ORIGINAL RESEARCH

Euphorbia neriifolia Leaf Juice on Mild and Moderate COVID-19 Patients: Implications in OMICRON Era

Md Enayet Ali Pramanik[1], M Morsed Zaman Miah[2], Istiak Ahmed[3], AZM Mostaque Hossain[4], M Nowshad Ali[5], Md Jawadul Haque[6], AKM Monoarul Islam[7], Rukhshana Akhter Jahan[8], Md Enamul Haque[9], Md Munzur Rahman[10], Md Sofikul Islam[11], Md Mahidul Alam[12], Prabir Mohan Basak[13], Ahmed Masiha Jamil[14], Sk Md Abdullah Al Mamun[15], Md Rezaul Islam[16], Md Masudur Rahman[17], HNM Shafikuzzaman[18], Md Ariful Alam Suman[19], Md Mozammel Hoq Badol[20], Mosfiqur Rahman[21], Md Sharif Hasan[22], Md Nazrul Islam Mondal[23], Md Mamun Kabir[24], Mohammad Motiur Rahman[25], Humayra Haque[26], Mamun Al Mahtab[27], Sheikh Mohammad Fazle Akbar[28]

Abstract

Coronavirus disease-2019 (COVID-19) has shattered the public health delivery system of most of the countries of the world. COVID-19 displays variable clinical presentations. The severe COVID-19 represents a fulminant pathological condition and most of the patients run a downhill course if extensive medical measures are not adopted. The major challenges about COVID-19 are related to develop strategies to manage huge populations of mild and moderate cases of COVID-19 with two realistic purposes: (1) early negativity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and (2) arrest of progression of moderate COVID-19 patients from developing severe complications. Although several medications have been repurposed for these purposes, none of these have passed the test of time in global perspective. Thus, there remains a pressing need to develop new and novel innovative management strategies for these patients as new variants of SARS-CoV-2 have been destroying the normal public health delivery system of different countries from time to time. The study presented here has checked the safety and efficacy of a herbal medication, leaves of *Euphorbia neriifolia* Linn (*E. neriifolia*), in mild and moderate COVID-19 patients. Sixty patients (30 mild COVID-19 and 30 moderate COVID-19) were enrolled in the study. Fifteen mild COVID-19 patients received standard of care (SOC) management, and the remaining 15 patients received SOC plus *E. neriifolia*. The moderate COVID-19 patients similarly received either SOC ($N = 15$) or SOC plus *E. neriifolia* ($N = 15$). Although there were marked diversity regarding biochemical parameters of these patients at entry, the moderate COVID-19 patients receiving *E. neriifolia* showed decrease in C-reactive protein and D-dimer and increase in oxygen saturation 7 days after trial commencement. However, these improvements were not detected in moderate COVID-19 patients receiving SOC. Hospital staying was significantly lower in both mild and moderate COVID-19 patients receiving SOC plus *E. neriifolia* than those receiving only SOC. Taken together, it may be proposed that usage of *E. neriifolia* may have beneficial effects regarding management for COVID-19 patients, especially for those in developing and resource-constrained countries, although a conclusive statement may not be given due to small sample size. This herbal medication is also pertinent in the context of emergence of OMICRON variant of COVID-19 as the overload of SARS-CoV-2-infecetd patients may be addressed considerably by this medication without hospitalization, if proper communication between patients and physicians can be ensured.

Keywords: Coronavirus disease-2019, *Euphorbia neriifolia*, Mild and moderate COVID-19, Severe acute respiratory syndrome coronavirus 2.

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Introduction

Coronaviruses of different strains have been causing significant outbreaks of acute respiratory diseases globally especially over the past two decades. In 2002, severe acute respiratory syndrome (SARS) emerged in East Asia,[1] and later on, in 2012, the Middle East respiratory syndrome (MERS) was associated with an outbreak of corona virus in the Middle East.[2] Recently, the world faced an unprecedented catastrophe of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreaks and coronavirus disease of 2019 (COVID-19) from late 2019.[3]

After the outbreak of SARS-CoV-2 at the end of 2019, the virus spread exponentially in almost all parts of the world and the trend is still persisting.[4] The World Health Organization (WHO) declared the COVID-19 a pandemic on March 11, 2020.[5] Along with time, various new variants of SARS-CoV-2 were detected (notably alpha, beta, gamma, and delta, and some others) around the world.[6] Recently, another new variant of SARS-CoV-2, named OMICRON, have devasted the world, and as of today, it seems that the OMICRON

[1]Key Laboratory of Zoological Systematics and Evolution, Institute of Zoology, College of Life Sciences, University of Chinese Academy of Sciences, Beijing, People's Republic of China; On-Farm Research Division, Bangladesh Agricultural Research Institute, Rajshahi, Bangladesh

[2]Department of Hematology, Rajshahi Medical College, Rajshahi, Bangladesh

[3]Department of Surgery, Rajshahi Medical College Hospital, Rajshahi, Bangladesh

[4]Rajshahi Medical University, Rajshahi, Bangladesh

[5]Department of Pediatric Surgery, Rajshahi Medical College, Rajshahi, Bangladesh

[6]Department of Community Medicine, Rajshahi Medical College, Rajshahi, Bangladesh

[7]Department of Nephrology, Rajshahi Medical College, Rajshahi, Bangladesh

[8]Department of Pathology, Rajshahi Medical College, Rajshahi, Bangladesh

variant is highly infectious, but possibly less pathogenic.[7] As of January 25, 2022, the total number of confirmed SARS-CoV-2 infection has surpassed 335 million, with a cumulative death of 5.62 million.[8] Bangladesh, a country of 164 million, has reported 1.58 million confirmed SARS-CoV-2-positive cases and more than 28,000 COVID-19-related deaths.[8]

There are two significant spectrums of handling the present pandemic: (1) containment of SARS-CoV-2 infection and (2) management of COVID-19 patients. To achieve the first target, at the onset of the pandemic, WHO advocated for implementing 3T approaches (Testing, Treating, and Tracing) for containment of SARS-CoV-2.[9] Most of the countries have also adopted several measures that expand from local lockdown to national blockade with several other approaches.[10,11] Finally, various prophylactic vaccines of different natures and compositions have been developed to block the transmission of SARS-CoV-2.[12] As of today, 4.4 billion doses of vaccine have been administered at least once, and 3.7 billion people worldwide are fully vaccinated. Patients receiving booster doses of vaccine have also reached 448 million.[8]

Regarding the treatment of COVID-19 patients, several medications and approaches have been applied. The SARS-CoV-2 infection and pathogenesis of COVID-19 are highly versatile. In some infected persons, the patients remain almost completely unaware of their infectious status, whereas, the virus causes asymptomatic or mild symptoms in more than 85% patients. On the other hand, some patients develop subjective symptoms and other progress to serious pathological lesions with inflammation of lung and involvement of multi-organ pathologies. Most of these patients take a downhill course. Thus, the management strategies of COVID-19 patients are highly heterogeneous and these extend from the usage of simple medications like analgesics and antihistamines to application of antibiotics, antivirals, steroids, blood thinning drugs, immune modulators, and support of O_2 inhalation with care in the intensive care unit (ICU).[13] However, it remains to ascertain the efficacy of these medications because a double-blinded randomized trial could not affirm the utility of most of these drugs, and most importantly, there has been no magic bullet to manage COVID-19.[14] However, these medications are endowed with several adverse effects and some of these may have long-lasting adverse effects. These facts indicate that there is a pressing need to develop alternative and patient-friendly management approaches for COVID-19 patients, at least for the majority of the COVID-19 patients those who attend health facilities either as mild or moderate COVID-19 patients. In this regard, we provided our attention to an herbal medication for the management of major bulk of patients with mild and moderate COVID-19.

Euphorbia neriifolia Linn. (*E. neriifolia*) is a spiny herb popularly known as "Dudhsor" in Bangladesh. It is of South-Asian origin and available in India, Sri Lanka, Taiwan, and Bangladesh. The plant *E. neriifolia*, especially the leaves, has been reported to possess a wide range of medicinal properties and the leaves have been recommended for whooping cough, pneumonia, bronchial infections, common cold, and antithrombotic activity with no significant adverse effects.[15–18]

In Bangladesh, the second wave of COVID-19 was started from March 2021. The case finding and death have been alarming in the Indian border adjacent districts, including Rajshahi and Chapainawabganj. In the Rajshahi division, the mean number of daily attacks and deaths was around 400 and 20, respectively. In these prevailing circumstances, leaf juice of *E. neriifolia* emerged as a new hope for managing COVID-19 patients, especially those with mild and moderate symptoms of COVID-19. As the leaf juice of *E. neriifolia* was used previously in some respiratory tract diseases without any significant adverse effects, several patients with COVID-19 (around 2000 COVID-19 mild-to-moderate RT-RCR-positive COVID-19 patients in the Rajshahi region) have taken the leaf juice of *E. neriifolia* by themselves (personal observations). However, this approach was not scientifically verified, adopted, and analyzed. In this context, we attempted to undertake a preliminary study to explore the safety and efficacy of leaf juice of *E. neriifolia*, if any, on mild and moderate COVID-19 patients in the Rajshahi area of Bangladesh.

[9–11]Department of Ortho-Surgery, Rajshahi Medical College, Rajshahi, Bangladesh

[12–15]Department of Medicine, Rajshahi Medical College, Rajshahi, Bangladesh

[16,17]Department of Respiratory Medicine, Rajshahi Medical College, Rajshahi, Bangladesh

[18,19]Department of Surgery, Rajshahi Medical College, Rajshahi, Bangladesh

[20]Department of Biochemistry, Rajshahi Medical College, Rajshahi, Bangladesh

[21]Department of Medicine, Rajshahi Medical College Hospital, Rajshahi, Bangladesh

[22]Department of Cardiology, Mymensingh Medical College Hospital, Mymensingh, Bangladesh

[23]Department of Population Science and Human Resource Development, University of Rajshahi, Bangladesh

[24,25]Covid Unit, Rajshahi Medical College Hospital, Rajshahi, Bangladesh

[26]Department of Anaesthesia, Analgesia and Intensive Care Unit, Chattragram Medical College, Chattragram, Bangladesh

[27]Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[28]Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan and Miyakawa Memorial Research Foundation, Tokyo, Japan

Corresponding Author: MEA Pramanik, Key Laboratory of Zoological Systematics and Evolution, Institute of Zoology, College of Life Sciences, University of Chinese Academy of Sciences, Beijing, People's Republic of China; On-Farm Research Division, Bangladesh Agricultural Research Institute, Rajshahi, Bangladesh, Phone: +880 1744 530588, e-mail: enayet.bari.bd@gmail.com

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Materials and Methods

Study Design

The study was of open-level, observational, controlled one with one arm receiving standard of care (SOC) management plus *E. neriifolia*, and the other arm received only SOC management. All patients enrolled in this study were positive for SARS-CoV-2 by RT-PCR assessment of nasal swab. The study was conducted at Rajshahi Medical College Hospital, Rajshahi, Bangladesh, during July 10, 2021, to August 10, 2021, with follow-up that is still ongoing.

Sampling and Management Strategies

The study was conducted in 60 patients that composed patients with both mild and moderate COVID-19. The patients with COVID-19 were explained about the nature and purpose of the therapy. They were also informed about possible adverse effects. When the patients provided written consent, they were enrolled in the study and the trial was started. When a total of 60 patients in 4 groups were properly analyzed (15 patients in each group), the trial received its target and analysis was accomplished. The inclusion criteria included mild or moderate COVID-19. All patients were positive for SARS-CoV-2 by PCR within the last 48 hours. Mild COVID-19 was considered when the patients were presented with fever, cough, sore throat, fatigue, mild dyspnea, anosmia, and diarrhea. The oxygen saturation level of mild COVID patients should be ≥94%. The moderate COVID-19 patients also had clinical symptoms similar to mild COVID-19 patients. However, COVID-19 patients with oxygen saturation between 88 and 93% were regarded as moderate COVID-19 patients. The patients were divided into two groups. Group A ($n = 30$) contained mild COVID-19 patients and Group B ($n = 30$) for moderate COVID-19 patients. Patients of both groups were subdivided into two subgroups based on management strategy. Fifteen patients with mild COVID-19 and 15 patients with moderate COVID-19 received standard of care SOC (SOC) management. SOC included drugs such as paracetamol, oral antibiotic, fexofenadine or antihistaminic drugs, and montelukast. Some other drugs, such as blood thinning drug, were given to some patients. Oxygen inhalation was given to patients as and when necessary. The remaining patients (15 patients with mild COVID-19 and 15 with moderate COVID-19) received SOC plus *E. neriifolia* leaf juice for 10 days. The patient's profile has been shown in Figure 1.

Dose and Procedure to Take of *E. neriifolia* Leaves Juice

Moderate-to-mature leaf of *E. neriifolia* was collected from Rajshahi City and Barind areas of Rajshahi, Bangladesh. In this trial, the plant was identified by taxonomist Dr Md Enayet Ali Pramanik, Senior Scientific Officer, Bangladesh Agricultural Research Institute, Rajshahi, Bangladesh. Dr Enayet was trained by taxonomist Dr Liang Ai-Ping, Institute of Zoology, Key Laboratory of Zoological and Systematics and Evolution, Chinese Academy of Sciences, Beijing, China (personal communication). The average weight of leaves was from 8 to 10 g. The leaves were washed under flowing tap water. Then the patient chewed two leaves and swallowed the juice. The little remaining amount of fiber was expelled out from the mouth. The leaf was given thrice daily for 10 days.

Data Collection and Management Strategy

All the patients were evaluated clinically on daily basis at the hospital. Laboratory tests were done on the day of admission, and 7 and 14 days after admission. All patients were positive for SARS-CoV-2 by RT-PCR during the admission. Repeat RT-PCR was done 7 and 14 days after commencement of therapy. Mortality, hospital staying, the need for oxygen and oxygen consumption, and transition to severe COVID-19 were also observed for each patient. The patients were discharged from hospitals when the study team found improvement of clinical symptoms with improvement of biochemical parameters. However, they attended on day 7 and 14 for RT-PCR as shown in the inclusion criteria. In accordance with local regulatory requirements, the patients and his/her relations were explained fully about this study, and informed consent was obtained in writing by the approved signature from each patient or the patient's legal relation.

Data Analysis and Statistical Procedure

Data were statistically analyzed by specific tests for the variables. Quantitative variables such as laboratory test reports were analyzed by student's *t*-test, ANOVA, and correlation test. One-tailed or two-tailed statistical analysis was done based on the necessity. Qualitative variables such as clinical features will be analyzed by Chi-square test, mean, and standard deviation. A comprehensive flow chart of the study has been shown in Table 1.

Results

Patients Profile, Comorbidities, and Presenting Symptoms

The study design has been mentioned in the Materials and Methods section. When a total of 60 patients in 4 groups were properly analyzed, the trial was ended and the analysis was accomplished. Most of the patients were below 40 years (66.66%) and there was a male predominance (68.33%). Different types

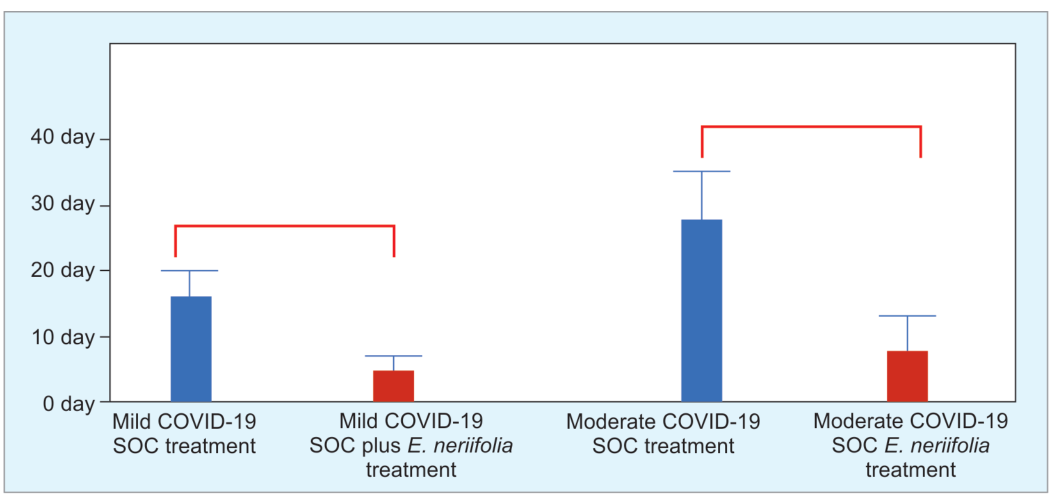

Fig. 1: Duration of hospital staying. The p value is <0.0000 in comparison to groups as shown by red lines

Table 1: The flow chart of the study

Age: 7–60 years' old Tested RT-PCR-positive COVID-19 patients Hospitalized patients			
Test: CBC, Ferritin, CRP, Chest X-ray, Oxygen saturation level First day: Admitted patient			
Mild patient Oxygen saturation ≥94% Any of the following common symptoms of COVID-19 such as fever, cough, sore throat, fatigue, mild dyspnea, anosmia, and diarrhea		Moderate patient Oxygen saturation 88–93% Any of the following common symptoms of COVID-19 such as fever, cough, sore throat, fatigue, mild dyspnea, anosmia, and diarrhea	
Standard of Care (SOC)	SOC plus *E. neriifolia*	SOC	SOC plus *E. neriifolia*
Moderate-to-mature leaf of *E. neriifolia* weighting from 8 to 10 g Chew two leaves and swallow the juice Dose: three times daily (8 hourly).		Moderate-to-mature leaf of *E. neriifolia* Leaves weight 8–10 g for single dose Chew two leaves and swallow the juice Dose: Three times daily (8 hourly).	
Test: CBC, Ferritin, CRP, Chest X-ray, Oxygen saturation level Day 7 and 14: Admit and Discharge patient			
Hierarchical analysis: Mortality, hospital stay, need of oxygen and oxygen consumption, transition to severe COVID-19.			
After discharge, follow-up was done either physically or over telephone for next 6 months to assess study outcomes, additional safety information, and adverse effects, if any.			

Table 2: Demographic features, treatment approaches, and clinical outcomes of patients with COVID-19 ($N = 60$)

Variables	*Number (n)*	*Percentage (%)*
Age (in years)		
≤40	40	66.66
41–60	10	16.67
>60	10	16.67
Sex		
Male	41	68.33
Female	19	31.67
Comorbidities and preexisting pathologies (multiresponses)		
Hypertension	37	61.67
Diabetes mellitus	32	53.35
Cardiac (heart failure, coronary artery disease, cardiomyopathies)	32	53.33
Asthma	29	48.33
Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)	26	43.33
Chronic lung disease (COPD, interstitial lung disease, pulmonary hypertension, bronchopulmonary dysplasia, bronchiectasis, cystic fibrosis)	25	41.67
Tuberculosis	12	20
Chronic liver disease (cirrhosis, nonalcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)	10	16.67
Mental health disorders (mood disorders including depression and schizophrenia spectrum disorders)	10	16.67
Chronic kidney disease	8	13.33
Use of corticosteroids or other immunosuppressive medications	6	10
Cancer	5	8.33
Cerebrovascular diseases	4	6.67

Data are shown as numerical values as well as percentage of total patients. COVID-19, coronavirus disease in 2019; COPD, chronic obstructive pulmonary disease

of comorbidities were found in majority of patients as shown in Table 2. Some of the patients had multiple comorbidities. The presenting symptoms were highly variable and extended from apparently simple cough to difficulty of breathing. A detailed description of basic profile and comorbidities has been cited in Table 3. On the day of therapy commencement, the patients were complained of several presenting symptoms. Most of the patients complained of weakness ($N = 60$), body aches and pains ($N = 55$), cough ($N = 54$), difficulty of breathing ($N = 49$), sore throat ($N = 48$), running nose ($N = 46$), chest pain ($N = 43$), skin rash ($N = 40$), headache ($N = 38$), loss of taste ($N = 36$), red eye ($N = 29$), and diarrhea ($N = 15$). Forty-five patients had body

Table 3: Outcomes from control (SOC) treatment of 15 mild COVID-19 patients ($N = 60$)

Variables	*Days of admission (mean ± SD)*	*7 days after admission (mean ± SD)*	*14 days after admission (mean ± SD)*	*p values (days: 1, 7)*	*p values (days: 7, 14)*
RBS (mmol/L)	7.313 ± 3.634	7.313 ± 3.634	7.388 ± 3.395	0.5000, **1.0000**	0.4493, **0.8986**
WBC (K/μL)	14.347 ± 12.171	23.800 ± 17.921	19.733 ± 5.257	0.0002**, **0.0004****	0.1976, **0.3953**
Neutrophil (%)	64.467 ± 11.874	97.867 ± 13.522	80.067 ± 27.215	0.0000**, **0.0000****	0.0128**, **0.0257***
RBC (million/dL)	5.185 ± 2.145	48.080 ± 163.493	6.042 ± 1.819	0.1635, **0.3270**	0.1674, **0.3348**
Hemoglobin (g/dL)	12.720 ± 1.543	15.435 ± 2.840	14.229 ± 2.116	0.0042**, **0.0085****	0.1032, **0.2063**
Platelets (K/μL)	192.267 ± 74.622	245.533 ± 109.744	256.333 ± 109.017	0.0789, **0.1578**	0.2380, **0.4760**
S. Ferritin (ng/mL)	183.060 ± 115.985	345.200 ± 102.482	115.600 ± 65.19	0.0000**, **0.0000****	0.0000**, **0.0000****
CRP (mg/L)	8.077 ± 11.46	19.800 ± 12.639	18.067 ± 4.284	0.0003**, **0.0007****	0.3027, **0.6054**
D-dimer (μg/mL)	0.471 ± 0.173	1.100 ± 0.774	0.508 ± 0.192	0.0053**, **0.0105****	0.0067**, **0.0134****
O_2 saturation at room air (%) at day 1	96.133 ± 1.060	91.133 ± 2.200	95.267 ± 1.100	0.0000**, **0.0000****	0.0000**, **0.0000****

COVID-19, coronavirus disease in 2019; RBS, random blood sugar; WBC, white blood count; RBC, red blood cell; CRP, C-reactive protein; S. Ferritin, serum ferritin; SOC, standard of care; O_2, oxygen. Data are shown as mean ± standard deviation. Statistical significance was considered when p value was <0.01 and <0.05 and shown as ** and * mark, respectively. p value = normal value one-tail and bold value two-tail, calculated with 5% level of significance

temperature less than 99.5°C and 15 had temperature above this. The entry of patients was dependent on the diagnosis of mild or moderate COVID-19 and comorbidities were not a factor for treatment choice. The criteria of discharge were containment of COVID-19-related symptoms so that they can be managed in their houses after discharge. Although some patients were discharged from hospitals early, all patients attended the 7- and 14-day follow-up to provide us with insights regarding the role of the herbal medicine in COVID-19 patients. Follow-up data have been provided at three points: at entry, 7, and 14 days after admission. Although some patients were hospitalized for long duration, the data after 14 days would not be given as per protocol. Of the 60 patients in this cohort, only one patient died. However, he was from control group and did not receive any herbal medication.

In order to have proper insights about the role of herbal plant on kinetics of various parameters, the data of three different points (date of admission, 7 and 14 days after admission) have been shown in Tables 4 to 7.

Role of SOC in Mild COVID-19 Patients

Different parameters of interest of 15 patients with mild COVID-19 patients receiving only SOC have been documented in Table 3. Management of mild COVID-19 patients by SOC showed diverse variations about positive and negative changes of various parameters. The mean ratio of neutrophil was increased by day 7 compared to basal level. The levels of hemoglobin and platelets also showed positive improvements at day 7 compared to day 1. Oxygen saturation showed variable characteristics, decreasing on day 7 but increasing on day 14. The levels of CRP increased and decreased on day 7 and remain almost unchanged on day 14.

Role of SOC Plus *E. neriifolia* in Mild COVID-19 Patients

The tabulated data in Table 4 show information about relevant parameters of 15 patients with mild COVID-19 and those received SOC plus *E. neriifolia*.

Usage of *E. neriifolia* with SOC in 15 patients with mild COVID-19 exhibited improvements of D-Dimer at day 7 and oxygen saturation on day 7 and day 14.

Role of SOC in Moderate COVID-19 Patients

When 15 moderate COVID-19 patients were treated by only SOC, levels of CRP, D-Dimer, and oxygen saturation showed variable kinetics but they did not show statistical significance compared to basal levels (Table 5).

Role of SOC Plus *E. neriifolia* in Moderate COVID-19 Patients

As shown in Table 6, the addition of *E. neriifolia* with SOC for treating 15 moderate patients with COVID-19 showed significant effect on decrease of CRP and D-Dimer. Also, the oxygen saturation improved from a mean level of 91.5% to a mean level of 97.1% on day 7 and 96.6% on day 14.

Short Hospital Staying of Patients with Moderate COVID-19 due to Usage of *E. neriifolia*

The most dramatic effect of *E. neriifolia* was evident regarding SARS-CoV-2 negativity and hospital staying of COVID-19 patients. The duration of hospital staying decreased significantly due to usage of *E. neriifolia* in both mild and moderate COVID-19 patients (Fig. 1, Table 7).

Table 4: Outcomes from SOC + *Euphorbia neriifolia* treatment for mild COVID-19 patients ($N = 60$)

Variables	*Days of admission (mean ± SD)*	*7 days after admission (mean ± SD)*	*14 days after admission (mean ± SD)*	*p values (days: 1, 7)*	*p values (days: 7, 14)*
RBS (mmol/L)	5.397 ± 1.477	5.711 ± 1.171	5.489 ± 1.035	0.0461*, **0.0921**	0.1110, **0.2220**
WBC (K/μL)	4.873 ± 0.951	5.296 ± 0.720	5.173 ± 0.645	0.0405* **0.0810**	0.2893, **0.5787**
Neutrophil (%)	52.800 ± 8.082	52.667 ± 6.253	48.200 ± 5.583	0.4799, **0.9597**	0.0323* **0.0646**
RBC (million/dL)	4.678 ± 0.52	4.462 ± 0.32	4.719 ± 0.450	0.0042**, **0.0013****	0.0510*, **0.1020**
Hemoglobin (g/dL)	12.871 ± 1.125	12.586 ± 0.533	12.569 ± 0.559	0.1986, **0.3973**	0.4561, **0.9122**
Platelets (K/μL)	205.800 ± 37.130	244.533 ± 24.101	274.933 ± 58.105	0.0018**, **0.0037****	0.0304*, **0.0608**
S. Ferritin (ng/mL)	47.700 ± 58.08	46.133 ± 15.547	56.733 ± 45.514	0.4545/ **0.9091**	0.2158/ **0.4316**
CRP (mg/L)	3.581 ± 3.28	2.800 ± 1.32	3.200 ± 1.61	0.2155, **0.4309**	0.2166, **0.4332**
D-dimer (μg/mL)	0.267 ± 0.122	0.192 ± 0.066	0.211 ± 0.052	0.0091**, **0.0181****	0.2438, **0.4876**
O_2 saturation at room air (%) at day 1	95.867 ± 0.743	97.200 ± 1.56	96.400 ± 1.24	0.0070**, **0.0139****	0.0140**, **0.0281***

COVID-19, coronavirus disease in 2019; RBS, random blood sugar; WBC, white blood count; RBC, red blood cell; CRP, C-reactive protein; S. Ferritin, serum ferritin; SOC, standard of care, O_2, oxygen. Data are shown as mean ± standard deviation. Statistical significance was considered when *p* value was <0.01 and <0.05 and shown as ** and * mark, respectively. *p* value = normal value one-tail and bold value two-tail, calculated with 5% level of significance

Table 5: Outcomes from control (SOC) treatment for moderate COVID-19 patients ($N = 60$)

Variables	*Days of admission (mean ± SD)*	*7 days after admission (mean ± SD)*	*14 days after admission (mean ± SD)*	*p values (days: 1, 7)*	*p values (days:7, 14)*
RBS (mmol/L)	14.817 ± 6.270	15.682 ± 5.024	15.781 ± 4.02	0.1098, **0.2197**	0.2295, **0.4590**
WBC (K/μL)	23.720 ± 29.96	28.600 ± 18.86	15.286 ± 3.19	0.0943, **0.1886**	0.0055**, **0.0109****
Neutrophil (%)	82.333 ± 9.225	93.667 ± 28.205	64.929 ± 36.199	0.0702, **0.1404**	0.0133**, **0.0266***
RBC (million/dL)	6.217 ± 2.310	6.784 ± 2.25	7.614 ± 3.045	0.1600, **0.3200**	0.1964, **0.3928**
Hemoglobin (g/dL)	13.287 ± 1.961	13.847 ± 3.811	13.039 ± 2.226	0.2861, **0.5723**	0.1460, **0.2921**
Platelets (K/μL)	269.067 ± 131.412	201.667 ± 97.081	212.714 ± 96.302	0.0281*, **0.0562***	0.4310, **0.8620**
S. Ferritin (ng/mL)	1187.721 ± 1887.504	525.533 ± 286.826	123.643 ± 67.068	0.0745, **0.1491**	0.0000**, **0.0000****
CRP (mg/L)	36.100 ± 46.05	38.733 ± 15.668	29.714 ± 11.391	0.4164, **0.8328**	0.0103**, **0.0206***
D-dimer (μg/mL)	6.387 ± 19.192	5.360 ± 14.330	1.221 ± 0.611	0.2962, **0.5924**	0.1292, **0.2583**
O_2 saturation at room air (%) at day 1	89.000 ± 2.50	89.400 ± 3.961	93.929 ± 1.072	0.3360, **0.6719**	0.3948, **0.7897**

COVID-19, coronavirus disease in 2019; RBS, random blood sugar; WBC, white blood count; RBC, red blood cell; CRP, C-reactive protein; S. Ferritin, serum ferritin; SOC, standard of care, O_2, oxygen. Data are shown as mean ± standard deviation. Statistical significance was considered when *p* value was <0.01 and <0.05 and shown as ** and * mark, respectively. *p* value = normal value one-tail and bold value two-tail, calculated with 5% level of significance

Table 6: Outcomes from SOC + *Euphorbia neriifolia* treatment for moderate COVID-19 patients ($N = 60$)

Variables	*Day of admission (mean ± SD)*	*7 days after admission (mean ± SD)*	*14 days after admission (mean ± SD)*	*p values (days:1, 7)*	*p values (days: 7, 14)*
RBS (mmol/L)	7.901 ± 2.900	5.145 ± 0.706	5.190 ± 0.600	0.0003**, **0.0005****	0.4047, **0.8094**
WBC (K/μL)	8.624 ± 2.373	5.651 ± 0.77	5.123 ± 0.807	0.0001**, **0.0003****	0.0370*, **0.0741**
Neutrophil (%)	68.333 ± 10.486	54.800 ± 7.720	48.267 ± 5.007	0.0002**, **0.0004****	0.0086**, **0.0171****
Lymphocytes (%)	30.933 ± 13.79	28.467 ± 5.263	30.067 ± 6.147	0.2539, **0.5078**	0.2394, **0.4789**
Monocyte (%)	3.400 ± 1.805	3.800 ± 1.014	3.267 ± 1.033	0.0167**, **0.0335***	0.0016**, **0.0032****
Eosinophil (%)	2.200 ± 1.373	2.200 ± 0.676	1.933 ± 0.884	0.5, **1**	0.2063, **0.4125**
RBC (million/dL)	4.950 ± 0.853	4.999 ± 0.514	4.695 ± 0.425	0.4131, **0.8262**	0.0848, **0.1696**
Hemoglobin (g/dL)	16.902 ± 14.268	12.647 ± 0.632	12.800 ± 0.785	0.1349, **0.2697**	0.2432, **0.4863**
Platelets (K/μL)	251.133 ± 71.06	244.467 ± 27.383	233.400 ± 53.097	0.3483, **0.6967**	0.1989, **0.3978**
S. Ferritin (ng/mL)	277.764 ± 275.372	116.067 ± 66.263	79.200 ± 47.531	0.118, **0.0236***	0.0085** **0.0171****
CRP (mg/L)	29.443 ± 34.637	5.333 ± 2.059	3.600 ± 1.549	0.0077**, **0.0154****	0.0146**, **0.0292***
D-dimer (μg/mL)	0.548 ± 0.407	0.289 ± 0.111	0.202 ± 0.051	0.0074**, **0.0147***	0.0083**, **0.0223***
O_2 saturation at room air (%) at day 1	91.533 ± 1.959	97.133 ± 1.457	96.600 ± 1.40	0.0000**, **0.0000****	0.0045**, **0.0032****

COVID-19, coronavirus disease in 2019; RBS, random blood sugar; WBC, white blood count; RBC, red blood cell; CRP, C-reactive protein; S. Ferritin, serum ferritin; SOC, standard of care, O_2, oxygen. Data are shown as mean ± standard deviation. Statistical significance was considered when *p* value was <0.01 and <0.05 and shown as ** and * mark, respectively. *p* value = normal value one tail and bold value two tail, calculate with 5% level of significance

Table 7: Duration of hospitalization and SARS-CoV-2 negativity in different groups

Variables	*Mean ± SD*	*p values (one-tail)*	*p values (two-tails)*
Clinical outcomes mild COVID-19 patients for SOC and SOC + *Euphorbia neriifolia* treatment			
Duration of hospital stay-day for mild COVID-19 patients for SOC treatment (control)	17.333 ± 3.416 (17; 10–36)	0.0000**	0.0000**
Duration of hospital stay-day for mild COVID-19 patients for SOC + *E. neriifolia* treatment	4.200 ± 1.014 (4; 2–8)		
Clinical outcomes moderate COVID-19 patients for SOC and SOC + *Euphorbia neriifolia* treatment			
Duration of hospital stay-day for moderate COVID-19 patients for SOC treatment (control)	29.400 ± 8.365 (30; 12–45)	0.0000**	0.0000**
Duration of hospital stay-day for moderate COVID-19 patients for SOC + *E. neriifolia* treatment	8.467 ± 3.739 (7; 4–12)		

Data are shown as mean ± standard deviation. Statistical significance was considered when *p* value was <0.01 and <0.05 and shown as ** and * mark, respectively. *p* value calculated with 5% level of significance

Discussion

At the starting point of 2022, the world has been facing a serious paradigm of COVID-19 pandemic that is going to shatter the social, economic, and physiological well-beings of billions of human beings. After more than 2 years of SARS-CoV-2 pandemic, now we have been facing an extremely difficult variant of SARS-CoV-2, OMICRON, containing huge amount of mutations at spike protein. Thus, the efficacy of vaccines has become questionable and it is elusive how the world would face this highly infectious and less pathogenic variant of SARS-CoV-2. Almost one to two million new confirmed cases of SARS-CoV-2 have been detected on a daily basis for the last 1 week, mostly in developed countries like USA, UK, and European Union (EU) as well as Australia and India. It seems that soon the OMICRON strain of SARS-CoV-2 would flood the entire world. This will eventually destroy the healthcare delivery system of the entire world as preparations for tackling millions of patients on daily basis were not on agenda. It is noteworthy to mention that COVID-19 with severe complications like pneumonia or multiple organ failure or acute respiratory distress needs hospitalization and sophisticated treatment for their survival. However, most of the patients suffering from OMICRON variant seem to be asymptomatic or with mild or moderate symptoms, although it is too early to draw a conclusion about this at this point as development of new mutations in OMICRON may alter its pathogenicity.

The study presented here is an observation study and represented a preliminary study. This was accomplished at a hospital in Bangladesh, a developing country with 164 million people to assess safety and efficacy of a herbal medicine, *E. neriifolia*, in mild and moderate patients of COVID-19. The study is endowed with several limitations as this is a pilot study and needs to be confirmed by studies in larger cohort and multicenter approaches. We only enrolled 60 patients and half of them received SOC and the remaining received SOC plus *E. neriifolia*. The eminent part of the study in the context of pandemic of OMICRON variant of SARS-CoV-2, the herbal plant, may have some practical usage.

The first is the use of *E. neriifolia* is safe as there were no notable adverse effects or alteration of critical laboratory parameters in patients receiving *E. neriifolia*. The next, CRP and D-dimer, two eminent markers of COVID-19 patients reduced significantly in moderate COVID-19 patients receiving SOC plus *E. neriifolia*. However, the alteration of these parameters was not so visible in patients receiving only SOC. Finally, the most important fact is the duration of hospital stay. Patients receiving *E. neriifolin* had significantly lesser hospital stay compared to patients receiving only SOC.

It is now an open question regarding the real impact of this study. There are several limitations of this study. The sample size is low and is not representative. Under the prevailing condition of COVID-19 pandemic, a randomized, double-blinded, control trial with proper power cannot be conducted in a developing country like Bangladesh. However, we used a control group. The patients in both groups could not be properly randomized and that is a reality during a pandemic. This study was not conducted with patients with OMICRON strain, but the study clearly shows the initial promise of early PCR negativity of SARS-CoV-2 and quick release from hospital due to improvement of clinical conditions and laboratory parameters. These are two challenging issues that must be addressed in COVID-19 patients with OMICRON strain during the next several months.

In conclusion, although this is an observational study, it shows that *E. neriifolia* may of practical implication at this age of infection with OMICRON strain when we require quick negativity of SARS-CoV-2 and early hospital discharge to maintain the ongoing healthcare delivery services to provide more attention to serious and complicated cases of COVID-19. In fact, treatment with *E. neriifolia* may be given at residential set-up without admitting to the hospital.

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