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RESEARCH ARTICLE

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Phase III randomized clinical trial of BV-4051, an Ayurvedic polyherbal formulation in moderate SARS-CoV-2 infections and its impact on inflammatory biomarkers

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Abstract

SARS-CoV-2 virus and its variants continue to be a challenge inspite of widespread vaccination and preventive measures. We hypothesized an oral, safe polyherbal formulation with antiinflammatory properties may improve the clinical outcome of this disease. BV-4051, a formulation from four Ayurvedic plants namely Ashwagandha, Boswellia, Ginger and Turmeric was used for the treatment of hospitalized moderate COVID-19 patients along with standard of care (SOC). Patients were randomly assigned to receive BV-4051 or placebo tablets for 14 days, at four sites in India during late 2020 to early 2021. Among 208 randomized subjects, 175 completed the study. In BV-4051 group the mean reduction in duration of illness ($p = 0.036$), alleviation and severity scores of several symptoms like fever, cough, smell, and taste disorders were statistically significant ($p \leq 0.05$). A sub-set analysis of subjects treated with or without Remdesivir as SOC showed mean reduction in duration of illness in BV-4051 ($p = 0.030$), and severity scores ($p \leq 0.05$). Mean difference in Interleukin-6 was statistically significant ($p = 0.042$) on BV-4051 without Remdesivir. BV-4051 may reduce duration of illness, symptoms severity, Interleukin-6, and prevent the incidence of COVID-19 complications. It may have an adjunctive effect with other SOC. Larger extensive clinical testing may give a better understanding of its effect.

KEYWORDS
ARTOVID-20®, Ayurveda, Covid-19, herbal, interleukin-6, Remdesivir

1 | INTRODUCTION

Aggressive global vaccination efforts, widespread public healthcare measures, and a better understanding of treatment modalities provide a significant improvement in the management of the SARS-CoV2 pandemic. However, in many developing countries and also among certain populations in developed nations, the disease and its variants continue to cause significant morbidity, mortality, and economic impact (World Bank Report, 2022).

Immune hyperactivation in COVID-19 is precipitated by a surge of critical immune mediators including Tumor Necrosis Factor (TNF), Interferon-Gamma (IFN-γ), and Interleukin-6 (IL-6) that leads to respiratory failure, shock, and multi-organ dysfunction (Ablamunits & Lepsy, 2022; Herold et al., 2020; Mandel et al., 2020). There have

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been recommendations for various therapies led by antivirals, such as Remdesivir (Gottlieb et al., 2021). Tocilizumab, an IL-6 inhibitor has been authorized for the treatment of hospitalized adults and pediatric patients. It has shown mixed results, but it did not improve survival (Salama et al., 2021). The scope of TNF inhibitors and Anti-Cytokine antibody therapy for global use is limited due to availability, scalability, and cost in developing countries (Batista & Foti, 2021; Izadi et al., 2021). Several small molecules are under clinical trials (Zhao et al., 2022). Two antiviral drugs, PAXLOVID™ and Molnupiravir have received FDA authorization in moderate COVID-19 (Bernal et al., 2022; Whitley, 2022).

Vaccination is one of the best options to prevent spread, reduce risk of severe illness, hospitalization, and death. However, new variants remain a challenge and it is not fully known how effective or safe the vaccinations are in larger populations, younger age groups, and against new variants (Abdalhamid et al., 2022; Trunfio et al., 2021). Vaccination of the masses in underdeveloped countries still poses a challenge (Sheikh et al., 2021; United Nations News, 2022). Breakthrough infections and re-infection are of concern especially with immunocompromised people, and those who in their profession may be more exposed to the virus (Accorsi et al., 2022; Trunfio et al., 2021). Another challenge is those who do not wish to be vaccinated, and hence have a 13 times higher risk of being infected and a 68 times higher risk of dying from COVID-19 (Birhane et al., 2021; Gao et al., 2022). Hence, we need safe and affordable products that are best to treat COVID-19 infection, that can be used as prophylactic for pre and post exposure, and ideally have immunomodulatory actions.

Various plants and their derivatives have been studied in multiple countries of the world as preventive and therapeutic agents in the fight against coronavirus (Boozari & Hosseinzadeh, 2020; Kumar et al., 2022). The Indian Systems of Medicine, Chinese herbal medicines (CHM), and Traditional Chinese Medicine (TCM) are being advocated as adjunctive treatments with standard of care, to improve outcomes (Ahmad et al., 2021; Fan et al., 2020; Xiong et al., 2020).

Early in the pandemic, it was realized that a cytokine storm leads to severity of disease (Feldman et al., 2020). We hypothesized that a multitargeted inflammation inhibitor may be the key to improve the outcome for these patients. Thus, we designed a double-blind placebo-controlled clinical study with BV-4051, an oral and safe Ayurvedic polyherbal tablet, for the treatment of COVID-19 subjects. The formulation has previously shown inhibition of IL-6, Rheumatoid factor, and C-Reactive protein (CRP) in rheumatoid arthritis patients and TNF in other inflammatory conditions (Chopra et al., 2000; Dey et al., 2014). BV-4051 was known as RA-1, RA-11, and BV-9238 in different research codes during different stages of development. It contains specialized extracts of four medicinal plants namely Ashwagandha (*Withania somnifera*, Family Solanaceae), Shallaki (*Boswellia serrata*, Family Burseraceae), Ginger (*Zingiber officinale*, Family Zingiberaceae), and Turmeric (*Curcuma longa*, Family Zingiberaceae).

All four herbs have shown either immunomodulatory, antiinflammatory, and/or antiviral properties. The plants have been studied individually for their potential in the SARS-CoV-2 infections. *Withania somnifera* has been proposed as an opportunity for repurposing in Covid-19 (Saggam et al., 2021). Another study showed that withanone from *Withania somnifera* may reduce the glycosylation of SARS-CoV-2 and inhibit viral replication (Patil et al., 2021). *Withania somnifera* has also been shown to improve cardiorespiratory endurance and recovery, which may help in COVID-19 (Tiwari et al., 2021). Turmeric has antiviral potential against dengue virus (Ichsyani et al., 2017) and against H5N1 viral infections (Sornpet et al., 2017). Ginger counteracts H9N2 virus in a dose-dependent manner (Rasool et al., 2017), and has antiviral activity against human respiratory syncytial virus in human respiratory tract cell lines (Chang et al., 2013). Boswellia was seen useful in the enhancing adaptive immune response in mild to moderate symptoms of COVID-19 (Gomaa et al., 2021).

The proprietary combination in this study has shown efficacy in randomized clinical trials in rheumatoid arthritis and osteoarthritis (Chopra et al., 2000; Chopra et al., 2004; Chopra et al., 2018). Furthermore, it has proven to be very safe in extensive pre-clinical, clinical, genotoxicity, acute and chronic toxicity studies, hERG Channel blockade and Cytochrome P450 enzyme studies (Dey et al., 2014; Dey et al., 2015). The plant materials under study have been identified, authenticated, and deposited in a Government of India Herbarium, namely Central Council for Research in Ayurvedic Sciences (CCRAS) based in Pune, India. The voucher numbers are *W. somnifera* (4390), *B. serrata* (4391), *C. longa* (4392), and *Z. officinale* (4393). The use of resources and work has been approved by the National Biodiversity Authority of India. We hypothesized that BV-4051 can potentially inhibit the cytokine storm in COVID-19, and hence may prevent the morbidity and mortality.

2 | MATERIALS AND METHODS

The four cultivated plants in BV-4051 were extracted by a proprietary process to yield the maximum bio-actives keeping in natural form (Chitre & Dey, 2014). The extracts used in this study were obtained from qualified suppliers that conform to the authenticity and proprietary method. Each extract was standardized using High-Performance Liquid Chromatography (HPLC), High-Performance Thin-Layer Chromatography (HPTLC) and Spectrophotometry to yield the exact percentage of bio-active compounds. Each extract was tested for absence of pesticides, residual solvent levels and heavy metals. The extracts were formulated in exact ratio and manufactured into tablet form by a proprietary method following Current Good Manufacturing Practices (cGMP). The placebo tablets consisted of inert ingredients namely microcrystalline cellulose, dicalcium phosphate and magnesium stearate; combined and formulated in same shape, size and color to match the active tablets, and also manufactured following cGMP standards.

2.1 | Study design

A multi-center, randomized, double-blind, placebo-controlled Phase III clinical study was conducted to assess the safety and efficacy of BV-

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4051 tablets combined with the current standard of care (SOC) and its impact on inflammatory biomarkers in subjects with uncomplicated moderate SARS-CoV-2 infections. The study was conducted from September 2020 to April 2021 during the first and second waves of the Covid-19 pandemic in India. The second wave largely consisted of the Delta or B.1.617 variant (Sarkar et al., 2021; Udani, 2021). This variant was highly transmissible, and led to more than 400,000 new reported cases per day and record number of deaths. Majority of the subjects in this study were recruited during the second wave. A further sub-set analysis was conducted on subjects who were treated with Remdesivir as SOC, using the same primary and secondary end points.

Based on comparative trials in population at that time, we estimated for determination of sample size, a one-sided log rank test with an overall sample size of 170 subjects (85 in the treatment group and 85 in the placebo group) would achieve 80% power at a 0.025 significance level to detect a hazard ratio of 1.67. Considering 6% dropouts in the study, total 180 subjects (90 in the treatment group and 90 in the placebo group) were to be enrolled in the study.

The study was conducted in compliance with the principles of the Declaration of Helsinki, International Council for Harmonization - Good Clinical Practice guidelines, and regulatory guidelines of Indian Council of Medical Research (ICMR) and Department of AYUSH. All required study documentation has been archived as required by regulatory authorities. The study was managed by a global Clinical Research Organization (CRO) based in San Jose, California, USA. The protocol was also filed with the Drug Control General of India, ICMR and AYUSH. The study is registered in Clinical Trials Registry of India with details as follows: CTRI/2020/09/027817. http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=46041&EncHid=&userName=BV-4051

Approval of the Institutional Review Boards/Independent Ethics Committees (EC) of the protocol, any protocol amendments, and informed consent forms were mandatory. The EC approvals are available in the Supplement section of this manuscript. Subject participation was voluntary. The Flow Chart of Study Design is per Figure 1. This study was conducted at four tertiary care, in-patient hospital study centers in a competitive enrollment method. Full details are provided in the Protocol and Statistical Analysis Plan available with a full text of this article.

2.2 | Inclusion and Exclusion criteria

Male and female subjects, aged 18–65 years with moderate COVID-19 infections who were already hospitalized, with temperature ≥ 38°C (100.4 °F); plus at least one respiratory symptom (nasal congestion, sore throat, cough, breathing difficulty); and at least one constitutional symptom (aches/pains, fatigue, headache, chills, or sweats) were screened. Only those subjects with confirmed SARS-CoV-2 infection by Reverse Transcription – Polymerase Chain Reaction (RT-PCR) prior to Visit 1 were included. All female subjects of child-bearing potential and male subjects and their spouse/partner had to agree to use a medically acceptable method of contraception throughout the entire study period, and for 30 days for females and 90 days for males after study discontinuation.

Subjects with severe COVID-19 infection requiring intensive inpatient treatment were excluded. Subjects requiring systemic antiviral therapy prior to screening or those on immunomodulators, interferon inducers, homeopathic, or hormonal (other than hormone replacement) therapy were also excluded. Use of corticosteroids as part of the SOC was permitted. Subjects who had uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg), diabetes, asthma (any current or recent, not childhood if resolved), COPD, cardiac, hepatic, renal (eGFR<60) and hematopoietic disorders, neurological disease, compromised immune system (including patients on immunosuppressant therapy, or those with cancer within the past 5 years or human immunodeficiency virus [HIV] infection), endocrine disorders (including thyroid disorders), anatomical nasal obstruction (including polyps and septal deviation) were also excluded. Other exclusion criteria were clinically obese subjects with BMI ≥40, recent history (within 6 months) of alcoholism or substance abuse, participation in other clinical trial within 1 month or during the study, pregnant or breast-feeding female subjects, known allergy to components of study medication, previous history of difficulty swallowing capsules or tablets; and any other associated disease or condition which, in the opinion of the investigator, may have restricted or impeded participation in the study or affect the study results.

2.3 | Efficacy endpoints

The primary endpoint was improvement in reducing the duration and severity of illness compared to placebo. Investigational product (BV-4051 or placebo) was started within 48 h and no more than 96 h after onset of symptoms. A standard severity score of 0–3 scale was used to determine the overall score (Treanor et al., 2000). Subjects participating in the trials were required to self-assess the Covid-19 associated symptoms as "none or 0," "mild or 1," "moderate or 2," and "severe or 3." (Figure S1 Symptom Assessment Card [SAC] in Supplement section). The duration of illness and time to improvement was calculated from the time of treatment initiation to the time when all symptoms including fever, nasal congestion, sore throat, cough, breathing difficulty, aches and pains, fatigue, headaches, chills/sweat, diarrhea, vomiting, smell and taste disorders were assessed as "none" or "mild" (score 1 or 0), and stable for at least 24 h. Alleviation of fever was defined as oral temperature lower than 37.3°C (99.1 °F) and stable for at least 24 h (Cairns et al., 2022; Srivastava et al., 2021; Tamiflu® Prescribing Data, 2012).

Secondary endpoints were the severity scores, and reduction in duration of alleviation of individual symptoms from time 0 to the time at which the symptom was less than or equal to mild and stable for at least 24 h. The percentage of subjects experiencing alleviation of COVID-19 symptoms at every 24 h post first dose to the end of Day 14 and the average of severity scores every 24 h post first dose to the end of Day 14 were studied. Also included were an author-developed questionnaire

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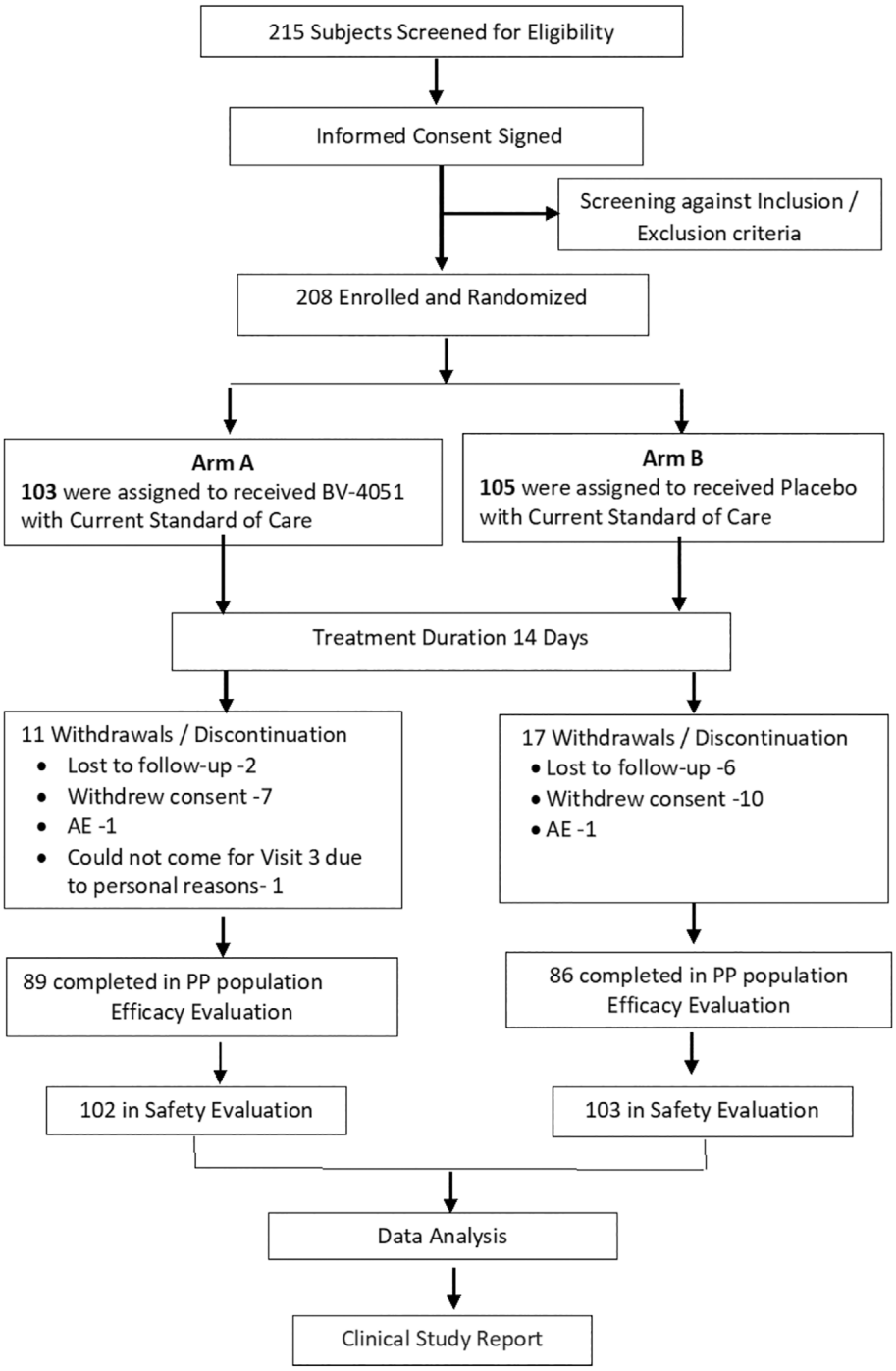

FIGURE 1 Trial design and flow chart

for self-assessment of Quality of Life (QOL) (Figure S2 QOL card in Supplement section), hospitalization rate of subjects with severe COVID-19 symptoms requiring intensive inpatient treatment, and the percentage of subjects that experienced complications. Both the SAC and QOL cards were filled by study subjects, verified by the Study Coordinator at each site, and data were entered in the electronic Case Report Forms (e-CRF). This was further reviewed by the Clinical Research Associates at each site from the Clinical Research Organization (CRO), and the source data was verified for accuracy and proper entry into the e-CRF.

Exploratory endpoints were improvement in biomarkers namely IL-6, TNF, CRP, Erythrocyte Sedimentation Rate (ESR) and Lactate Dehydrogenase (LDH) (Emadi et al., 2020). Safety was assessed by monitoring and recording all adverse events (AEs), regular physical examinations, hematology, chemistry, and 12-lead-electrocardiograms. Any other medications for COVID-19 other than allowed by SOC were not permitted.

2.4 | Statistical analysis

All statistical analyses were performed using SAS® Version 9.4 or higher (SAS Institute Inc., USA,). The mean duration of illness and of

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alleviation of individual symptoms was compared using Mann–Whitney *U*-test between test and placebo groups. For the change from baseline summaries, the baseline value was the value/measurement recorded/taken at the baseline visit. Mean reduction in duration of alleviation of individual symptoms, including fever, from time 0 (first administration of study medication) to the time at which the symptom is less than or equal to mild and stable for at least 24 h was compared between treatment and placebo using non-parametric Mann–Whitney *U*-test. Proportion of subjects experiencing alleviation of COVID-19 symptoms at every 24 h post first dose to the end of Day 14 was compared between treatment and placebo groups using chi-square test. The average of severity scores every 24 h post first dose to the end of Day 14 was compared between treatment and placebo groups using repeated measures ANOVA. Scores of Quality-of-Life assessment based on the self-assessment questionnaire was compared between treatment and placebo groups using repeated measures ANOVA. Proportion of subjects experiencing complications or worsening of symptoms was compared between treatment and placebo groups using chi-square test. A summary of Adverse Events (AEs) including the number and percentage of subjects with any AEs, treatment emergent adverse events (TEAEs), serious adverse events (SAEs), drug-related AEs, drug-related SAEs, discontinuations and incidence was analyzed.

A p value ≤0.05 was considered to be statistically significant. All analyses were performed according to ITT (Intent-to-Treat), PP (Per Protocol), and Safety Analysis population. For this manuscript, only the PP analyses has been reported for all efficacy endpoints. The Adverse Events results are based on Safety set of analysis.

3 | RESULTS

3.1 | Subjects

A total of 215 subjects were screened, 208 were randomized, 3 subjects withdrew consent, and 205 subjects took 1,776 mg of BV-4051 or placebo twice a day after meals for 14 days. 103 subjects received BV-4051, and 102 subjects received placebo. 196 subjects were analyzed under Intent to Treat (ITT) set, 175 (86.1%) subjects were analyzed under Per Protocol (PP) set and 205 (98.6%) subjects were analyzed under Safety set. 175 subjects completed the study of which 89 subjects received BV-4051 with SOC, and 86 subjects received Placebo with SOC. Total 30 subjects did not complete the 14 days of treatment and were not included in final PP analysis. Of these two subjects withdrew consent after randomization, two subjects withdrew due to adverse events, one subject was unable to come for Visit 3 due to personal reasons, 17 subjects withdrew consent at various times during the study, and eight subjects were lost to follow up.

All demographic characteristics like gender, mean age, race, body weight, height, and BMI were well-balanced between the groups (Table 1). The SOC treatment was per Investigator's discretion following the applicable Indian Council of Medical Research (ICMR) guidelines at that time, and consisted mainly of analgesics, antibiotics, cough syrups, and corticosteroids. Since these were subjects with moderate Covid-19, almost all received steroids. The average dose of steroids was 4 mg once or twice per day. More than 50% subjects took Remdesivir as part of SOC.

TABLE 1 Demographic and clinical characteristics at baseline[a]

Characteristic (Unit)	Statistics	BV-4051 ($N = 102$)	Placebo ($N = 103$)	Total ($N = 205$)
Gender				
Male	*n* (%)	72 (70.6)	71 (68.9)	143 (69.8)
Female	*n* (%)	30 (29.4)	32 (31.1)	62 (30.2)
Age (Years)	*N*	43.0 (12.34)	41.7 (11.74)	42.4 (12.03)
Race				
Asian	*n* (%)	99 (97.1)	99 (96.1)	198 (96.6)
Caucasian	*n* (%)	3 (2.9)	4 (3.9)	7 (3.4)
Height (cms)	*n* (%)	165.9 (9.21)	166.4 (9.95)	166.2 (9.57)
Weight (kg)	*n* (%)	69.2 (10.95)	67.7 (10.39)	68.5 (10.67)
BMI (kg/m^2)	*n* (%)	25.2 (3.57)	24.5 (3.26)	24.8 (3.43)
Subjects with at least one medical history	*n* (%)	9 (8.8)	12 (11.7)	21 (10.2)
Central Nervous System	*n* (%)	1 (1.0)	1 (1.0)	2 (1.0)
Ear Nose and Throat	*n* (%)	1 (1.0)	0	1 (0.5)
Respiratory	*n* (%)	1 (1.0)	3 (2.9)	4 (2.0)
Gastro-intestinal	*n* (%)	0	1 (1.0)	1 (0.5)
Musculoskeletal	*n* (%)	2 (2.0)	3 (2.9)	5 (2.4)
Skin conditions	*n* (%)	0	1 (1.0)	1 (0.5)

Note: N = number of subjects in specified treatment group; n = number of subjects in specified category. Percentages are based on the number of subjects in the specified treatment group.

[a]The values shown are based on available data.

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3.2 | Primary and secondary efficacy endpoints

The mean difference of reduction in duration of illness between the two groups was statistically significant ($p = 0.036$) (Table 2). Subjects experienced significant alleviation of fever on Day 4 ($p = 0.034$) (Table 2). The mean Severity Scores of nasal congestion, sore throat, cough, fatigue, headache, diarrhea, smell, and taste disorder decreased greater in BV-4051 group than in placebo group and were statistically significant (Table 2). In several parameters, on several days, patients in BV-4051 group had improvement; but did not achieve statistically significant levels. The mean Quality-of-Life score was improved gradually in both groups by Day 14, but was not statistically significant (Figure S3). The biomarkers showed improvement but did not reach statistical significance. There were no complications or significant protocol deviations during the entire conduct of the study.

3.3 | Safety and adverse events

There were total 13 AEs reported in five (2.4%) subjects (two in BV-4051, three in Placebo group). Of the total AEs, four were in BV-4051 and nine were in Placebo group. All the AEs were moderate in severity, resolved during study and were noted to be unrelated to the study product. Most common AEs were increase in LDH (1.5%), CRP (1.5%) and TNF (1.0%). Other reported AEs were inflammation in limbs, increase in glucose, increase in IL-6, hypertension, and vomiting (0.5%). While the biomarkers were exploratory endpoints in the study, extremely high values were considered as AEs by the Principal Investigators and recorded as such. Hematology, biochemistry, urinalysis, and 12-lead-electrocardiograms did not show any noteworthy changes.

3.4 | Efficacy subset analysis with remdesivir

53 subjects received BV-4051 with Remdesivir, and 47 subjects received placebo with Remdesivir. In subjects with BV-4051 and Remdesivir, the mean duration required for reduction of illness was less [7.8 (±3.23) days] compared to placebo and Remdesivir [8.9 (±2.95) days]. The median duration of illness was 8.0 days for BV-4051 with Remdesivir and 10.0 days for placebo with Remdesivir, and was statistically significant ($p = 0.030$) (Table 3). The mean

TABLE 2 Primary and secondary efficacy analysis with severity scores of symptoms

Primary efficacy end point	**BV-4051 $n = 89$**	**Placebo $n = 86$**	***p* value***
Reduction in duration of illness (in Days) Mean	7.1 (3.31)	8.0 (3.47)	**0.036***
Median	8.0	9.0	
Alleviation of Fever (Day 4) *n* (%)	19.0 (34.5)	10.0 (16.9)	**0.034***

Secondary efficacy end points: Severity scores of symptoms												
	Day 1			**Day 7**			**Day 8**			**Day 13**		
Symptoms	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***
Nasal Congestion	2.0 (1.21)	2.2 (1.18)	0.356	1.2 (0.96)	1.5 (0.90)	**0.050***	1.1 (0.88)	1.4 (0.88)	0.052	0.1 (0.30)	0.2 (0.35)	0.123
Sore Throat	2.1 1.08)	2.3 (1.05)	0.292	1.2 (0.89)	1.5 (0.89)	0.091	1.1 (0.84)	1.3 (0.85)	0.078	0.1 (0.25)	0.2 (0.37)	**0.011***
Cough	2.2 (0.97)	2.3 (0.98)	0.706	1.2 (0.86)	1.4 (0.82)	0.140	1.0 (0.78)	1.2 (0.77)	0.090	0.1 (0.21)	0.2 (0.35)	**0.014***
Breathing Difficulty	2.0 (1.13)	2.2 (1.15)	0.415	1.1 (0.88)	1.3 (0.91)	0.151	0.9 (0.77)	1.1 (0.78)	0.167	0.1 (0.23)	0.1 (0.30)	0.176
Aches and pains	2.2 (1.01)	2.3 (0.95)	0.345	1.1 (0.79)	1.2 (0.79)	0.411	0.9 (0.68)	1.0 (0.72)	0.089	0.1 (0.26)	0.1 (0.33)	0.735
Fatigue	2.1 (1.05)	2.2 (1.03)	0.620	1.0 (0.80)	1.2 (0.78)	0.130	0.8 (0.69)	1.1 (0.68)	**0.021***	0.1 (0.43)	0.2 (0.38)	0.438
Headache	2.1 (1.09)	2.1 (1.08)	0.711	1.0 (0.73)	1.2 (0.79)	0.117	0.8 (0.69)	1.0 (0.73)	0.082	0.1 (0.20)	0.1 (0.28)	0.335
Chills or Sweats	2.0 (1.13)	2.2 (1.03)	0.285	0.9 (0.77)	1.1 (0.82)	0.088	0.8 (0.69)	1.0 (0.76)	0.144	0.0 (0.19)	0.1 (0.25)	0.365
Diarrhea	1.8 (1.35)	2.0 (1.24)	0.253	0.9 (0.83)	1.2 (0.89)	0.081	0.8 (0.74)	1.0 (0.79)	**0.043***	0.0 (0.14)	0.1 (0.19)	0.346
Vomiting	1.8 (1.38)	2.0 (1.27)	0.200	0.9 (0.80)	1.1 (0.88)	0.066	0.8 (0.75)	1.0 (0.81)	0.062	0.0 (0.14)	0.1 (0.22)	0.197
Smell Disorders	1.9 (1.22)	2.1 (1.17)	0.362	1.0 (0.83)	1.2 (0.82)	0.062	0.9 (0.74)	1.1 (0.73)	0.108	0.0 (0.18)	0.2 (0.36)	**0.004***
Taste Disorders	2.0 (1.18)	2.1 (1.15)	0.587	1.0 (0.82)	1.2 (0.83)	0.143	0.8 (0.75)	1.0 (0.73)	0.096	0.0 (0.18)	0.2 (0.39)	**0.004***

Note: n = number of subjects in specified category. Note 1: p value* is calculated for between group data using repeated measures ANOVA. Note 2: *Median difference, 95% CI and p value is calculated for non-parametric Mann–Whitney U-test. Note 3: Duration of illness = the length of time to alleviation of all symptoms including fever and other symptoms including breathing difficulty, nasal congestion, sore throat, cough, headache, body ache, fatigue, diarrhea, vomiting, chills or sweats, taste and smell disorders. p values of ≤ 0.05 are statistically significant and bold.

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Severity Scores of nasal congestion, sore throat, cough, fatigue, headache, diarrhea, smell and taste disorder decreased considerably in BV-4051 with Remdesivir group than in placebo with Remdesivir group and were statistically significant (Table 3). Higher number of subjects on BV-4051 with Remdesivir had alleviation of taste disorder on Day 5 ($p = 0.026$); for fever ($p = 0.011$), nasal congestion ($p = 0.027$), headache ($p = 0.025$) on Day 7; and sore throat on Day 10 ($p = 0.032$) (Table 4). The mean (SD) Quality-of-Life score improved gradually in both groups by Day 14 but was not statistically significant.

In subjects on BV-4051 without Remdesivir, the mean difference in IL-6 values on Day 14 between the two groups was statistically significant ($p = 0.042$). The mean change in IL-6 from baseline in BV-4051 without Remdesivir group was also statistically significant ($p = 0.044$). In subjects with Remdesivir, this difference was not statistically significant. Although reduction in other biomarkers were noted, these were not statistically significant (Table S1).

4 | DISCUSSION

The present study was conducted with a natural Ayurvedic polyherbal formulation BV-4051, containing a proprietary combination of Ashwagandha, Boswellia, Ginger, and Turmeric. It was evaluated in a randomized clinical trial in hospitalized moderate Covid-19 patients for the first time in this study. BV-4051 significantly reduced the duration of Covid-19 illness and severity scores of individual symptoms. In the subset analyses, the BV-4051 with Remdesivir group had statistically significant reduction in duration of illness and of severity scores of various symptoms, versus those on Remdesivir and placebo. This may also point to an adjunctive or additive effect of BV-4051 to current standard of care.

Various biomarkers are associated with COVID-19 progression. Of these, IL-6 appears to be the most important driver of immune dysregulation and acute respiratory distress (Magro, 2020), and predictor of mortality (Han et al., 2020). The WHO has recommended IL-6 receptor blockers, with corticosteroids in critically ill patients

TABLE 3 Primary and secondary efficacy analysis with remdesivir group

Primary efficacy end point	**BV-4051 with Remdesivir $n = 53$**	**Placebo with Remdesivir $n = 47$**	***p* value***
Reduction in duration of illness (in Days)^ Mean (SD)	7.8 (3.23)	8.9 (2.95)	**0.030***
Median^	8.0	10.0	

Secondary efficacy end points: Severity scores of symptoms												
	Day 1			**Day 7**			**Day 8**			**Day 11**		
Symptoms	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***	**BV-4051 Mean (SD)**	**Placebo Mean (SD)**	***p* value***
Nasal Congestion	2.5 (0.97)	2.6 (1.01)	0.540	1.4 (0.88)	1.8 (0.72)	**0.014***	1.3 (0.81)	1.7 (0.75)	**0.022***	0.7 (0.62)	0.8 (0.55)	0.285
Sore Throat	2.4 (0.93)	2.6 (0.99)	0.500	1.5 (0.78)	1.8 (0.73)	**0.033***	1.2 (0.77)	1.6 (0.70)	**0.012***	0.6 (0.64)	0.8 (0.53)	**0.036***
Cough	2.5 (0.81)	2.6 (0.79)	0.505	1.4 (0.77)	1.6 (0.67)	0.135	1.2 (0.68)	1.5 (0.63)	**0.016***	0.6 (0.54)	0.8 (0.51)	0.075
Breathing Difficulty	2.3 (1.01)	2.6 (0.75)	0.099	1.3 (0.81)	1.6 (0.77)	0.086	1.1 (0.72)	1.3 (0.70)	0.116	0.5 (0.52)	0.6 (0.48)	0.125
Aches and pains	2.4 (0.97)	2.5 (0.96)	0.434	1.3 (0.75)	1.3 (0.73)	0.554	0.9 (0.66)	1.2 (0.66)	**0.024***	0.4 (0.51)	0.6 (0.47)	0.185
Fatigue	2.4 (0.94)	2.5 (0.87)	0.493	1.2 (0.77)	1.4 (0.63)	0.121	0.9 (0.67)	1.3 (0.56)	**0.002***	0.5 (0.61)	0.6 (0.52)	0.156
Headache	2.4 (0.95)	2.5 (0.96)	0.644	1.2 (0.64)	1.4 (0.66)	0.066	0.9 (0.65)	1.2 (0.69)	**0.031***	0.4 (0.47)	0.6 (0.54)	**0.025***
Chills or Sweats	2.3 (1.03)	2.5 (0.93)	0.405	1.1 (0.69)	1.4 (0.72)	0.071	1.0 (0.63)	1.2 (0.74)	0.179	0.4 (0.52)	0.6 (0.52)	0.106
Diarrhea	2.1 (1.24)	2.4 (1.08)	0.198	1.1 (0.77)	1.4 (0.78)	0.103	0.9 (0.71)	1.2 (0.75)	0.056	0.3 (0.47)	0.5 (0.48)	**0.044***
Vomiting	2.1 (1.25)	2.5 (1.03)	0.160	1.1 (0.75)	1.4 (0.76)	**0.043***	0.9 (0.71)	1.2 (0.77)	**0.044***	0.3 (0.48)	0.5 (0.49)	0.081*
Smell Disorders	2.3 (1.05)	2.5 (0.95)	0.341	1.2 (0.77)	1.5 (0.74)	**0.048***	1.0 (0.69)	1.3 (0.66)	**0.037***	0.4 (0.50)	0.6 (0.48)	**0.041***
Taste Disorders	2.3 (0.99)	2.5 (0.94)	0.492	1.2 (0.77)	1.5 (0.75)	0.101	1.0 (0.71)	1.2 (0.67)	0.056	0.4 (0.48)	0.6 (0.48)	**0.043***

Note: n = number of subjects in specified category. Note 1: p value* is calculated for between group data using repeated measures ANOVA. Note 2: ^Median difference, 95% CI and p value is calculated for non-parametric Mann–Whitney U-test. Note 3: Duration of illness = the length of time to alleviation of all symptoms including fever and other symptoms including breathing difficulty, nasal congestion, sore throat, cough, headache, body ache, fatigue, diarrhea, vomiting, chills or sweats, taste and smell disorders. p values of ≤ 0.05 are statistically significant and bold.

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TABLE 4 Subjects experiencing alleviation by remdesivir group

Symptoms			BV-4051 $n = 53$	Placebo $n = 47$	p value*
Fever	Subjects with Moderate or Severe symptoms	n	12	10	
Day 7	Subjects without Alleviation	n	4	9	
	Subjects with Alleviation	n	8	1	**0.011***
Nasal Congestion	Subjects with Moderate or Severe symptoms	n	38	40	
Day 7	Subjects without Alleviation	n	31	39	
	Subjects with Alleviation	n	7	1	**0.027***
Headache	Subjects with Moderate or Severe symptoms	n	30	32	
Day 7	Subjects without Alleviation+	n	17	27	
	Subjects with Alleviation	n	13	5	**0.025***
Sore Throat	Subjects with Moderate or Severe symptom	n	16	17	
Day 10	Subjects without Alleviation	n	7	14	
	Subjects with Alleviation	n	9	3	**0.032***
Taste Disorder	Subjects with Moderate or Severe symptoms	n	39	40	
Day 5	Subjects without Alleviation	n	34	40	
	Subjects with Alleviation	n	5	0	**0.026***

Note: n = Number of Subjects in specified category on specified day. Alleviation symptoms: Symptom is less than or equal to mild (score is 1 or 0) and stable for at least 24 h. Note 1: *p value is calculated between group data using Fisher's Exact test. p values of ≤ 0.05 are statistically significant and bold.

(Chen et al., 2021). In the present study, in the subset analysis, there was decrease in IL-6 in subjects on BV-4051 who did not receive Remdesivir. At the same time there was a significant rise in IL-6 in the placebo group. This may suggest a strong immuno-modulatory effect of BV-4051.

The study would have benefited if quantitative PCR was available widely, as it is now. It would be good to study BV-4051 (Tradename ARTOVID-20®) in a larger population that is multi-ethnic, over multiple continents, and against other viruses. It may be interesting to see a comparative study of BV-4051 against other natural therapies such as TCM. In this study, we had to give SOC for ethical reasons along with investigational product or placebo. It would be useful to explore how BV-4051 will work independent of SOC in Covid-19 and its complications.

5 | CONCLUSION

The study formulation BV-4051 (ARTOVID-20®) can reduce the duration of illness, severity of symptoms, and ultimately prevent the incidence of COVID-19 complications and boost immunity. BV-4051 helps in reduction of inflammatory biomarker like Interleukin-6. It shows benefits when administered along with Remdesivir; and may have an adjunctive effect with other standard of care. As an affordable oral, natural plant-based product, BV-4051 may have a place as a pre-COVID exposure prophylactic strategy and a post-exposure therapeutic modality, especially in high-risk populations and in essential services. Additional studies may be warranted to further demonstrate the efficacy, and for use as a long-term broad-spectrum immuno-modulator against variants of COVID-19 and other viral infections.

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None.

CONFLICT OF INTEREST

Deepa Chitre, MD has shares in Bioved Pharmaceuticals, Inc.; Satej Nadkarni, PhD and Debendranath Dey, PhD have stock options in Bioved Pharmaceuticals, Inc.

DATA AVAILABILITY STATEMENT

All of the individual participant data collected during the trial, Study Protocol, Statistical Analytical Plan, Informed Consent Form and Clinical Study Report shall be available immediately after publication, for a period of 5 years. Researchers who provide an interest and methodologically sound proposal should contact dchitre@bioved.com with a copy to snadkarni@bioved.com. To gain access, researchers will need to sign a data access agreement.

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REFERENCES

Abdalhamid, B., Donahue, M., Kamal-Ahmed, I., Strand, K., Mitchell, E., & Iwen, P. C. (2022). Identification of SARS-CoV-2 variants of concern in vaccine-breakthrough infections. *Journal of Infection in Developing Countries*, *16*(4), 580–582. https://doi.org/10.3855/jidc.15458

Ablamunits, V., & Lepsy, C. (2022). Blocking TNF signaling may save lives in COVID-19 infection. *Molecular Biology Reports*, *49*(3), 2303–2309. https://doi.org/10.1007/s11033-022-07166-x

Accorsi, E. K., Britton, A., Fleming-Dutra, K. E., Smith, Z. R., Shang, N., Derado, G., … Verani, J. R. (2022). Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. *Journal of the American Medical Association*, *327*(7), 639–651. https://doi.org/10.1001/jama.2022.0470

Ahmad, S., Zahiruddin, S., Parveen, B., Basist, P., Parveen, A., Gaurav, P. R., & Ahmad, M. (2021). Indian medicinal plants and formulations and their potential against COVID-19-preclinical and clinical research. *Frontiers in Pharmacology*, *11*, 578970. https://doi.org/10.3389/fphar.2020.578970

Batista, C. M., & Foti, L. (2021). Anti-SARS-CoV-2 and anti-cytokine storm neutralizing antibody therapies against COVID-19: update, challenges, and perspectives. *International Immunopharmacology*, *3*, 108036. https://doi.org/10.1016/j.intimp.2021.108036

Bernal, A. J., Gomes da Silva, M. M., Musungaie, D. B., Kovalchuk, E., Gonzalez, A., Reyes, V. D., … De Anda, C. (2022). Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *The New England Journal of Medicine*, *386*(6), 509–520. https://doi.org/10.1056/NEJMoa2116044

Birhane, M., Bressler, S., Chang, G., Clark, T., Dorough, L., Fischer, M., … Trujillo, A. (2021). COVID-19 Vaccine breakthrough infections reported to CDC - United States. *Morbidity and Mortality Weekly Report*, *70*, 792–793. https://doi.org/10.15585/mmwr.mm7021e3

Boozari, M., & Hosseinzadeh, H. (2020). Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies. *Phytotherapy Research*, *35*(2), 864–876. https://doi.org/10.1002/ptr.6873

Cairns, D. M., Dulko, D., Griffiths, J. K., Golan, Y., Cohen, T., Trinquart, L., … Selker, H. P. (2022). Efficacy of niclosamide vs placebo in SARS-CoV-2 respiratory viral clearance, viral shedding, and duration of symptoms among patients with mild to moderate COVID-19: A Phase 2 randomized clinical trial. *JAMA Network Open*, *5*(2), e2144942. https://doi.org/10.1001/jamanetworkopen.2021.44942

Chang, J. S., Wang, K. C., Yeh, C. F., Shieh, D. E., & Chiang, L. C. (2013). Fresh ginger (Zingiber officinale) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *Journal of Ethnopharmacology*, *145*(1), 146–151. https://doi.org/10.1016/j.jep.2012.10.043

Chen, T., Lin, X., Zhao, Y., Sun, Y., Tian, J., Yang, Z., … Feng, M. L. (2021). A low-producing haplotype of interleukin-6 disrupting CTCF binding is protective against Severe COVID-19. *Clinical Microbiology*, *12*(5), e01372-21. https://doi.org/10.1128/mBio.01372-21

Chitre D. and Dey D. (2014). *Method for extraction of fractions containing pharmacologically active ingredients with less cytotoxicity from one or more plants*. US Patent issued 8,808,769. https://uspto.gov

Chopra, A., Lavin, P., Patwardhan, B., & Chitre, D. (2000). Randomized double-blind placebo- controlled trial of efficacy and safety in rheumatoid arthritis. *Journal of Rheumatology*, *27*, 1365–1372 PMID: 10852255.

Chopra, A., Lavin, P., Patwardhan, B., & Chitre, D. (2004). Randomized double-blind placebo-controlled trial of efficacy and safety, in particular VAS and WOMAC, in osteoarthritis of Knee. *Journal of Clinical Rheumatology*, *10*, 236–245.

Chopra, A., Saluja, M., Kianifard, T., Chitre, D., & Venugopalan, A. (2018). Long term effectiveness of RA- 1 as a monotherapy and in combination with disease modifying anti-rheumatic drugs in the treatment of rheumatoid arthritis. *Journal of Ayurveda and Integrative Medicine*, *9*(3), 201–208. https://doi.org/10.4103/0975-9476.72620

Dey, D., Chaskar, S., Athavale, N., & Chitre, D. (2014). Inhibition of LPS-induced TNF-α and NO production in mouse macrophage and inflammatory response in rat animal models by a novel ayurvedic formulation, BV-9238. *Phytotherapy Research*, *28*(10), 1479–1485. https://doi.org/10.1002/ptr.5151

Dey, D., Chaskar, S., Athavale, N., & Chitre, D. (2015). Acute and chronic toxicity, cytochrome p450 enzyme inhibition, and HERG channel blockade studies with a polyherbal, ayurvedic formulation for inflammation. *BioMed Research International*, *2015*, Article ID 971982. https://doi.org/10.1155/2015/971982

Emadi, A., Chua, J. V., Talwani, R., Bentzen, S. M., & Baddley, J. (2020). Safety and efficacy of imatinib for hospitalized adults with COVID-19: A structured summary of a study protocol for a randomized controlled trial. *Trials*, *21*(1), 897. https://doi.org/10.1186/s13063-020-04819-9

Fan, A. Y., Gu, S., Alemi, S. F., & Research Group for Evidence-based Chinese Medicine. (2020). Chinese herbal medicine for COVID-19 current evidence with systematic review and meta-analysis. *Journal of Integrative Medicine*, *18*(5), 385–394. https://doi.org/10.1016/j.joim.2020.07.008

Feldman, M., Maini, R. M., Woody, J. N., Holgate, S. T., Winter, G., Rowland, M., … Hussell, T. (2020). Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet*, *395*(10234), 1407–1409. https://doi.org/10.1016/S0140-6736(20)30858-8

Gao, L., Xiuying, M., Jiao, Y.-M., & Wang, F.-S. (2022). Reinfection and breakthrough Infection of SARS-CoV-2: An emerging challenge that is threatening our world. *Infectious Diseases and Immunity*, *2*(1), 29–23. https://doi.org/10.1097/ID9.0000000000000027

Gomaa, A. A., Mohamed, H. S., Abd-Ellatief, R. B., & Gomaa, M. A. (2021). Boswellic acids/Boswellia serrata extract as a potential COVID-19 therapeutic agent in the elderly. *Inflammopharmacology*, *29*(4), 1033–1048. https://doi.org/10.1007/s10787-021-00841-8

Gottlieb, R. L., Vaca, C. E., Paredes, R., Mera, J., Webb, B. J., Perez, G., … Hill, J. A. (2021). Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *The New England Journal of Medicine*, *386*, 305–331. https://doi.org/10.1056/nejmoa2116846

Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., … Xia, Y. (2020). Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerging Microbes & Infections*, *9*(1), 1123–1130. https://doi.org/10.1080/22221751.2020.1770129

Herold, T., Jurinovic, V., Arnreich, C., Lipworth, B. J., Hellmuth, J. C., von Bergwelt-Baildon, M., … Weinberger, T. (2020). Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *The Journal of Allergy and Clinical Immunology*, *146*(1), 128–136.e4. https://doi.org/10.1016/j.jaci.2020.05.008

Ichsyani, M., Ridhanya, A., Risanti, M., Desti, H., Ceria, R., & Putri, D. (2017). Antiviral effects of *Curcuma longa* L. against dengue virus in vitro and in vivo. *IOP Conference Series: Earth and Environmental Science*, *101*, 12005. https://doi.org/10.1088/1755-1315/101/1/012005

Izadi, Z., Brenner, E. J., Mahil, S. K., Dand, N., Yiu, Z. Z., Yazdany, J., … Cruz-Machado, A. R. (2021). Association between tumor necrosis factor inhibitors and the risk of hospitalization or death among patients with immune-mediated inflammatory disease and COVID-19. *JAMA Network Open*, *4*(10), e2129639. https://doi.org/10.1001/jamanetworkopen.2021.29639

Kumar, A., Rai, A., Khan, M. S., Amit, K., Haque, Z. U., Fazil, M., & Rabbani, G. (2022). Role of herbal medicines in the management of patients with Covid-19: A systematic review and meta-analysis of

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randomized controlled trials. *Journal of Traditional and Complementary Medicine*, *12*(1), 100–113. https://doi.org/10.1016/j.jtcme.2022.01.002

Magro, G. (2020). SARS-CoV-2 and COVID-19: Is interleukin-6 (IL-6) the 'culprit lesion' of ARDS onset? What is there besides Tocilizumab? *Cytokine X*, *2*(2), 100029. https://doi.org/10.1016/j.cytox.2020.100029

Mandel, M., Harari, G., Gurevich, M., & Achiron, A. (2020). Cytokine prediction of mortality in COVID19 patients. *Cytokine*, *134*, 155190. https://doi.org/10.1016/j.cyto.2020.155190

Patil, V. S., Hupparage, V. B., Malgi, A. P., Deshpande, S. H., Patil, S. A., & Mallapur, S. P. (2021). Dual inhibition of COVID-19 spike glycoprotein and main protease 3CLpro by Withanone from *Withania somnifera*. *Chinese Herbal Medicines*, *13*(3), 359–369. https://doi.org/10.1016/j.chmed.2021.06.002

Rasool, A., Khan, M. U. R., Ali, M. A., Anjum, A. A., Ahmed, I., Aslam, A., … Nawaz, M. (2017). Anti-Avian influenza virus H9N2 activity of aqueous extracts of Zingiber officinalis (Ginger) and Allium sativum (Garlic) in chick embryos. *Pakistan Journal of Pharmaceutical Sciences*, *30*(4), 1341–1344.

Saggam, A., Limgaokar, K., Borse, C.-G. P., Dixit, S., Tillu, G., & Patwardhan, B. (2021). *Withania somnifera* (L.) Dunal: Opportunity for Clinical repurposing in COVID-19 Management. *Frontiers in Pharmacology*, *12*, 623795. https://doi.org/10.3389/fphar.2021.623795

Salama, C., Han, J., Yau, L., Reiss, W. G., Kramer, B., Neidhart, J. D., … Mohan, S. V. (2021). Tocilizumab in patients hospitalized with Covid-19 pneumonia. *The New England Journal of Medicine*, *384*, 20–30. https://doi.org/10.1056/NEJMoa2030340

Sarkar, A., Chakrabarti, A. K., & Dutta, S. (2021). Covid-19 infection in India: A comparative analysis of the second wave with the first wave. *Pathogens*, *10*(9), 1222. https://doi.org/10.3390/pathogens10091222

Sheikh, A. B., Pal, S., Javed, N., & Shekhar, R. (2021). COVID-19 vaccination in developing nations: Challenges and opportunities for innovation. *Infectious Disease Reports*, *13*(2), 429–436. https://doi.org/10.3390/idr13020041

Sornpet, B., Potha, T., Tragoolpua, Y., & Pringproa, K. (2017). Antiviral activity of five Asian medicinal plant crude extracts against highly pathogenic H5N1 avian influenza virus. *Asian Pacific Journal of Tropical Medicine*, *10*(9), 871–876. https://doi.org/10.1016/j.aptm.2017.08.010

Srivastava, A., Rengaraju, M., Srivastava, S., Narayanan, V., Gupta, V., Upadhayay, R., … Velmurugan, A. (2021). Efficacy of two siddha polyherbal decoctions, Nilavembu Kudineer and Kaba Sura Kudineer, along with standard allopathy treatment in the management of mild to moderate symptomatic COVID-19 patients-a double-blind, placebo-controlled, clinical trial. *Trials*, *22*(1), 570. https://doi.org/10.1186/s13063-021-05478-0

Tamiflu® Prescribing Data (2012). *TAMIFLU® (oseltamivir phosphate) capsules for oral use, TAMIFLU® (oseltamivir phosphate) capsules for oral suspension*. Full prescribing information. Page 18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf

Tiwari, S., Gupta, S. K., & Pathak, A. K. (2021). A double-blind, randomized, placebo-controlled trail on the effect of Ashwagandha (*Withania somnifera* dunal) root extract in improving cardiorespiratory endurance and recovery in healthy athletic adults. *Journal of Ethnopharmacology*, *272*, 113929. https://doi.org/10.1016/j.jep.2021.113929

Treanor, J. J., Hayden, F. G., Vrooman, P. S., Barbarash, R., Bettis, R., Riff, D., … Mills, R. G. (2000). Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *Journal of the American Medical Association*, *283*(8), 1016–1024. https://doi.org/10.1001/jama.283.8.1016

Trunfio, M., Verga, F., Ghisetti, V., Burdino, E., Emanuele, T., Bonora, S., … Calcagno, A. (2021). Clinical phenotype and contagiousness of early breakthrough SARS-CoV-2 infections after BNT162b2 COVID-19 mRNA vaccine: A Parallel Cohort Study in Healthcare Workers. *Vaccine*, *9*(12), 1377. https://doi.org/10.3390/vaccines9121377

Udani, S. (2021). India grapples with second wave of Covid-19. *Lancet*, *2*(6), E238. https://doi.org/10.1016/S2666-5247(21)00123-3

United Nations News. (2022). *UN analysis shows link between lack of vaccine equity and widening poverty gap*. https://news.un.org/en/story/2022/03/1114762

Whitley, R. (2022). Molnupiravir - A Step toward orally bioavailable therapies for Covid-19. *The New England Journal of Medicine*, *386*, 592–593. https://doi.org/10.1056/NEJMe2117814

World Bank Report (2022). https://www.worldbank.org/en/publication/wdr2022/brief/chapter-1-introduction-the-economic-impacts-of-the-covid-19-crisis

Xiong, X., Wang, P., Su, K., Cho, W. C., & Xing, Y. (2020). Chinese herbal medicine for coronavirus disease 2019: A systematic review and meta-analysis. *Pharmacological Research*, *160*, 105056. https://doi.org/10.1016/j.phrs.2020.105056

Zhao, L., Li, S., & Zhong, W. (2022). Mechanism of action of small-molecule agents in ongoing clinical trials for SARS-CoV-2: A review. *Frontiers in Pharmacology*, *13*, 840639. https://doi.org/10.3389/fphar.2022.840639

Placeholder Text

SUPPORTING INFORMATION

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

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