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RESEARCH ARTICLE

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# Efficacy of Covexir® (*Ferula foetida* oleo-gum) treatment in symptomatic improvement of patients with mild to moderate COVID-19: A randomized, double-blind, placebo-controlled trial

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## Abstract

The SARS-CoV-2 COVID-19 pandemic has emerged as an unprecedented emergency state in healthcare system and global challenge. In recent decade, the function of exogenous $H_2S$ in the treatment of respiratory diseases has been investigated using $H_2S$-donor agents. *Ferula foetida* is a medicinal plant that is traditionally used in respiratory diseases including asthma and viral respiratory diseases. The oleo-gum of this plant is a rich source of several organic sulfides including thiophenes, disulfides and polysulfide derivatives, which can act as $H_2S$-donor agents. The purpose of this study was to investigate the efficacy of Covexir® (*F. foetida* oleo-gum) treatment as a rich source of $H_2S$-donor compounds in clinical presentations of patients with COVID-19. The efficacy of Covexir® was evaluated in a randomized, double-blind, placebo-controlled trial in outpatients with COVID-19. Covexir® could significantly inhibit cough when compared to the placebo group ($p < .01$ and $p < 001$, respectively). Moreover, there was a significant difference ($p < 001$) between the two groups in dyspnea symptom at follow-up interval of 7 day after receiving Covexir®. Furthermore, on days 3 and 7, statistically significant differences were observed in myalgia, anorexia, anosmia, and sense of taste severity between two groups. Our findings revealed that Covexir® was very safe in the treatment of COVID-19 patients with mild to moderate symptoms and it can be recommended to improve clinical presentations of patients with COVID-19 such as cough, shortness of breath, myalgia, anorexia, anosmia, and sense of taste.

**KEYWORDS**
COVID-19, *Ferula foetida*, $H_2S$ donors, medicinal plants, natural sulfur compounds

## 1 | INTRODUCTION

Coronaviruses are enveloped positive-sense single-stranded RNA viruses with the largest genome size among RNA viruses (Woo, Huang, Lau, & Yuen, 2010). The novel coronavirus (COVID-19) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a major public health and global concern with a fast rapid spread from its origin in Wuhan to the other countries (C. Wang,

Horby, Hayden, & Gao, 2020). Till February 24, 2022 around 430,192,784 cases of COVID-19 and 5,936,712 deaths have been reported across 220 countries and territories (Coronavirus Outbreak, 2020) and also the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on March 11, 2020 (Organization, 2020). The signs and symptoms of SARS-CoV-2 infection vary depending on the severity of the disease. Mild fever, chills, dry cough, sore throat, headache, nasal congestion, and myalgia are common symptoms of upper respiratory tract viral infection in patients with mild to moderate COVID-19 illness. Some patients show gastrointestinal infection symptoms such as diarrhea and vomiting. In complicated forms of COVID-19, massive lung damage leads to the moderate to severe Pneumonia, Acute Respiratory Distress Syndrome (ARDS), and death (Jiang et al., 2020; Namburi, Jadhav, Kumar, & Hadole, 2020). Although, no decisive treatment of COVID-19 infection has emerged yet, a number of medicines have been suggested for the treatment of COVID-19 such as lopinavir/ritonavir, remdesivir, imatinib, tocilizumab, infliximab, and artesunate (Lamontagne et al., 2020; Nicola et al., 2020). Consequently, considering the severity of the disease and the limited number of approved and accessible medicines, it is critical to discover and develop a drug that is effective and safe in COVID-19 patients.

In recent decades, hydrogen sulfide ($H_2S$) has been recognized as a modulator of numerous biological activities, and its depletion has been associated with a variety of diseases. $H_2S$ at physiological levels has anti-inflammatory effects throughout the body and acts as a peroxonitrite and reactive oxygen species (ROS) scavengers (Calderone, Martelli, Testai, Citi, & Breschi, 2016). Endogenous $H_2S$, as well as low doses of exogenous $H_2S$ enhance respiratory function by regulation of mucolytic activity and decreasing mucus viscosity (Bazhanov, Ansar, Ivanciuc, Garofalo, & Casola, 2017). Interaction with disulfide bonds leads to the breakage of mucins (Costantino, Lampa, & Nappi, 2006). $H_2S$ also increased endothelial NOS expression and NO bioavailability, therefore the airways are protected indirectly against viral infection diseases (King et al., 2014). In recent decade, the function of exogenous $H_2S$ in the treatment of respiratory diseases has been investigated using $H_2S$-donor agents. Recently, Citi et al. (2020) reviewed the role of $H_2S$ and $H_2S$-donor agents in COVID-19. Herein, a randomized, double-blind, placebo-controlled trial was conducted on non-hospitalized patients with COVID-19 to assess the efficacy of *F. foetida* treatment as a rich source of $H_2S$-donor compounds.

*Ferula foetida* (Bunge) Regel is a medicinal plant that is endemic to Iran and Afghanistan. It also known as "Hing," has demonstrated different pharmacological properties such as antioxidant, anti-inflammatory, antibacterial, antidiabetic, anticancer, and several other properties that is due to the presence of several pharmaceutical phytoconstituents (Kareparamban, Nikam, Jadhav, & Kadam, 2012). Traditionally, the oleo-gum of this plant has a long history of medical use in respiratory diseases including asthma and viral respiratory diseases (Healthcare, 2004). *F. foetida* oleo-gum is a rich source of several organic sulfides including thiophenes, disulfides and polysulfide derivatives which gives off a unique garlic-onion smell (Duan et al., 2002; Khalilova, Bobakulov, Aripova, & Abdullaev, 2013; Sagyndykova, Imanbayeva, Suleimen, & Ishmuratova, 2019). Regarding rational for the use of polysulfide compounds as a kind of $H_2S$ donors and background of the medicinal application of *F. foetida* oleo-gum in viral respiratory diseases, we decided to design a clinical trial on the efficacy of *F. foetida* oleo-gum in COVID-19 treatment.

## 2 | MATERIAL AND METHODS

### 2.1 | Drug preparation

#### 2.1.1 | Preparation of Covexir®

The dried oleo-gum of *F. foetida* was mixed with microcrystalline cellulose in a 65:35 ratio. The resultant mixture was powdered using a mixer. After that, hard capsules were filled with the powder. Each capsule contained 400 mg of blended powder (260 mg dried oleo-gum +140 mg microcrystalline cellulose). Placebo drugs were prepared using only microcrystalline cellulose. Due to the smell of *F. foetida*, which is similar to the garlic-onion smell and to blind the study, we used a little amount of the oil of *F. foetida* oleo-gum inside the container cap containing placebo capsules.

### 2.2 | Standardization of Covexir®

#### 2.2.1 | Plant material

Oleo gum was collected from *F. foetida* root exudates and the plant was identified by Prof. Emami and Ms. Souzani (Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences) and was deposited at the Herbarium of the Mashhad University of Medical Sciences, School of Pharmacy, Mashhad, Iran. *F. foetida* oleo gum was also tested qualitatively (using thin layer chromatography and NMR analysis, see supporting information) and quantitatively (using GC–MS and qH-NMR analysis).

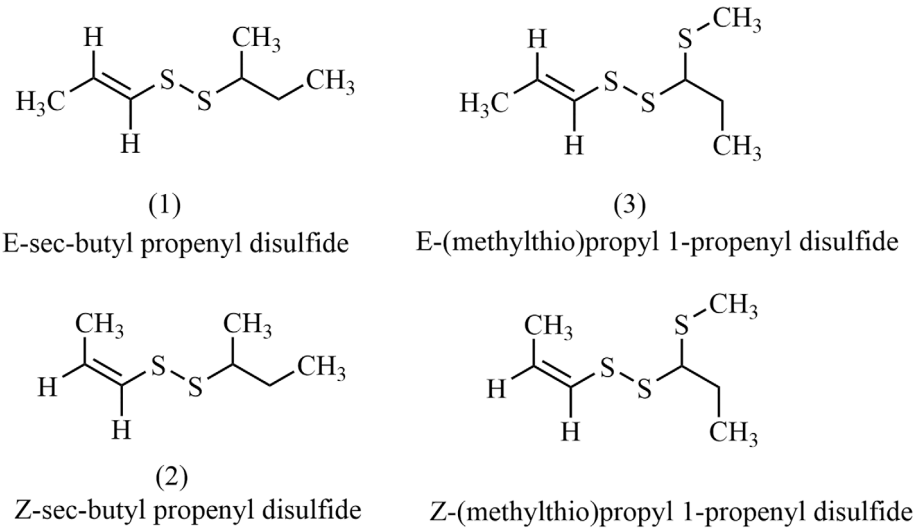
#### 2.2.2 | Chemicals

Dichloromethane ($CH_2Cl_2$), petroleum ether (PE), ethyl acetate (EtOAc), and methanol (MeOH) were purchased from Dr. Mojallali Company (Iran). Deuterated chloroform ($CDCl_3$) and was acquired from Sigma (USA). Analytical TLC (Silica gel 60 $F_{254}$), silica gel for column chromatography (230–400), and preparative TLC (Silica gel 60 $GF_{254}$) were prepared from Merck (Germany).

#### 2.2.3 | Extraction and purification of main sulfur compounds

The oleo-gum resin of *F. foetida* (200 g) were twice extracted with $CH_2Cl_2$ (2 L × 2) at room temperature using a maceration method.

**FIGURE 1** Major sulfide compounds detected in *F. foetida*




The dried $CH_2Cl_2$ extract (40 g) was fractionated by column chromatography (CC) on silica gel (230–400 mesh, 100× 7 cm) and eluted with petroleum ether/ethyl acetate mixtures of increasing polarity (20/1 to 0/100). On the basis of the isolation of major compounds, fractions F5 and F9 were selected for further purification by PTLC (petroleum ether [100%] under UV spectrometer at 254 nm) that afforded E/Z-sec-butyl propenyl disulfide (1) and E/Z(methylthio)propyl 1-propenyl disulfide (2), respectively (Figure 1).

### 2.2.4 | Sample preparation for GC–MS analyses

*Preparation of standard solutions*

For the preparation of calibration curves, stock standard solution was provided by dissolving and diluting exact amounts (3 mg) of E/Z-sec-butyl propenyl disulfide and E/Z(methylthio)propyl 1-propenyl disulfide (3 mg) dissolved in volumetric flask contained a 3 ml ethyl acetate. Working standard solutions (0.01–1 mg/ml) were prepared by diluting the stock solution with ethyl acetate. Each standard solution was injected three times to GC–MS for analysis.

*Sample preparation*

Oily petroleum ether extracts (5.000 mg) of crude oleo-gum of *F. foetida* and Covexir® were weighed into separate 10 ml volumetric flasks and diluted with petroleum ether (1 mg/ml). Each sample was injected three times to GC–MS for analysis.

### 2.2.5 | GC–MS analysis

The GC–MS operating was carried by GC–MS on PAL RTC 120 sampler, connected to Agilent 7890B series gas chromatograph and Agilent 5977A series mass spectrometer, equipped with a capillary HP-5MS column (30 m × 250 μm I.D., film thickness 0.25 μm). The carrier gas was Helium at a flow rate of 1 ml /min and temperature program was as follows: 5 min at 50°C, raised to 3°C/min to 140°C, 10 min at 240°C, and finally held isothermally for 10 min, the split ratio was 1:10. The total analysis run was 55 min. For MS detection, an electron ionization (EI) mode at 70 eV using full-scan mode from m/z 40–500 was used. The quadrupole and the ion source temperatures were 150 and 230°C, respectively. Quantification of the relative value of each component was calculated based on relative amounts of area without considering the calibration factor.

## 2.3 | Study design

### 2.3.1 | Clinical trial site

The present study is a double-blind, randomized, placebo-controlled trial to evaluate the efficacy of *F. foetida* treatment in clinical presentations of patients with confirmed COVID-19 based on clinical signs and symptoms as well as radiographic manifestations on lung CT scan. This study was conducted at the Emergency Department of Hashemi-nejad Hospital, Mashhad, Iran. The protocol of this trial was approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethics ID: IR.MUMS.REC.1399.071 and it was registered at the Iranian Registry of Clinical Trials with Registration No.: IRCT20200413047053N1).

Prior to participating in the trial, all patients or their legal representatives signed an informed consent form.

The principal investigator and/or co-principal investigator also verbally explained the necessary information. Furthermore, demographic data and medical history of patients were collected and documented.

### 2.3.2 | Inclusion criteria

Patients who met the following criteria were included in the study: Age group of 18 years to 80 years old of both genders. Patients having mild to moderate COVID-19 disease based on clinical signs and

symptoms as well as radiographic manifestations on lung CT scan. The enrolled patients were also eligible for outpatient care and were advised not to take any drugs outside the trial protocol. Patients who do not have cirrhosis, hepatitis, or other serious liver disorders, as well as severe renal failure, a history of cancer treatment with chemotherapy, patients who do not have an allergic history and do not use cytotoxic drugs or corticosteroids, patients who are not pregnant or lactating, and patients who do not have a history of autoimmune diseases. Patients with underlying respiratory disease, hypothyroidism, cardiovascular disease, hypertension, and diabetes were included in this clinical trial study.

### 2.3.3 | Exclusion criteria

Patients who met the following criteria were excluded from the trial: Any hypersensitivity to Covexir®, including allergies, hives, and skin rashes; gastrointestinal symptoms from Covexir®, including nausea, diarrhea, and vomiting; pregnancy during the study period; refusal to sign the informed consent form; taking medicines outside of the Covid-19 treatment protocol; decrease in SPO2 level; requirement to be hospitalized due to the patient's deteriorating condition.

### 2.3.4 | Randomization and blinding

Patients were randomly allocated in the following two groups: Covexir®/routine care group and placebo/routine care group. Each of the 62 patients would be assigned a number between 1 and 62 which is randomized by using random.org/integers in two columns. The numbers of the first column were assigned to group A, and the second column was assigned to group B. With a lottery method, each column (A or B) was assigned to intervention or control groups. Researchers and patients were blinded to the treatment allocation until after completion of the trial.

### 2.3.5 | Intervention

Patients were randomly assigned to one of the following arms of the trial using the permutation block method after receiving written consent from the patient: Covexir® twice a day with the standard care of treatment for 7 days, and placebo with the standard care of treatment for 7 days. Azithromycin 500 mg once daily, hydroxychloroquine 200 mg twice daily for 5 days, and acetaminophen 500 mg tablets were used as standard care of treatment (this protocol was used in the beginning of COVID-19 widespread) (Lamontagne et al., 2020). Covexir® and placebo capsules were prepared in the Pharmaceutics Laboratory of School of Pharmacy, Mashhad, Iran. Patients in the intervention groups took capsules containing 260 mg of *F. foetida* oleo-gum orally twice daily for 7 days in addition to a standard care of treatment. Patients in the control group received placebo capsules twice daily for 7 days with a standard care of treatment. The Covexir® and placebo capsules were administered at 12-h intervals after breakfast and dinner. The patients had the right to leave the study at any time.

### 2.3.6 | Measurements

After enrolling patients in the study, demographic data and the initial clinical symptoms of the patients such as fever, severity of myalgia, cough and shortness of breath as well as their oxygen saturation level ($SpO_2$) were observed and recorded in Case Report Form (CRF). Other parameters such as CBC, CRP, ESR, and chest CT results were also recorded on day 1 in both groups. Patients were contacted on the third and seventh days for follow-up visits at home and were questioned about taking medications other than the routine COVID-19 treatment as well as their clinical symptoms such as body temperature, cough severity, shortness of breath, myalgia severity, and any side effects of Covexir® administration. An infectious disease specialist and a nurse visited and scored the patients' clinical manifestations in the baseline and then the follow-up sessions were performed by a nurse.

### 2.3.7 | Clinical measurements and observations

Fever and the body temperature were measured by an infrared thermometer and recorded in degrees Celsius (°C). $SpO_2$ level was observed using a pulse oximeter and recorded in terms of saturation percentage.

CT scans were interpreted by radiologist. Involvement of the lobes can be in the form of Ground glass Opacity (GGO), Consolidation or nodules. The total CT score was determined as the sum of lung involvement (5 lobes, score 0–4 for each lobe, range, 0 none, 20 maximum). Scores of 4 to 8 are considered mild to moderate severity type of disease, while scores of more than 8 are considered severe type of disease.

Cough symptoms were scored on a scale of 0 to 3 in terms of severity. Score 0 indicates no cough, score 1 indicates a mild cough, score 2 indicates a moderate cough, and score 3 indicates a severe cough (Dutt et al., 2021).

The grade of dyspnea symptoms was categorized based upon a severity from 0 to 4 scale. Grade 0 indicates no shortness of breath except on strenuous exercise. Grade 1 indicates shortness of breath when hurrying or walking up a slight hill. Grade 2 indicates walks slower than contemporaries on the level because of shortness of breath or has to stop for breath when walking at own pace. Grade 3 indicates shortness of breath after walking 100 m or after a few minutes on the level and stopping for breathing. Grade 4 indicates shortness of breath while leaving the house, performing daily activities, or when getting dressed or undressed (Dutt et al., 2021). The symptoms of cough, myalgia, sense of taste, anosmia, and anorexia were scored based upon severity from 0 to 3 scale: 0 = no symptom, 1 = mild, 2 = moderate, and 3 = severe (Huskisson, 1974; Machado, Grilo, & Crosby, 2017; Seok, Shim, Rhee, & Kim, 2017; Starr, 1985).

C-Reactive Protein (CRP) was measured quantitatively on day 3 and 7, and represented in terms of mg/L (Normal range: 0–6 mg/L).

### 2.4 | Statistical analysis

Quantitative data including CRP level were reported as mean ± standard deviation and differences with $p$-value <.05 were considered significant. We used student's $t$-test for the evaluation of CRP levels. The qualitative variables including cough, shortness of breath, myalgia, anorexia, anosmia, and sense of taste were considered to be as ordinal variables. The non-parametric Mann–Whitney $U$ test was used to test differences between ordinal variables.

## 3 | RESULTS

### 3.1 | Identification of sulfur compounds from *F. foetida* oleo-gum

The purified sulfide compounds were identified with NMR and GC–MS methods (Figure S1–S6). In GC–MS analysis, these components were identified by the calculation of their retention indices (RI) under temperature-programmed conditions for n-alkanes ($C_8$–$C_{20}$) and comparison of the RI calculated as well as their mass fragmentation patterns. In addition, these compounds were approved by NMR method. ($^1$H-NMR data for purified compounds are available as supporting information) (Table S1). According to analysis, we found two main sulfur compounds, namely, E/Z-sec-butyl propenyl disulfide and E/Z (methylthio)propyl 1-propenyl disulfide (Figure 1).

In addition, these sulfur compounds were quantitatively determined using GC–MS in both raw material (*F. foetida* oleo-gum) and final formulation (Covexir®) to be 1.97% for compounds 1 and 2, and 2.77% for compounds 3 and 4 (Figure 1).

### 3.2 | Demographic details and patient enrollment summary

Between August 6, 2019, and February 9, 2020, 59 patients with mild to moderate COVID-19 ($SpO_2$ > 92%) were evaluated for eligibility. Overall, 62 out of 85 patients were found to be eligible for the study. The informed consent was obtained from all 55 patients. Finally, 50 patients enrolled in the study, of which 30 patients were assigned to the intervention group and 20 patients were assigned to the control group. A total of three patients voluntarily withdrew from the study. Due to an incorrect phone number and failure to answer the phone for follow-up visits, six patients withdrew from the study. A CONSORT flow diagram of the study is depicted in Figure 2.

The mean ± *SD* age of the patients in this study was 47.26 ± 16.04 years, and 68% of the patients were male. There were no statistically significant differences (i.e., $p$ > .05) in demographic characteristics such as gender, age, weight, etc. Patients were balanced in terms of demographics characteristics in both two intervention and placebo groups. The most common comorbidity was diabetes, followed by hypertension and cardiovascular diseases. The Covexir® group had 13 complicated patients, whereas the placebo group had just 6 complicated patients. The Covexir® group had 5 patients with cardiovascular disease, whereas the placebo group had no patients with cardiovascular disease. Furthermore, there were more patients with diabetes and hypertension in the Covexir® group (7 and 5 patients, respectively) than in the placebo group (3 and 1 patients, respectively) (Table 1).

### 3.3 | Effect on cough severity

Patients randomized to the Covexir®/routine care group significantly inhibited cough when compared to the randomized placebo/routine care group on days 3 and 7 ($p$-value = .004 and .000, respectively) (Figure 3). Statistically significant differences were observed in cough severity within the Covexir®/routine care group between days 1 and 3 ($p$ < 001) and days 3 and 7 ($p$ < 001) (Table 2).

### 3.4 | Effect on shortness of breath

Shortness of breath was significantly different between two groups on day one ($p$-value = .015), and those in the intervention group had more severe dyspnea than those of placebo group. Seven days after receiving the interventions, there was a significant difference between the two groups in dyspnea ($p$-value = .000), indicating that the Covexir®/routine care group improved significantly compared to the placebo/routine care group (Figure 4). Furthermore, statistically significant differences were observed in shortness of breath severity within the Covexir®/routine care group between days 1 and 3 ($p$ < 001) and days 3 and 7 ($p$ < 001) (Table 2).

### 3.5 | Effect on myalgia

Statistically significant differences were observed in myalgia severity on days 3 and 7 ($p$-value = .000 and .015, respectively) and the intervention group experienced less myalgia than that of placebo group, especially 3 days after receiving Covexir® (Figure S7). Furthermore, statistically significant differences were observed in myalgia severity within the Covexir®/routine care group between days 1 and 3 ($p$ < 05), and days 3 and 7 ($p$ < 01) (Table 2).

### 3.6 | Effect on anorexia

A statistically significant difference in anorexia severity was found between intervention and placebo groups on days 3 and 7 ($p$-value = .01 and .01, respectively), indicating that the intervention group experienced less anorexia during treatment than that of placebo

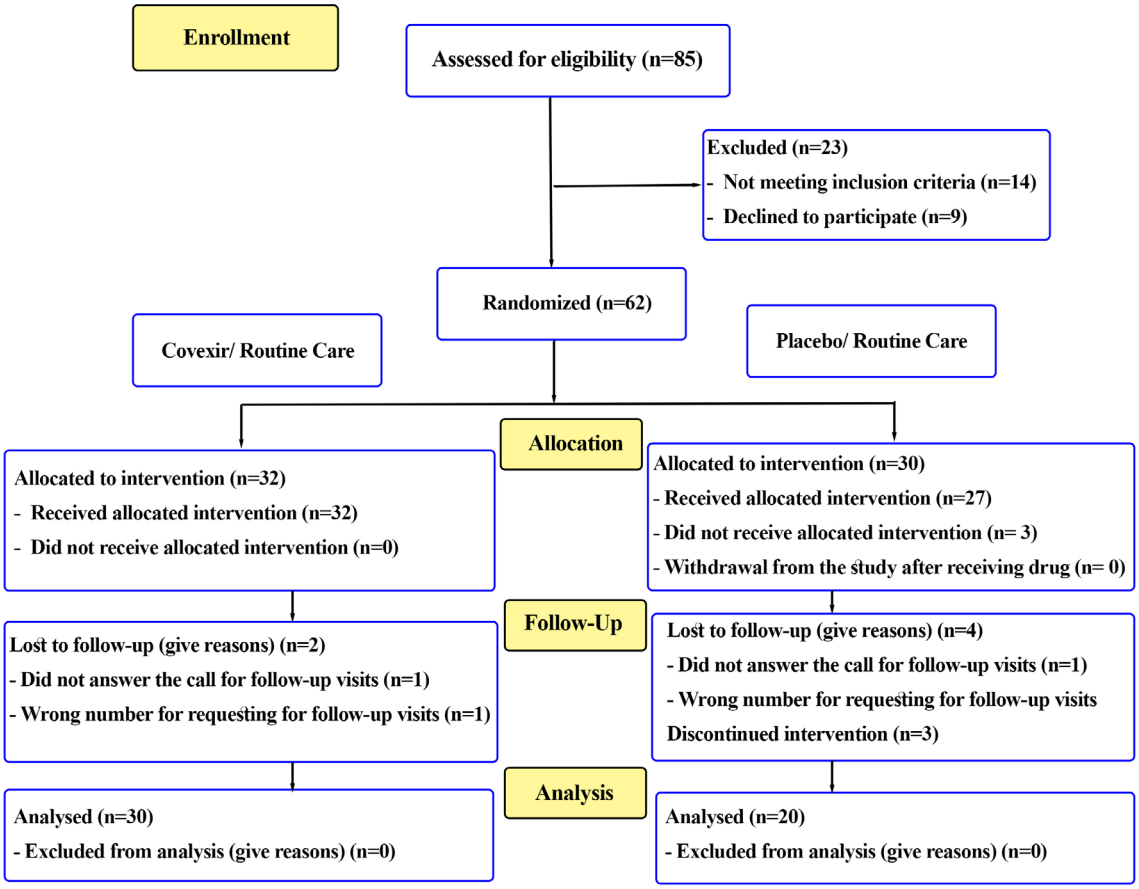



**FIGURE 2** CONSORT flow diagram

group (Figure S8). Moreover, there were statistically significant differences in anorexia severity within the intervention group between days 1 and 3 ($p < 05$), and days 3 and 7 ($p < 01$), while no significant difference was found within placebo/routine care group (Table 2).

## 3.7 | Effect on anosmia

The Covexir®/routine care group exhibited significantly better anosmia status on days 3 and 7 when compared to the placebo/routine care group ($p$-value = .00 and .000, respectively). A statistically significant difference in anosmia improvement was also found between days 1 and 3 ($p < 01$) and days 3 and 7 ($p < 01$) within the Covexir®/routine care group (Table 2). Within the placebo/routine care group, no significant difference was observed (Figure S9).

## 3.8 | Effect on sense of taste

On days 3 and 7, there were statistically significant differences in sense of taste severity ($p$-value = .02 and .002, respectively), and the intervention group had a superior feeling in terms of taste. Within the Covexir®/routine care group, a statistically significant difference in the improvement of sense of taste was also found between days 1 and 3 ($p < 01$), and days 3 and 7 ($p < 01$). In the placebo/routine care group, there was a significant difference in the status of sense of taste between days 1 and 3 ($p < 05$) and days 3 and 7 ($p < 05$) (Figure S10).

## 3.9 | Effect on CRP level

There was a 27.01% reduction in CRP level in Covexir®/routine care group whereas a 12.06% reduction in placebo/routine care group. In total, no statistically significant difference was observed in CRP level between the groups ($p > .05$) (Table 2).

## 3.10 | Covexir® side effects

No specific side effects were observed in the clinical study of Covexir®. Gastrointestinal complications such as bloating and nausea were merely recorded in a few patients (Table 2).

**TABLE 1** Patients demographic data

| Characteristics | Covexir®/ routine care (30 patients) | | | | | Placebo/routine (20 patients) | | | | | *p* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Sex, no. (%)* | | | | | | | | | | | |
| Male | 70% (21) | | | | | 65% (13) | | | | | >.05 |
| Female | 30% (9) | | | | | 35% (7) | | | | | >.05 |
| *Age, y* | 48.86 | | | | | 44.85 | | | | | >.05 |
| *Weight, kg* | 80.93 | | | | | 74.6 | | | | | >.05 |
| *Smoking, no. (%)* | | | | | | | | | | | |
| Yes | 0 (0) | | | | | 0 (0) | | | | | >.05 |
| No | 30 (100) | | | | | 20 (100) | | | | | >.05 |
| *Lung CT-scan involvement, no. (%)* | | | | | | | | | | | |
| Scores of 4 to 8 | 28 (93.34) | | | | | 17 (85) | | | | | >.05 |
| Score less than 4 | 0 (0) | | | | | 0 (0) | | | | | >.05 |
| None (without CT-scan) | 2 (6.66) | | | | | 3 (15) | | | | | >.05 |
| *C-reactive protein, mg/dl* | 37.98 | | | | | 40.57 | | | | | >.05 |
| *Coexisting conditions, no. (%)* | | | | | | | | | | | |
| Cardiovascular disease | 5 (16.66) | | | | | 0 (0) | | | | | >.05 |
| Hypertension | 5 (16.66) | | | | | 1 (5) | | | | | >.05 |
| Diabetes | 7 (23.33) | | | | | 3 (15) | | | | | >.05 |
| Asthma | 0 (0) | | | | | 0 (0) | | | | | >.05 |
| Hypothyroidism | 0 (0) | | | | | 1 (5) | | | | | >.05 |
| *Baseline clinical manifestation* | | | | | | | | | | | |
| Cough | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 | |
| | 16.60% | 30.00% | 20.00% | 26.60% | 6.60% | 20.00% | 25.00% | 45.00% | 0.00% | 10.00% | >.05 |
| Shortness of breath | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 | |
| | 10.00% | 13.30% | 46.60% | 30.00% | 0.00% | 35.00% | 25.00% | 25.00% | 15.00% | 0.00% | 0.015* |
| Myalgia | Score 0 | Score 1 | Score 2 | Score 3 | | Score 0 | Score 1 | Score 2 | Score 3 | | |
| | 56.66% | 10.00% | 16.67% | 46.67% | | 45.00% | 15.00% | 30.00% | 10.00% | | >.05 |
| Anorexia | Score 0 | Score 1 | Score 2 | Score 3 | | Score 0 | Score 1 | Score 2 | Score 3 | | |
| | 16.66% | 10.00% | 26.67% | 16.67% | | 20.00% | 10.00% | 20.00% | 50.00% | | >.05 |
| Anosmia | Score 0 | Score 1 | Score 2 | Score 3 | | Score 0 | Score 1 | Score 2 | Score 3 | | |
| | 63.34% | 3.33% | 6.66% | 30.00% | | 35.00% | 5.00% | 30.00% | 30.00% | | >.05 |
| Sense of taste | Score 0 | Score 1 | Score 2 | Score 3 | | Score 0 | Score 1 | Score 2 | Score 3 | | |
| | 56.64% | 3.33% | 10.00% | 30.00% | | 25.00% | 0.00% | 10.00% | 30.00% | | >.05 |

*Note: p* >.05 non-significant. **p* < 05, ***p* < 01, ****p* < 001 when compared between two treatment arm. Student's *t*-test and the non-parametric Mann–Whitney *U* test were used for the evaluation quantitative and qualitative data, respectively.
Abbreviations: CT-Scan, Computed Tomography Scan; kg, kilogram; No, Number; y, year.

## 4 | DISCUSSION

According to several research, there are numerous important medicinal herbs with antiviral activity that can be used to treat viral infections or as a supportive treatment (Shi, Wang, Li, et al., 2021; Shi, Wang, Yao, et al., 2021). Medicinal plants can interfere with COVID-19 pathogenesis by reducing SARS-CoV-2 replication and entrance into host cells.

Some of the antiviral medicinal plant species are citrus Spp., *Allium sativum*, *Allium cepa*, *Nigella sativa*, and *Mentha piperita* are the most favorable medicinal plants that can be used as an effective treatment in the management of COVID-19 (Demeke, Woldeyohanins, & Kifle, 2021; Sapra et al., 2021). For example, efficacy of *Nigella sativa* oil treatment was evaluated in patients with COVID-19 and the findings revealed that patients receiving *Nigella sativa* oil treatment had a shorter mean time to recover when compared to the control group (Koshak et al., 2021).

The current study was a randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of Covexir® in combination with routine care in clinical presentations of non-hospitalized patients with COVID-19. Our findings revealed that Covexir® significantly improved clinical presentations of COVID-19 including cough, dyspnea, myalgia, anorexia, anosmia, and sense of taste as compared with placebo. However, no statistically significant difference was observed in CRP level between Covexir® and placebo

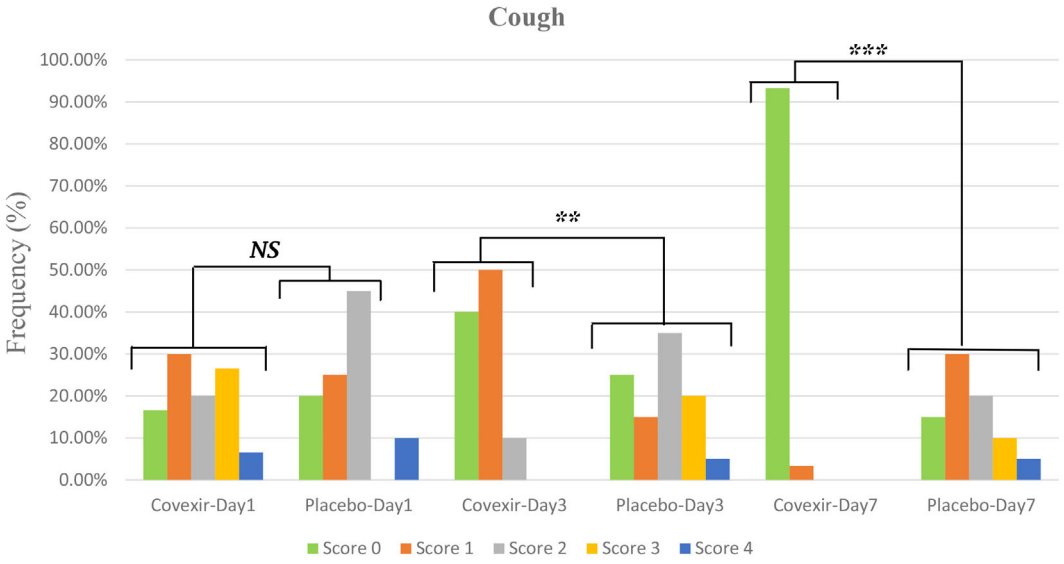



**FIGURE 3** Effect on cough severity. The severity of cough in patients randomized to the Covexir®/routine care group significantly reduced when compared to the randomized placebo/routine care group on days 3 and 7

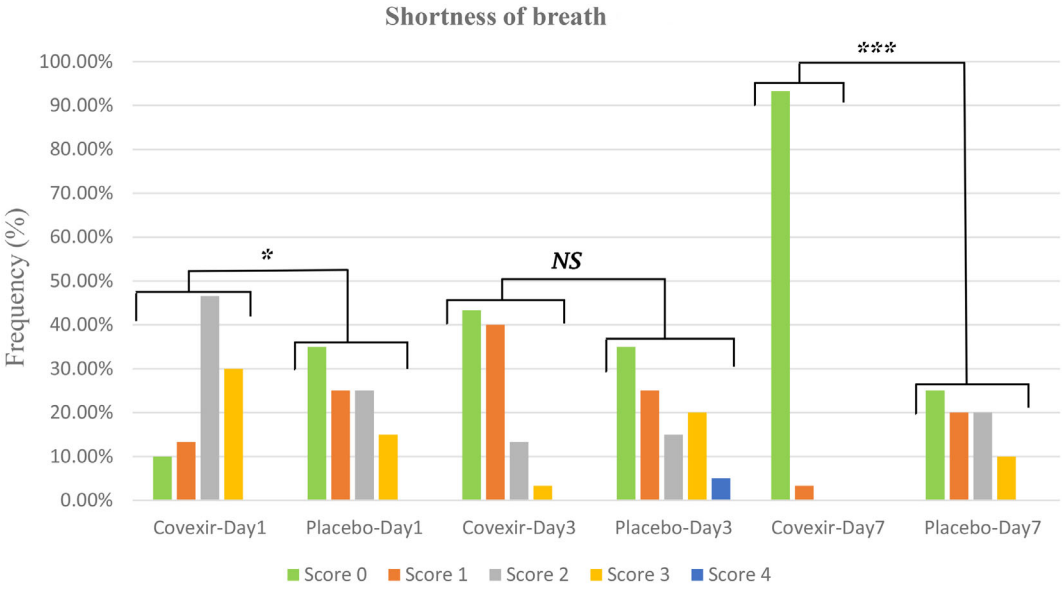



**FIGURE 4** Effect on shortness of breath severity. Shortness of breath severity in Covexir®/routine care group significantly improved when compared to the placebo/routine care group

groups. Most of the patients stated the amelioration of shortness of breath and cough severity, particularly in the early days of Covexir® administration.

$H_2S$ is recognized as a physiological mediator and signaling molecule that is produced endogenously. Currently, a wide number of natural and synthetic molecules have been identified as potent $H_2S$ donors and some of them are in clinical trials to evaluate their efficacy in treating a variety of diseases, including diabetes, atherosclerosis, cardiovascular diseases, inflammation, neurodegeneration, cancer, sepsis, as well as asthma and other disorders (Jiang et al., 2018; Polhemus et al., 2015; Wallace & Wang, 2015; Wang, 2012). When organic polysulfides, trisulfides, disulfides, and thiols react with biological thiols like glutathione (GSH), they release $H_2S$ (Pluth et al., 2015). Disulfides usually release $H_2S$ at a slower rate than trisulfides (Benavides et al., 2007; Liang, Wu, Wong, & Huang, 2015).

According to a recent study by Renieris et al. (2020) COVID-19 patients with a favorable outcome had a higher level of $H_2S$ than patients with severe COVID-19 pneumonia. They also found that serum $H_2S$ exhibited a negative correlation with interleukin-6 (IL-6) and a positive correlation with the lymphocyte count. This findings implies that decreased $H_2S$ bioavailability may be an indicator of increased pro-inflammatory responses, and administration of $H_2S$-donor agents could be considered as a therapeutic strategy to restore $H_2S$ plasma levels in order to counteract the severe consequences of

**TABLE 2** The most common clinical presentations of non-hospitalized patients on day 1, 3, and 7

| Clinical presentation | Covexir®/routine care | | | | | Placebo/routine care | | | | | *p* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Cough* | | | | | | | | | | | |
| | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 | *p* value |
| Day 1 | 16.60% | 30.00% | 20.00% | 26.60% | 6.60% | 20.00% | 25.00% | 45.00% | 0.00% | 10.00% | .5 |
| Day 3 | 40.00% | 50.00% | 10.00% | 0.00% | 0.00% | 25.00% | 15.00% | 35.00% | 20.00% | 5.00% | .004** |
| Day 7 | 93.33% | 3.33% | 0.00% | 0.00% | 0.00% | 15.00% | 30.00% | 20.00% | 10.00% | 5.00% | .000*** |
| *Shortness of breath* | | | | | | | | | | | |
| Day 1 | 10.00% | 13.30% | 46.60% | 30.00% | 0.00% | 35.00% | 25.00% | 25.00% | 15.00% | 0.00% | .015* |
| Day 3 | 43.33% | 40.00% | 13.33% | 3.33% | 0.00% | 35.00% | 25.00% | 15.00% | 20.00% | 5.00% | .1 |
| Day 7 | 93.33% | 3.33% | 0.00% | 0.00% | 0.00% | 25.00% | 20.00% | 20.00% | 10.00% | 0.00% | .000*** |
| *Myalgia* | | | | | | | | | | | |
| | Score 0 | Score 1 | Score 2 | Score 3 | | Score 0 | Score 1 | Score 2 | Score 3 | | *p* value |
| Day 1 | 56.66% | 10.00% | 16.67% | 46.67% | | 45.00% | 15.00% | 30.00% | 10.00% | | .33 |
| Day 3 | 66.67% | 23.33% | 6.67% | 0.00% | | 40.00% | 30.00% | 25.00% | 5.00% | | .000*** |
| Day 7 | 90.00% | 3.33% | 3.33% | 0.00% | | 50.00% | 15.00% | 15.00% | 0.00% | | .015* |
| *Anorexia* | | | | | | | | | | | |
| Day 1 | 16.66% | 10.00% | 26.67% | 16.67% | | 20.00% | 10.00% | 20.00% | 50.00% | | .98 |
| Day 3 | 30.00% | 36.67% | 23.33% | 10.00% | | 20.00% | 10.00% | 30.00% | 40.00% | | .01** |
| Day 7 | 73.34% | 13.33% | 10.00% | 0.00% | | 35.00% | 10.00% | 25.00% | 5.00% | | .01** |
| *Anosmia* | | | | | | | | | | | |
| | Score 0 | Score 1 | Score 2 | Score 3 | | Score 0 | Score 1 | Score 2 | Score 3 | | *p* value |
| Day 1 | 63.34% | 3.33% | 6.66% | 30.00% | | 35.00% | 5.00% | 30.00% | 30.00% | | .1 |
| Day 3 | 76.64% | 10.00% | 3.33% | 10.00% | | 45.00% | 5.00% | 30.00% | 20.00% | | .01** |
| Day 7 | 90.00% | 0.00% | 3.33% | 3.33% | | 35.00% | 10.00% | 15.00% | 20.00% | | .000*** |
| *Sense of taste* | | | | | | | | | | | |
| Day 1 | 56.64% | 3.33% | 10.00% | 30.00% | | 25.00% | 0.00% | 10.00% | 30.00% | | .1 |
| Day 3 | 70.00% | 16.66% | 6.66% | 6.67% | | 45.00% | 0.00% | 40.00% | 15.00% | | .02* |
| Day 7 | 86.66% | 3.33% | 0.00% | 6.67% | | 40.00% | 10.00% | 20.00% | 10.00% | | .002** |

*Note*: The non-parametric Mann–Whitney *U* test was used to test differences between ordinal variables including cough, shortness of breath, myalgia, anorexia, anosmia, and sense of taste.
*$p < 05$. **$p < 01$. ***$p < 001$ when compared between two treatment arm.

COVID-19 infection (Renieris et al., 2020). It has been suggested that IL-6 is the key pro-inflammatory mediator in the cytokine storm that resulted in severe lung injury, respiratory distress, and higher mortality rate in COVID-19 patients (Gubernatorova, Gorshkova, Polinova, & Drutskaya, 2020). Faller et al. (Faller et al., 2018) found that slow $H_2S$ donors had anti-inflammatory effects and lowered the levels of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 in a rat model of LPS-induced lung inflammation (Faller et al., 2018). Moreover, $H_2S$ suppresses IL-8 expression while greatly increasing anti-inflammatory IL-10 levels in the lung and plasma (Faller et al., 2018).

COVID-19-associated pulmonary disease is exacerbated by neutrophil infiltration in the lungs. Interestingly, $H_2S$ and disulfides inhibit the recruitment of inflammatory cells in the lungs, particularly neutrophil infiltration (Faller et al., 2018; Liu et al., 2018; Zanardo et al., 2006). Furthermore, $H_2S$ donors diminish the stability of thrombus generated in the vessels, making thrombolysis easier, and this function has been attributed to a reduction in platelet–leukocyte aggregation formation (Finsterbusch, Schrottmaier, Kral-Pointner, Salzmann, & Assinger, 2018; Grambow et al., 2017). $H_2S$ also inhibits the production of reactive oxygen species (ROS) in neutrophils, thus enhancing the ability of $H_2S$-donors in the prophylaxis of acute lung injury (Faller et al., 2018). Lucarini et al investigated the lung protective effects of sulforaphane as a natural $H_2S$-donor in a mouse model of LPS-induced acute lung injury. Findings revealed that sulforaphane diminished proinflammatory mediator release and improved mitochondrial function and energy metabolism through the transcription factor Nrf2 (Lucarini et al., 2018). The presence of $H_2S$-donors increases nuclear translocation of Nrf2 and thus increases the expression of both antioxidant genes and protection against oxidative damage (Gojon & Morales, 2020).

In a rat model of LPS-induced pulmonary inflammation, GYY4137, a slow-release $H_2S$ donating molecule, reduced pro-inflammatory cytokines such as TNF, IL-1, and IL-6. It also exhibited antioxidant properties by increasing the activity of antioxidant enzymes including SOD and catalase in lung tissues, resulting in balance of GSH/GSSG ratio (Faller et al., 2018).

$H_2S$-donors downregulates NF-κB pathway by suppressing IKκβ enzyme activity and inhibiting NF-κB translocation into the nucleus, thus leading to the prevention of pulmonary vascular inflammation, pulmonary arterial hypertension and cytokine storm generation (Faller et al., 2018; Zhang et al., 2019).

Endogenous $H_2S$, as well as low doses of exogenous $H_2S$ enhance respiratory function by regulation of mucolytic activity and decreasing mucus viscosity (Bazhanov et al., 2017). Interaction with disulfide bonds leads to the breakage of mucins (Costantino et al., 2006). $H_2S$ activates ATP-sensitive potassium channels (KATP) on the cell membranes of bronchial smooth muscle cells, enhancing bronchodilation, while inhibiting Na+/K + –ATPase and calcium-sensitive potassium channels, stimulating electrolyte absorption and promoting mucociliary clearance (Pouokam & Althaus, 2016).

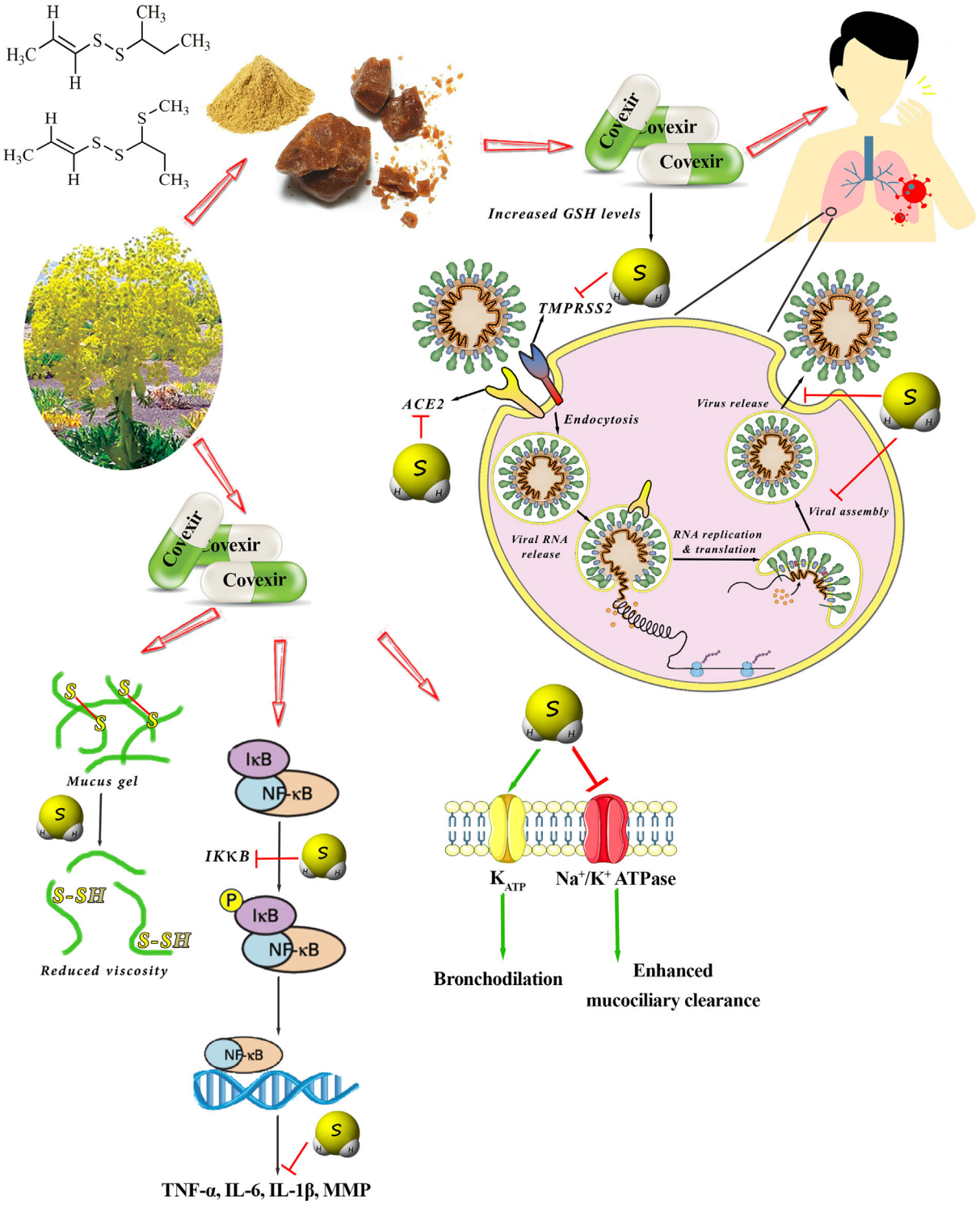



**FIGURE 5** The proposed mechanism of Covexir® against SARS-CoV2 infection

SARS-CoV-2 enters cells via two host proteins including angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). Yang (Yang, 2020) suggested that $H_2S$ may prevent SARS-CoV-2 from infecting host cells by interfering with ACE2 and TMPRSS2, suppress SARS-CoV-2 replication by inhibiting viral assembly and release, and protect against SARS-CoV-2-induced lung injury by immunosuppression and antiinflammatory effects (Citi et al., 2020).

*F. foetida* oleo-gum is a rich source of organic sulfides including thiophene, disulfides and polysulfide derivatives. In this study, E/Z-sec-butyl propenyl disulfide and E/Z(methylthio)propyl 1-propenyl disulfide were identified as the major compounds of *F. foetida* oleo-gum. According to the finding of this clinical trial, the efficacy of Covexir® in clinical presentations of non-hospitalized patients with COVID-19 has proven and it appears that Covexir® may act as a $H_2S$-donor agent against SARS-CoV-2-induced lung injury via its antiinflammation, antiviral, and antioxidant effects (Figure 5).

The main limitation of our study was the small size of the patients groups. It should be noted that the effect of Covexir® in the management of COVID-19 has not yet been determined. This primary evaluation is the first trial of Covexir® to gain insight into a larger multicentric study in the future.

## 5 | CONCLUSION

In conclusion, we showed that Covexir® was highly effective and very safe in the treatment of COVID-19 outpatients with mild to moderate symptoms. In this study, our findings also revealed that Covexir® can efficiently improve clinical presentations of patients with COVID-19 such as cough, shortness of breath, myalgia, anorexia, anosmia and sense of taste rather than placebo. Mechanistically, the major sulfur compounds of Covexir® may act as $H_2S$-donor agents against SARS-CoV-2-induced lung injury via their anti-inflammation, antiviral and antioxidant effects.

However, further studies are necessary to confirm this (and other) mechanism of action (s) of $H_2S$ releasing compounds of Covexir® in the treatment of COVID-19 patients.

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### CONFLICT OF INTEREST

The data presented in this article were further used by some of the authors to get emergency use authorization from Food and Drug Administration of Iran for the treatment of mild to moderate cases of COVID-19 under the brand name of Covexir®.

### DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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