in the BRH group were additionally given oral bromhexine hydrochloride (32 mg, three times a day) for 14 consecutive days. The results suggested that BRH had the advantage over placebo by improved results of chest computed tomography (CT) scans, need for oxygen therapy, and discharge rate within 20 days [25]. The results of another open-label nonrandomized comparative clinical trial showed that the combination of bromhexine with spironolactone was effective in treating COVID-19. The results of this study showed a faster normalization of the clinical condition, faster decrease in temperature (one and a half times), and reduced explanatory combined endpoint of the viral load or long duration of hospitalization (≥10 days) [26]. Another double-blind randomized clinical trial was conducted with parallel allocation at a 1 : 1 ratio with placebo of low doses of hydroxychloroquine plus bromhexine for 60 days. The results of this study showed for the first time that hydroxychloroquine plus bromhexine could function in disease prevention. This could help to provide prophylaxis to healthcare professionals worldwide. Therefore, the use of hydroxychloroquine and bromhexine in healthy healthcare professionals that are exposed to patients with confirmed or suspected COVID-19 may significantly reduce SARS-CoV-2 infection in this population [27]. Although bromhexine alone cannot cure all of the symptoms of SARS-CoV-2 infection, it could be an effective addition to control and prevent the disease progression along with other drugs that are used to treat COVID-19. However, further clinical trials are required for a definitive conclusion. Access to widely

Table. The most important clinical trials that evaluate the efficacy of bromohexine in COVID-19 (registered at Clinicaltrials.gov)
Таблица. Наиболее важные клинические исследования, в которых оценивается эффективность бромогексина при COVID-19 (зарегистрированы на сайте Clinicaltrials.gov)

Study title Название исследования	Combinations studied Исследуемые комбинации	Status Статус	ClinicalTrials.gov identifier Идентификатор на сайте ClinicalTrials.gov
Clinical Trial With N-acetylcysteine and Bromhexine for COVID-19 Клинические испытания N-ацетилцистеина и бромгексина при COVID-19	Препарат: Vitamin C Drug: NAC Drug: NAC + **BMX** Препарат: витамин С Препарат: NAC Препарат: NAC + **BMX**	Not yet recruiting Набор участников еще не проводится	NCT04928495
Use of Bromhexine and Hydroxychloroquine for Treatment of COVID-19 Pneumonia Применение бромгексина и гидроксихлорохина для лечения пневмонии при COVID-19	Drug: **BMX** oral tablet and/or hydroxychloroquine tablet Препарат: перорально таблетка **BMX** и/или таблетка гидроксихлорохина	Recruiting Проводится набор участников	NCT04355026
Low-dose Hydroxychloroquine and Bromhexine: a Novel Regimen for COVID-19 Prophylaxis in Healthcare Professionals Малые дозы гидроксихлорохина и бромгексина: новый режим профилактики COVID-19 у медицинских работников	Drug: Hydroxychloroquine sulfate Drug: BMX 8 mg Препарат: гидроксихлорохина сульфат Препарат: BMX 8 мг	Enrolling by invitation Участники приглашаются	NCT04340349
Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19) Оценка эффективности и безопасности бромгексина гидрохлорида в таблетках в сочетании со стандартным лечением/Стандартное лечение пациентов с предполагаемой и лёгкой формой новой коронавирусной пневмонии (COVID-19)	Drug: **BMX** Hydrochloride tablets Drug: Arbidol hydrochloride granules Drug: Recombinant human INF α2b spray Препарат: гидрохлорид **BMX**, таблетки Препарат: гидрохлорид арбидола, гранулы Препарат: рекомбинантный человеческий INF-α2b, спрей	Active, not recruiting Выполняется, набор участников не проводится	NCT04273763
BromhexIne and Spironolactone for CoronavirUs Infection requiring hospiTalization (BISCUIT) Бромгексин И Спиронолактон для лечения КоронаВирусной Инфекции, Требующей госпитализации (БИСКВИТ)	Drug: **BMX** and spironolactone Drug: Base therapy Препарат: **BMX** и спиронолактон Препарат: базовая терапия	Recruiting Проводится набор участников	NCT04424134
Prevention of Infection and Incidence of COVID-19 in Medical Personnel Assisting Patients With New Coronavirus Disease Профилактика заражения и заболеваемости COVID-19 медицинского персонала, оказывающего помощь пациентам с новой коронавирусной инфекцией	Drug: **BMX** hydrochloride Препарат: гидрохлорид **BMX**	Completed Завершено	NCT04405999

Abbreviations: N-acetylcysteine (NAC), bromhexine (BMX) and interferon (INF), Milligram (mg).

Аббревиатуры: N-ацетилцистеин (NAC), бромгексин (BMX) и интерферон (INF), миллиграмм (мг).

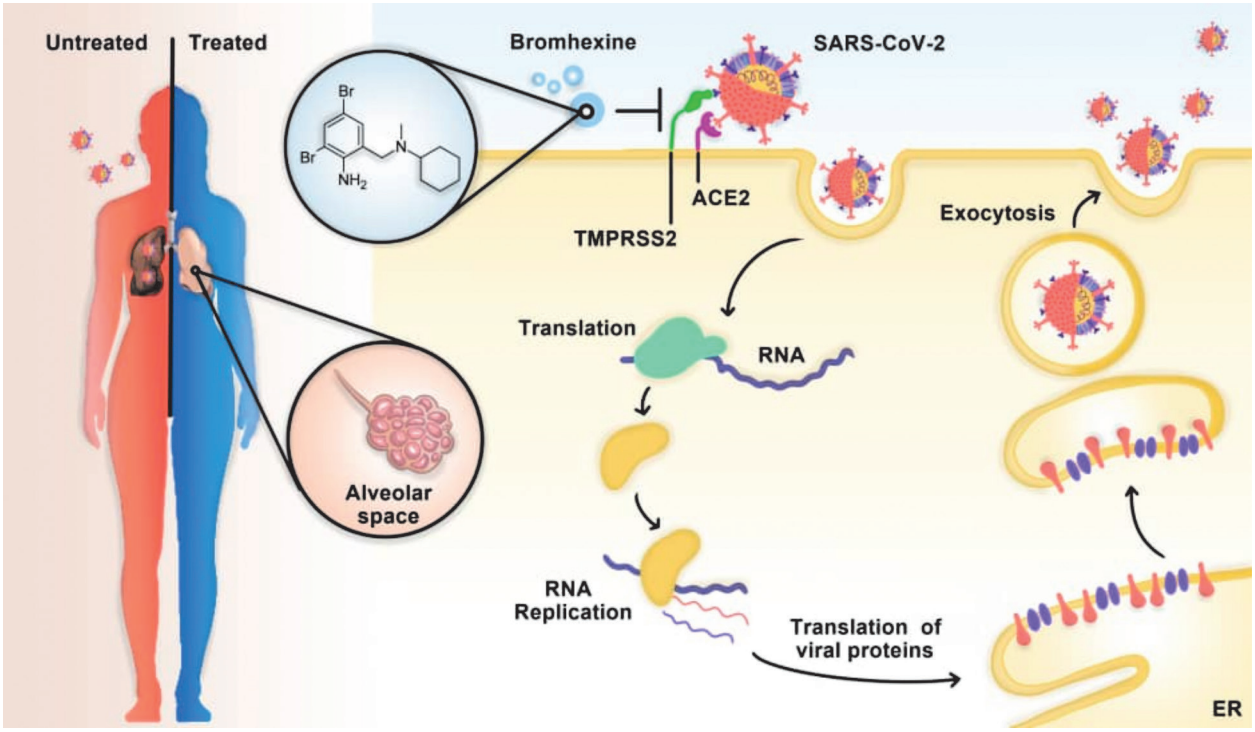

Figure. TMPRSS2 inhibition by bromhexine. TMPRSS2 is a protease that has a key role in the entry of SARS-CoV-2 into host cells. Following the binding of the viral S protein to the ACE2 receptors of the host cells, TMPRSS2 processes and activates the S protein on the epithelial cells. As a result, the membranes of the virus and host cell fuse. Therefore, bromhexine is a specific TMPRSS2 inhibitor that potentially inhibits the infectivity cycle of SARS-CoV-2 [**Abbreviations**: Endoplasmic reticulum (ER), Transmembrane serine protease 2 (TMPRSS2), Spike protein (S protein), and Angiotensin-converting enzyme 2 (ACE2)].

Рисунок. Ингибирование TMPRSS2 бромгексином. TMPRSS2 – протеаза, играющая ключевую роль в проникновении SARS-CoV-2 в клетку. После связывания вирусного S-белка с рецептором ACE2, TMPRSS2 процессирует и активирует S-белок на поверхности эпителиальной клетки. В результате происходит слияние мембран клетки и вирусной оболочки. Таким образом, бромгексин является специфичным ингибитором TMPRSS2, потенциально способным подавлять жизненный цикл SARS-CoV-2. [**Аббревиатуры**: эндоплазматический ретикулум (ER), трансмембранная сериновая протеаза 2 (TMPRSS2), спайковый белок (S-белок) и ангиотензинпревращающий фермент 2 (ACE2)].

available and inexpensive oral medications such as bromhexine may provide another effective layer of protection and help to end this pandemic soon, especially with the emergence of new variants and the challenges of mass vaccination faced by developing countries. Further investigation is required to assess whether the new variants are susceptible to post-exposure prophylaxis with bromhexine, and to gauge optimal dosing.

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